UNIVERSIDADE FEDERAL DE SANTA CATARINA
CENTRO DE CIÊNCIAS DA SAÚDE
PROGRAMA DE PÓS-GRADUAÇÃO EM NUTRIÇÃO

GILCIANE CEOLIN

DETERMINANTES DAS CONCENTRAÇÕES SÉRICAS DA VITAMINA D E A SUA ASSOCIAÇÃO COM SINTOMAS DEPRESSIVOS EM IDOSOS DE FLORIANÓPOLIS-SC

Florianópolis

2022

GILCIANE CEOLIN

DETERMINANTES DAS CONCENTRAÇÕES SÉRICAS DA VITAMINA D E A SUA ASSOCIAÇÃO COM SINTOMAS DEPRESSIVOS EM IDOSOS DE FLORIANÓPOLIS-SC

Tese submetida ao Programa de Pós-Graduação em Nutrição da Universidade Federal de Santa Catarina, como requisito para obtenção do título de Doutora em Nutrição.

Orientadora: Profa. Dra. Júlia Dubois Moreira
Coorientadora: Prof. Dra. Débora Kurrle Rieger Venske.

Florianópolis

2022

Ficha de identificação da obra elaborada pelo autor,
através do Programa de Geração Automática da Biblioteca Universitária da UFSC.

Ceolin, Gilciane
Determinantes das concentrações séricas da vitamina D e a sua associação com sintomas depressivos em idosos de Florianópolis-SC / Gilciane Ceolin ; orientadora, Júlia Dubois Moreira, coorientadora, Débora Kurrle Rieger Venske, 2022.
301 p.

Tese (doutorado) - Universidade Federal de Santa Catarina, Centro de Ciências da Saúde, Programa de Pós Graduação em Nutrição, Florianópolis, 2022.

Inclui referências.

1. Nutrição. 2. Vitamina D. 3. Sintomas Depressivos. 4. Envelhecimento. I. Moreira, Júlia Dubois. II. Venske, Débora Kurrle Rieger. III. Universidade Federal de Santa Catarina. Programa de Pós-Graduação em Nutrição. IV. Título.

Gilciane Ceolin

Determinantes das concentrações séricas da vitamina D e a sua associação com sintomas depressivos em idosos de Florianópolis-SC

O presente trabalho em nível de doutorado foi avaliado e aprovado por banca examinadora composta pelos seguintes membros:

Prof. Francisco de Assis Guedes de Vasconcelos, Dr.
Universidade Federal de Santa Catarina

Profa. Dirce Maria Lobo Marchioni, Dra.
Universidade de São Paulo

Profa. Flávia Fioruci Bezerra, Dra.
Universidade do Estado do Rio de Janeiro

Certificamos que esta é a versão original e final do trabalho de conclusão que foi julgado adequado para obtenção do título de doutor em Nutrição.

ICP-Edu
Documento assinado digitalmente
Ana Carolina Fernandes
Data: 24/01/2023 10:36:03-0300
CPF: ***.277.939-**
Verifique as assinaturas em https://v.ufsc.br

Coordenação do Programa de Pós-Graduação em Nutrição

ICP-Edu
Documento assinado digitalmente
Julia Dubois Moreira
Data: 09/01/2023 15:45:46-0300
CPF: ***.928.210-**
Verifique as assinaturas em https://v.ufsc.br

Profa. Júlia Dubois Moreira, Dra.
Orientadora

ICP-Edu
Documento assinado digitalmente
Debora Kurrle Rieger Venske
Data: 10/01/2023 16:44:00-0300
CPF: ***.182.830-**
Verifique as assinaturas em https://v.ufsc.br

Profa. Débora Kurrle Rieger Venske, Dra.
Co-orientadora

Florianópolis, 2022.

Dedico esse trabalho às mulheres que auxiliaram e influenciaram de muitas formas minha caminhada na construção dessa tese!

AGRADECIMENTOS

A construção dessa Tese de Doutorado foi lapidada ao longo de 4 anos e meio com base em parceiras e apoios que foram essenciais para a concretização e merecem ser agradecidas.

À minha família, pai **Gilmar Antônio Ceolin**, mãe **Mariza Ceolin**, avó **Elisa Maria Ceretta**, irmã **Simone Ceolin** e cunhado **Lucas Dal'Maso** pelo apoio incondicional em meio a diversas dificuldades que superamos, pelo incentivo, pelo suporte nos momentos mais difíceis e por compartilhar dos meus momentos mais felizes e de conquistas.

À Professora Orientadora, **Júlia Dubois Moreira**, Dra., pela sua paciência, acolhida, confiança, oportunidade e incentivo na construção do meu desenvolvimento e de minha tese ao longo desse período. Muito obrigada por compartilhar seu conhecimento e sua empatia!

À Professora Coorientadora, **Débora Kurrle Rieger Venske**, Dra., pelas valiosas contribuições, incentivo e parceria ao longo deste período.

À **Universidade Federal de Santa Catarina (UFSC)** e ao **Programa de Pós-Graduação em Nutrição (PPGN)**, pelas oportunidades enquanto doutoranda de crescimento e desenvolvimento proporcionadas, pelo ensino público de excelência disponibilizado.

À Professora **Elisa Brietzke**, Dra, que me recebeu no período de doutorado sanduíche, na ***Queen's University*** no Canadá. Muito obrigada pela oportunidade, pelo apoio, ensinamentos, incentivo e por toda sua empatia e parceria científica durante esse período que foi muito importante na minha carreira, para o desenvolvimento pessoal e da tese de doutorado.

Aos participantes do grupo de pesquisa ***NeuroMood Lab***, Prof. **Fabiano Gomes**, Dr., **Vitor Breda**, Dr., **Elena Koning**, Me., e a assistente de pesquisa **Yan Deng**, que compartilharam conhecimento, aprimoramento dos estudos desenvolvidos e pela parceria em publicações e apoio durante o período de doutorado sanduíche, além da amizade!

À ***Queen's University*** e ao ***Centre for Neuroscience Studies*****,** pelas oportunidades enquanto doutoranda visitante, pelo espaço e oportunidade de crescimento, pela disponibilidade e todo auxílio burocrático com a documentação para tornar possível a realização do doutorado sanduíche e parte dos estudos de minha tese de doutorado.

À **Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - CAPES**, pela concessão de bolsa de doutorado ao longo desses quatro anos, e pela concessão de bolsa de doutorado sanduíche de seis meses que possibilitou apoio financeiro e a oportunidade de desenvolver essa Tese.

Aos integrantes do grupo de estudos e pesquisa **Neurociência Nutricional Translacional**, que nos encontros semanais compartilharam conhecimento, auxílio, apoio e parcerias em artigos durante o período.

À professora Coordenadora **Eleonora d'Orsi**, professores, colegas e colaboradores do **EpiFloripa Idoso**, **Cassiano Ricardo Rech,** Dr., **Susana Cararo Confortin**, Dra., **Anna Quialheiro Abreu da Silva**, Dra., **Thamara Hübler Figueiró**, Dra., pela acolhida no grupo de pesquisa, pela oportunidade enriquecedora de aprender e participar de um estudo de base domiciliar e populacional, que agregou um importante aprendizado e proporcionou muitos frutos à essa Tese e pela parceria na produção e publicação de estudos. Agradeço também aos participantes do Estudo EpiFloripa Idoso, que aceitaram fazer parte da pesquisa e permitiram que eu pudesse desenvolver os estudos desta Tese.

Aos membros titulares da banca examinadora de qualificação e defesa, Professores **Francisco de Assis Guedes de Vasconcelos**, Dr., **Jean Pierre Oses**, Dr., **Manuella Pinto Kaster**, Dra., **Dirce Maria Lobo Marchioni**, Dra., **Flávia Fioruci Bezerra**, Dra., pela disponibilidade e dedicação em contribuir com este trabalho.

Aos Professores, **Antônio Augusto Moura da Silva**, Dr., **Luciana Antunes**, Dra., **Mateus Grellert**, Dr., pela parceria em artigos, pelas discussões e troca de conhecimento ao longo desse período.

Às amigas, **Vanessa Teixeira**, **Luísa Harumi Matsuo**, **Carla Elane Silva dos Santos**, **Flávia Ferreira**, **Karine Andrea Albiero**, **Bruna Mendes, Luna Dias de Oliveira**, **Jamilla Telles** e **Thaise Cadorin** por compartilharem comigo os momentos de angústia e alegria durante esse processo. Agradeço imensamente pela amizade, pelos conselhos, pelos risos compartilhados, por ter vocês por perto! Em especial à **Taís Thomsen Silveira** que além da amizade, compartilhou seus conhecimentos da língua inglesa, o que foi muito importante para a realização do doutorado sanduíche.

Á todos que contribuíram de alguma forma para essa conquista, muito obrigada!

RESUMO

CEOLIN, Gilciane. **Determinantes das concentrações séricas da vitamina D e a sua associação com sintomas depressivos em idosos de Florianópolis-SC**. Tese (doutorado em Nutrição). Programa de Pós-Graduação em Nutrição, Universidade Federal de Santa Catarina, Florianópolis, 2022.

Introdução: A população idosa tem sido considerada de risco tanto para hipovitaminose D (<30 ng/ml), quanto para depressão. Pesquisadores vêm discutindo o papel da vitamina D na depressão, no entanto, poucos estudos somente com idosos foram realizados, sendo necessário elucidar essa relação. **Objetivos:** Identificar os determinantes das concentrações séricas da vitamina D e avaliar a sua associação com sintomas depressivos em idosos de Florianópolis-SC. **Métodos:** Estudo multimétodos, que incluiu estudo de revisão narrativa, e estudo empírico longitudinal, observacional, de base populacional e domiciliar, com dados oriundos de 3 ondas de pesquisa do estudo de coorte EpiFloripa Idoso (linha de base em 2009-2010, onda 2 em 2013-2014, com subamostra de exames em 2014-2015, e onda 3 em 2017-2019). O nível sérico de 25-hidroxicolecalciferol [25(OH)D] foi mensurado pelo método de quimioluminescência. A escala de depressão geriátrica de 15 itens (GDS-15) foi usada para mensurar sintomas depressivos. No artigo 1, com dados da onda 2, foram verificadas as associações transversais entre fatores sociodemográficos, comportamentais e de saúde e 25(OH)D, através de regressão logística multinominal. No artigo 2, com dados da onda 2, foi investigado transversalmente os efeitos diretos da atividade física e adiposidade (percentual de gordura corporal, %G) na 25(OH)D, e o efeito indireto mediado pela adiposidade em um modelo de equações estruturais. Para o artigo 3, uma revisão narrativa da relação entre vitamina D e depressão, foi feita uma busca sistematizada nas principais bases de dados, de artigos publicados até abril de 2021. No artigo 4, uma revisão breve, foi realizada uma busca sistematizada para discutir a possível relação entre vitamina D, sintomas depressivos e pandemia por Covid-19. No artigo 5, com dados da onda 2, foi verificada a associação transversal entre 25(OH)D e sintomas depressivos através de regressão de Poisson. No artigo 6, com dados das ondas 2 e 3, foi analisado a associação longitudinal entre 25(OH)D e mudança na severidade de sintomas depressivos, a partir de uma regressão logística multinominal. Para o artigo 7, com dados das 3 ondas, foi verificado a associação longitudinal entre a adiposidade (índice de massa corporal - IMC, e circunferência da cintura) e a incidência de sintomas depressivos a partir da estimação de equações generalizadas. **Resultados:** No artigo 1 (n=574), 43,7% do idosos apresentaram insuficiência (21-29 ng/ml) e 23,4% deficiência (≤ 20 ng/ml) de 25(OH)D. Os fatores de risco

(p>0,05) para insuficiência foram o sexo feminino (RR=2,20), lipoproteína de baixa densidade (LDL ≥160mg/dl, RR=3,49), obesidade pelo IMC (≥30 kg/m^2, RR=2,37) e %G (Homens: ≥ 31% e Mulheres: ≥43%, RR=2,10). Para deficiência, o sexo feminino (RR=2,32), dependência em ≥4 atividades da vida diária (AVDs, RR=2,73), LDL (100-129mg/dl: RR=2,96; 130-159mg/dl: RR=4,56; ≥160mg/dl: RR=7,94), obesidade para IMC (RR=2,25) e %G (RR=3,62). A atividade física no lazer (≥150 min/semana) foi fator de proteção para ambos (insuficiência: RR=0,38 e deficiência: RR=0,29). No artigo 2 (n=574), a atividade física moderada e vigorosa (AFMV) teve efeito direto e positivo na 25(OH)D (β=0,11; P<0,05) e direto e negativo no %G (β= -0,11; P<0,05); o %G teve um efeito direto e negativo na 25(OH)D (β= -0,13; P<0,05) e de mediação na relação entre AFMV e 25(OH)D. No artigo 3, evidenciou-se uma maquinaria para transformação e uso da vitamina D no cérebro, e possíveis mecanismos de ações vinculados a depressão, entretanto há poucos estudos clínicos e longitudinais com idosos. No artigo 4, discutiu-se o possível papel da vitamina D nos sintomas depressivos e no Covid-19 durante a pandemia, entretanto os resultados não foram conclusivos. No artigo 5 (n=557), 15,8% dos idosos apresentaram sintomas depressivos (≥6 pontos) e aqueles com deficiência em 25(OH)D tiveram uma chance maior de ter sintomas depressivos (OR=2,27; p=0,038) comparado com suficiência (≥30 ng/ml). No artigo 6 (n=386), 12,6% dos participantes passaram a ter gravidade dos sintomas depressivos (≥6 pontos), 7,1% apresentaram deixaram de ter e 5,0% mantiveram, na onda 3; os idosos no menor quartil de 25(OH)D (4 a 20,6 ng/ml) apresentaram maior chance (OR=2,90; p=0,025) de apresentar sintomas depressivos na onda 3, em relação ao maior quartil (32,1 a 50 ng/ml). No artigo 7 (n=580), a incidência de sintomas depressivos (≥6 pontos) foi de 9,9%, e aqueles com obesidade (IMC ≥30 kg/m^2) apresentaram um risco relativo maior de ter sintoma depressivo na onda 3 (IRR=1,24, p=0,035). **Conclusão:** A partir dos resultados dos estudos de revisão foi possível identificar os mecanismos de ação da vitamina D na depressão, as possíveis interrelações frente a pandemia por covid-19, e evidenciar a necessidade de estudos longitudinais e clínicos, a fim de elucidar a relação. Entre os principais determinantes da vitamina D, foi identificado fatores modificáveis como a atividade física e a adiposidade. A adiposidade de forma longitudinal foi associada aos sintomas depressivos ao longo de 10 anos. Tanto de forma transversal, quanto longitudinal, os idosos que apresentavam deficiência de vitamina D tiveram maior risco de ter severidade nos sintomas depressivos.

Palavras-chave: Sintomas depressivos; Vitamina D; 25-Hidroxicolecaciferol; Envelhecimento; Idoso; Estudos de Coortes;

ABSTRACT

CEOLIN, Gilciane. **Determinants of serum Vitamin D concentration and the association with depressive symptoms in older adults from Florianopolis, SC**. Doctoral dissertation (PhD in Nutrition). Graduate Program in Nutrition, Federal University of Santa Catarina, Florianopolis, 2022.

Introduction: The older adult population has been considered at risk for both hypovitaminosis D (<30 ng/ml) and depression. Researchers have discussed the role of vitamin D in depression, however, few studies with older adults were published, then it is necessary to disentangle its association. **Objectives:** To identify the determinants of serum vitamin D concentrations and evaluate its association with depressive symptoms in older adults from Florianopolis-SC. **Methods:** Multimethod study, which included a narrative review and an empirical longitudinal, observational, population-based, and household study, with data from 3 collection wave from the EpiFloripa Aging cohort study (baseline in 2009-2010, wave 2 in 2013-2014 with a subsample of exams in 2014-2015, and wave 3 in 2017-2019). The serum level of 25-hydroxycholecalciferol [25(OH)D] was measured by the chemiluminescence method. The 15-item Geriatric Depression Scale (GDS-15) was used to measure depressive symptoms. In article 1, with data from wave 2, a cross-sectional association between sociodemographic, behavioral and health factors and 25(OH)D were verified through multinomial logistic regression. In article 2, with data from wave 2, a cross-sectional direct effect of physical activity and adiposity (measured by fat body percentage, %fat) on 25(OH)D, and the indirect effect mediated by adiposity were verified through the structural equation modeling. For article 3, a systematic search was carried out in the main databases to develop a narrative review of the relationship between vitamin D and depression. In article 4, a systematic search ws carried out for a brief review to discuss the possible relationship between vitamin D, depressive symptoms, and Covid-19 pandemic. In article 5, with data from wave 2, the cross-sectional association between 25(OH)D and depressive symptoms was verified through Poisson regression. In article 6, with data from waves 2 and 3, the longitudinal association between 25(OH)D and changes in the severity of depressive symptoms was analyzed based on a multinomial logistic regression. For article 7, with data from the 3 waves, the longitudinal association between adiposity (measured by body mass index - BMI, and waist circumference) and the incidence of depressive symptoms was verified from the generalized estimating equations. **Results:** In article 1 (n=574), 43.7% of older adults presented insufficiency (21-29 ng/ml), and 23,5% deficiency (≤ 20 ng/ml) in 25(OH)D. The risk factors for insufficiency were female sex

(RR=2.20), low-density lipoprotein cholesterol (LDL-C ≥160mg/dl, RR=3.49), obesity in BMI (≥30 kg/m^2, RR=2.37) and %fat (Men: ≥ 31% and Women: ≥43%; RR=2.10). For deficiency, the risk factors were female sex (RR=2.32), dependence on ≥4 activities of daily living (ADLs, RR=2.73), LDL-C (100-129mg/dl: RR=2.96; 130-159mg/dl: RR=4.56; ≥160mg/dl: RR=7.94), obesity in BMI (RR=2.25) e %fat (RR=3.62). Leisure-time physical activity (≥150 min/week) was a protective factor for both (insufficiency: RR=0.38 and deficiency: RR=0.29). In article 2 (n=574), moderate and vigorous physical activity (MVPA) had a direct and positive effect on 25(OH)D (β=0.11; P<0.05), and a direct and negative effect on %fat (β = -0.11; P<0.05); %fat had a direct and negative effect on 25(OH)D (β= -0.13; P<0.05), and a mediation effect on the association between MVPA and 25(OH)D. In article 3, a machinery for the transformation and use of vitamin D in the brain, and the possible mechanisms of action linked to depression were discussed, however, there are still few clinical and longitudinal studies with older adults. In article 4, the role of vitamin D in depressive symptoms and the Covid-19 during the pandemic time was discussed, however, the results to date were not conclusive. In article 5 (n=557), 15.8% of older adults presented depressive symptoms (≥6 points) and those with 25(OH)D deficiency had a higher odds ratio to depressive symptoms (OR=2.27; p=0.038) compared to sufficiency (≥30 ng/ml). In article 6 (n=386), 12.6% increased the severity of depressive symptoms (≥6 points), 7.1% decreased (≤5 points) and 5.0% remained with severity (≥6 points) in wave 3; those in the lowest quartile of 25(OH)D (4 to 20.6 ng/ml) were more likely to have depressive symptoms in wave 3 (OR=2.90; p=0.025) compared to the highest quartile (32.1 to 50 ng/ml). In article 7 (n=580), the incidence of depressive symptoms (≥6 points) was 9.9%; those with obesity (BMI ≥30 kg /m^2) had a higher relative risk of having depressive symptoms in wave 3 (IRR=1.24, p=0.035). **Conclusion:** From the results of the review studies, it was possible to identify the mechanisms of action of vitamin D in depression, the probable interrelationships in front of the covid-19 pandemic and highlight the need for longitudinal and clinical studies to elucidate its relationship. Among the main determinants of vitamin D, modifiable factors such as physical activity and adiposity were identified. Longitudinal adiposity was associated with depressive symptoms over 10 years. Both transversely and longitudinally analysis showed that older adults with vitamin D deficiency were at higher risk of having severe depressive symptoms.

Keywords: Depressive Symptoms; Vitamin D; Aging; Cohort Studies.

LISTA DE FIGURAS

LISTA DE QUADROS

LISTA DE ABREVIATURAS E SIGLAS

1,24,25(OH3D)	1,24,25-Trihidroxivitamina D
$1,25(OH)_2D$	1,25-di-hidroxivitamina D ou calcitriol
$24,25(OH)_2D$	24(R),25-dihidroxivitamina D
25(OH)D	25-Hidroxivitamina D
5-HIAA	ácido 5-hidroxiindolacético
5-HT	Serotonina
7-DHC	7-Deidrocolesterol
AAP	Academia Americana de Pediatria (do inglês *American Academy of Pediatrics*)
Acetil-CoA	acetilcoenzima A
ACTH	Hormônio adrenocorticotrófico
AGS	Sociedade Americana de Geriatria (do inglês *American Geriatrics Society*)
AMPA	α-amino-3-hidroxi-5-metil-4-isoxazolpropiônico (do inglês *α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid*)
ATP	Adenosina trifosfato
AVD	Atividades da vida diária
BDI	Escala de Depressão de Beck (do inglês *Beck Depression Inventory*)
BDNF	Fator neurotrófico derivado do cérebro (do inglês *Brain-derived neurotrophic factor*)
BH4	Tetra-hidrobiopterina
C^{2+}	Cálcio
CD36	do inglês *Cluster Determinant 36*
CDRS	Escala de classificação de distimia de Cornell (do inglês *Cornell Dysthymia Rating Scale)*
CEPSH	Comitê de Ética em Pesquisa com Seres Humanos
CES-D	Escala de Depressão do Centro de Estudos Epidemiológicos (do inglês *Center for Epidemiological Studies Depression Scale*)

CID 11	Classificação Internacional de Doenças para Estatística de Mortalidade e Morbidade (do inglês *International Classification of Diseases for Mortality and Morbidity Statistics – ICD 11*)
CLIA	Imunoensaios de quimioluminescência (do inglês *chemiluminescence immunoassays*)
COMT	catecol-o-metil transferase
CRH	Hormônio liberador de corticotrofina
CYP24A1	Enzima 24-hidroxilase
CYP27A1	Enzima 25-hidroxilase
CYP27B1	Enzima 1-α-hidroxilase
DACH	do inglês *Deutschland (Germany), Austria and Confoederatio Helvetica (Switzerland)*
DBP	Proteína ligadora de vitamina D (do inglês *vitamin D binding protein*)
DHCR7	7-Desidrocolesterol redutase
DSI	Instrumento de Triagem de Depressão (do inglês *The Depression Screening Instrument*)
DSM-5	Manual Diagnóstico e Estatístico de Transtornos Mentais (*Diagnostic and Satistical Manual of Mental Disorders*)
DXA	Densitômetro de dupla emissão com fonte de raios X (do inglês *Dual Energy X-ray Absorptiometry*)
ECT	Terapia eletroconvulsiva (do inglês *electroconvulsive therapy*)
ELISA	Ensaio de imunoabsorção enzimática
EROs	Espécies reativas de oxigênio (do inglês *reactive oxigen species*)
FGF23	Fator de crescimento dos fibroblastos 23 (do inglês *Fibroblast growth factor 23*)
fMRI	Imagem por ressonância magnética funcional (do inglês *Functional Magnetic Ressonance Imaging)*
GABA	Ácido gama-aminobutírico (do inglês *gamma-aminobutyric acid*)

GAD67	Enzima a glutamato descarboxilase
GBD	do inglês *Global Burden of Disease, Injuries, and Risk Factors*
GC	Glicocorticoide
GCLC	Glutamato-cisteína ligase (do inglês *Glutamate-cysteine ligase*)
GDNF	Fator neurotrófico derivado da glia (do inglês *Glial cell-derived neurotrophic factor*)
GDS	Escala de Deressão Geriátrica (do inglês *Geriatric Depression Scale*)
g-GT	g-Glutamil Transpeptidase
Glx	Metabólitos glutamato + glutamina
Gpx	Glutationa peroxidase
GR	glutationa redutase
HAM-D	Escala de depressão de Hamilton *(do inglês Hamilton Rating Scale for Depression)*
HPA	Eixo hipotálamo-pituitária-adrenal (do inglês *hypothalamic-pituitary-adrenal axis*)
HRSD	Escala de depressão de Hamilton *(do inglês Hamilton Rating Scale for Depression)*
IDO	Indolamina 2,3-dioxigenase
IFN- γW	Interferon
IL	Interleucinas
IMC	Índice de Massa Corporal
IOF	Fundação Internacional de Osteoporose (do inglês *International Osteoporosis Foundation*)
IOM	Instituto de Medicina (do inglês *Institute of Medicine*)
LC-MS/MS	Cromatografia líquida acoplada à espectrometria de massas em tandem (do inglês *Liquid chromatography coupled with tandem mass spectrometry*)
LDL	Lipoproteína de baixa densidade (do inglês *low-density lipoprotein*)

MADRS	Escala de classificação de depressão de Montgomery-Asberg (do inglês *Montgomery-Asberg Depression Rating Scale*)
MAO-A	Monoamina Oxidase-A (do inglês *Monoamine oxidase A*)
MARRS	(do inglês *Membrane Associated, Rapid Response Steroid binding receptor*)
MDI	Inventário de Depressão Maior (do inglês *Major Depression Inventory*)
NCX1	Trocador cálcio-sódio (do inglês *sodium-calcium exchanger*)
NF-κB	Fator nuclear kappa B (do inglês *Nuclear factor kappa B*)
NMDA	N-metil-d-aspartato (do inglês *N-methyl-d-aspartate*)
NPC1L1	do inglês *Niemann–Pick C1-Like 1*
NRF2	Fator nuclear eritróide-2 (do inglês nuclear factor eritroid-2)
OR	Razão de chances (do inglês *odds ratio*)
PDIA3	Proteína dissulfeto-isomerase A3 (do inglês *Protein disulfide-isomerase A3*)
PGE2	prostaglandina E2
PHQ	Questionário de saúde do paciente (do inglês *Patient Health Questionnnaire)*
PLAA	proteína ativadora de fosfolipase A2 (do inglês *phospholipase A2 activating protein*)
PLA2	Fosfolipase A2 (do inglês *phospholipase A2*)
PLC	Fosfolipase C (do inglês *phospholipase C*)
PMCA	Membrana plasmática cálcio-ATPase (do inglês *plasma membrane* Ca^{2+} *pump*)
PPGN	Programa de Pós-Graduação em Nutrição
PPGSC	Programa de Pós-Graduação em Saúde Coletiva
PTH	Hormônio da paratireoide (do inglês *Parathyroid hormone*)
PXR	Receptor ativado por pregnano (do inglês *Pregnane X receptor*)
RIA	Radioimunoensaio manual
RXR	Receptor retinóide X (do inglês *retinoid X receptor*)
SACN	Comitê Científico Consultivo em Nutrição (do inglês *Scientific Advisory Committee on Nutrition*)

SBEM	Sociedade Brasileira de Endocrinologia e Metabologia
SDS	Escala de autoavaliação de depressão de Zung *(do inglês Zung Self-Rating Depression Scale*)
SERT	Transportador de recaptação de serotonina (do inglês *serotonin reuptake transporter* ou 5-HTT)
SIM	Sistema de Informações sobre Mortalidade
SNC	Sistema Nervoso Central
SR-BI	do inglês *Scavenger Receptor Class B Type 1*
SRMR	Resíduo Quadrado Médio Padronizado (do inglês *Standardized Root Mean Square Residual*)
SXR	Receptor de esteróide e xenobiótico
TCLE	Termo de Consentimento Livre e Esclarecido
TH	Tirosina hidroxilase
TNF-α	Fator de necrose tumoral (do inglês *Tumor necrosis fator*)
TNN	Grupo de estudos em Neurociência Nutricional Translacional (do inglês *Translational Nutrition Neuroscience*)
TPH2	Enzima triptofano hidroxilase 2 (do inglês *Tryptophan hydroxylase 2*)
VDBP	Proteína de ligação à vitamina D (do inglês *Vitamin D-binding protein*)
VDR	Receptor de vitamina D (do inglês *vitamin D receptor*)
VDR-AP	do inglês *vitamin D receptor alternative pocket*
VDRE	Elementos responsivos à vitamina D (do inglês *vitamin D response elements*)
VDR-GP	do inglês *vitamin D receptor genomic pocket*
γ-GT	γ-Glutamil transpeptidase
%G	Percentual de gordura corporal

SUMÁRIO

1. INTRODUÇÃO

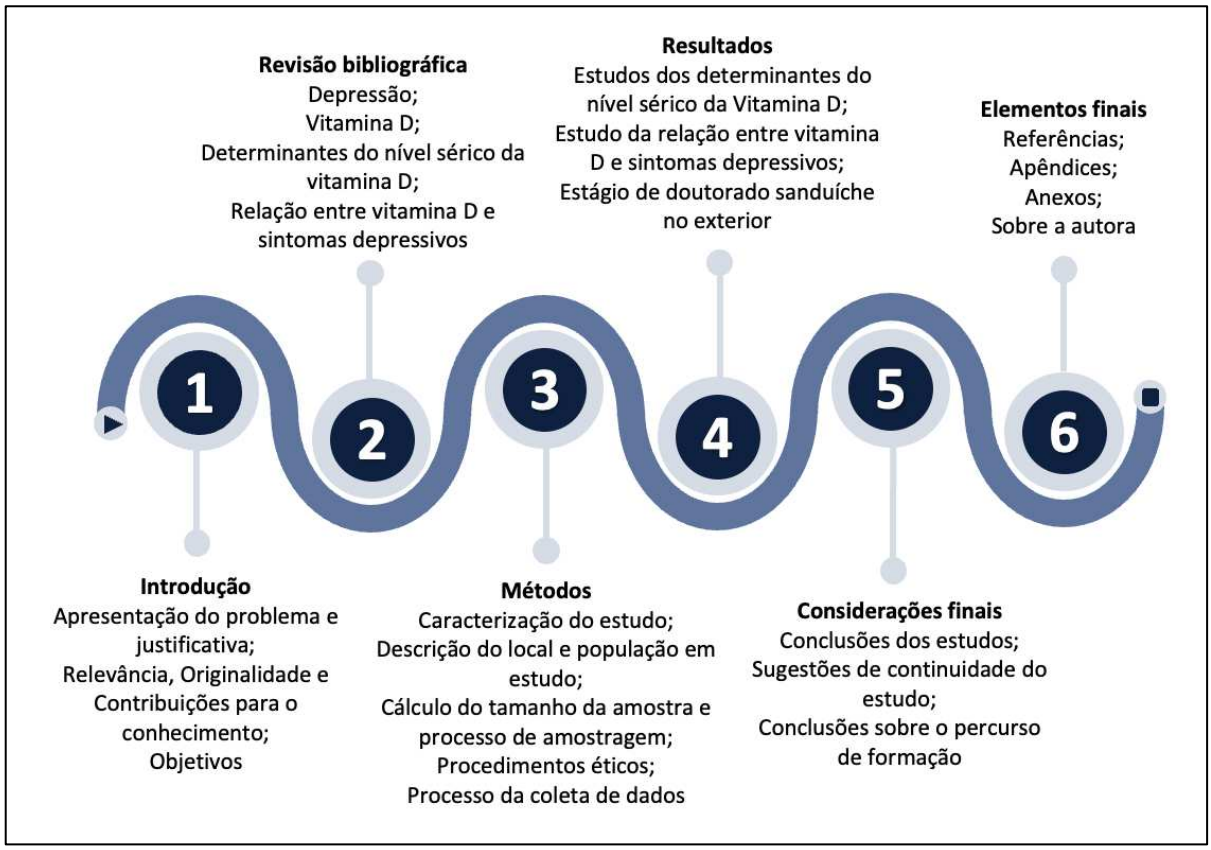
1.1 ESTRUTURA GERAL DO DOCUMENTO

A presente tese de doutorado, intitulada "Determinantes das concentrações séricas da vitamina D e a sua associação com sintomas depressivos em idosos de Florianópolis-SC" está inserido no Programa de Pós-Graduação em Nutrição (PPGN/UFSC), na linha de pesquisa 2, Estudo Dietético e Bioquímico relacionado com o estado nutricional. Faz parte do grupo de estudos em Neurociência Nutricional Translacional (TNN, do inglês *Translational Nutrition Neuroscience*), do grupo de pesquisa EpiFloripa Idoso, e possui parceria científica com o grupo de pesquisa e estudos Laboratório de Neurobiologia dos Transtornos do Humor (do inglês *Laboratory of Neurobiology of Mood Disorders-NeuroMood Lab*), coordenado pela Prof. Dra. Elisa Brietzke, a qual foi supervisora do estágio de doutorado sanduíche realizado durante o período de seis meses, no Centro de Estudos de Neurociências (do inglês *Centre for Neuroscience Studies*) da *Queen's University*, de Kingston, Ontário, Canadá.

Para a construção da tese, foram utilizados dados do estudo "Condições de Saúde de Idosos de Florianópolis – Estudo EpiFloripa Idoso" vinculado ao Programa de Pós-Graduação em Saúde Coletiva (PPGSC/UFSC). O EpiFloripa Idoso é um estudo realizado com a população idosa de Florianópolis-SC, teve sua primeira onda de coleta de dados domiciliares em 2009-2010 (linha de base); uma segunda coleta em 2013-2015 (acompanhamento), na qual os idosos foram entrevistados novamente e foram coletados dados clínicos/exames e testes físicos em uma subamostra; e a terceira onda de coleta em 2017-2019, na qual os idosos foram entrevistados novamente, e a amostra foi composta com a inserção de novos idosos no estudo, se tornando uma coorte aberta, na qual a doutoranda participou ativamente em todas as etapas de planejamento e execução da coleta de dados. Para a presente tese, foram utilizados dados disponíveis dos idosos em acompanhamento nas três ondas.

A presente tese está estruturada em capítulos conforme a figura 1. No capítulo 1, apresenta-se a Introdução; no capítulo 2, a Revisão Bibliográfica; no capítulo 3, a seção de Métodos; no capítulo 4, é apresentada a seção de Resultados da tese, a qual gerou a produção de 7 artigos, que estão subdivididos em três subitens; o capítulo 5, com as Considerações Finais; e por fim, apresentam-se as Referências, Apêndices (nota de imprensa, carta com a devolutiva para os idosos com os resultados da tese e post para mídias sociais); Anexos; e informações sobre a autora da tese.

Figura 1- Estrutura dos capítulos da tese



Fonte: elaborado pelos autores

1.2 APRESENTAÇÃO DO PROBLEMA E JUSTIFICATIVA

O transtorno depressivo maior (TDM), comumente chamado de depressão, é um transtorno mental baseado principalmente na caracterização de uma ampla gama de sintomas que incluem a mudança de humor e comportamento, classificada como leve, moderada ou grave, dependendo do número e da gravidade dos sintomas (AMERICAN PSYCHIATRIC ASSOCIATION, 2014). Os sintomas depressivos causam sofrimento clinicamente significativo ou prejuízo no funcionamento social, profissional, econômico e em outras áreas importantes da vida do indivíduo, causando inúmeras consequências, sendo o principal contribuinte para o suicídio em casos mais graves (AMERICAN PSYCHIATRIC ASSOCIATION, 2014; CHISHOLM et al., 2016; OLESEN et al., 2012; WORLD HEALTH ORGANIZATION, 2020).

O aumento do número de pessoas acometidas pela depressão é preocupante. Foi estimado em 2015 uma prevalência de 4,4% da população mundial, com maior proporção entre mulheres de 55 a 77 anos de 7,5% (WORLD HEALTH ORGANIZATION, 2017). Durante o ano de 2020 devido a pandemia do Coronavírus 2019 (Sars-Cov-2, COVID-19), globalmente houve

um aumento de 27,6% no diagnóstico de TDM (COVID-19 MENTAL DISORDERS COLLABORATORS, 2021). No Brasil, a prevalência de TDM em 2017 para população adulta e idosa combinada, era de 3,3% baseado nos estudos do *Global Burden of Disease, Injuries, and Risk Factors* (GBD), com maior proporção no estado de Santa Catarina de 3,8% (BONADIMAN et al., 2020). Um estudo anterior evidenciou prevalência de 8,6% na faixa de 60 a 64 anos e 10,3% de 70 anos ou mais (LOPES et al., 2016). A depressão quando rastreada por escalas de sintomas depressivos apresenta uma prevalência maior, entre 13 e 39% dependendo da região (BARCELOS-FERREIRA et al., 2010). Durante a pandemia do Covid-19, a frequência de pessoas que referiram diagnóstico médico de depressão variou de 7,2 a 17,5% (17,1% em Florianópolis/SC) entre as capitais brasileiras, com maior proporção na faixa etária de 55 a 64 anos e 65 anos ou mais (13,2 e 12,8%, respectivamente) (BRASIL, 2022).

Segundo uma das pesquisas do GBD, a depressão é a 2ª principal causa mundial de incapacidades (GLOBAL HEALTH METRICS, 2019). Houve um aumento expressivo na carga global de doenças em anos vividos com incapacidades, devido aos transtornos depressivos. Em 1990, a depressão apresentava-se na 4ª posição, passando e mantendo-se em 3ª entre 2007 e 2017, com um aumento de 33,4% da carga global em 2007 e de 14,3% em 2017 (JAMES et al., 2018). No Brasil, a carga global para os anos vividos com incapacidades foi estimada em 5%, ocupando a 4ª posição para ambos os sexos e idades (BONADIMAN et al., 2020). Em outro estudo brasileiro com dados do *GBD,* quando estratificado por sexo e idade (50 a 69 anos), apresentou-se em 9ª para homens e 3ª para mulheres, como principal causa de incapacidades (PASSOS et al., 2020).

Os transtornos mentais são um dos principais problemas em saúde pública, sendo que os transtornos de humor estão entre as doenças mentais com maior custo (CHISHOLM et al., 2016; DILUCA; OLESEN, 2014; KNAPP; WONG, 2020). Entretanto, segundo o *Mental Health Atlas* da Organização Mundial da Saúde (OMS), a estimativa do gasto médio global com saúde mental, é de apenas US$ 2,5 por pessoa anualmente (entre US$ 0,1 nos países de baixa renda, e US$ 21,7 nos países de alta renda), correspondendo por menos de 2% dos gastos com saúde em todo o mundo (WORLD HEALTH ORGANIZATION, 2018). Esse baixo orçamento é a principal razão para a grande lacuna entre as necessidades de saúde mental e a oferta de intervenção (KNAPP; WONG, 2020). A cobertura de tratamento para TDM continua baixa, em particular em países de baixa e média renda, com 8% comparado a 33% em locais de alta renda (MOITRA et al., 2022).

Existe uma urgente necessidade de identificação de fatores de riscos modificáveis associados a etiologia da depressão, para auxiliar estratégias de prevenção e tratamento,

principalmente em países de baixa e média renda (WHITEFORD et al., 2015; WORLD HEALTH ORGANIZATION, 2021). A depressão é uma doença complexa, desencadeada pela interação entre fatores sociais, psicológicos e biológicos, sendo que pessoas que passam por alguns eventos como luto, traumas, transições de vida, são mais propensas a desenvolver este transtorno (LI; D'ARCY; MENG, 2016; WORLD HEALTH ORGANIZATION, 2020). Em relação aos fatores biológicos, existe descrição de vários mecanismos que podem estar relacionados ao desenvolvimento da depressão como mecanismos genéticos, sistemas de neurotransmissores, sistemas neuroendócrinos, anatomia cerebral funcional e estrutural e cognição (KALTENBOECK; HARMER, 2018; OTTE et al., 2016). Dentre estes, os fatores nutricionais têm mostrado uma importante relação com a evolução, prevenção e tratamento de transtornos de humor (LAI et al., 2014). Alguns estudos pré-clínicos têm evidenciado efeitos da vitamina D na depressão e possíveis meios pelos quais ela pode atuar nos mecanismos biológicos relacionados a depressão, entretanto a base científica atual ainda não é conclusiva (CAMARGO et al., 2018; FEDOTOVA et al., 2016; LANDEL et al., 2018).

A vitamina D é uma vitamina lipossolúvel obtida pela alimentação na forma de vitamina D2 ou ergosterol, suplementação (D2 ou D3), mas é principalmente produzida pela pele quando exposta à luz solar, na forma de vitamina D3 ou colecalciferol (BIKLE, 2012; JÄPELT; JAKOBSEN, 2013). É considerada um hormônio secosteróide, com atuação bem estabelecida no metabolismo ósseo, atuando também na regulação da expressão gênica, proliferação e diferenciação celular e regulação do sistema imunológico, entre outros (JOHNSON; MOHN, 2015; NORMAN, 2012).

Alguns possíveis mecanismos e interação com sistema nervoso central (SNC) têm sido relacionados com a presença de receptores nucleares e de membrana, como o receptor de vitamina D (VDR) e proteína dissulfeto-isomerase A3 (PDIA3), e algumas enzimas do Citocromo P450, responsáveis pela transformação das diferentes formas da vitamina D (HE et al., 2020; LANDEL et al., 2018). Esses achados têm relacionado a vitamina D a ações anti-inflamatórias, regulação e interação com neurotransmissores de serotonina e dopamina e ainda homeostase de Cálcio (Ca^{2+}) via sistema glutamatérgico, ambos ligados aos caminhos fisiopatológicos da depressão (BERRIDGE, 2017; KESBY et al., 2011; MAYNE; BURNE, 2019; SMAGA et al., 2015). Todavia, o baixo nível sérico de vitamina D [25-hidroxivitamina D; 25(OH)D] tem sido relacionado a depressão (CEOLIN et al., 2022a).

A hipovitaminose D é considerada um problema de saúde pública, principalmente em idosos, grupo de risco para deficiência de 25(OH)D (<50 nmol/L ou 20 ng/ml), com prevalência de 41% no Brasil, 34% nos Estados Unidos, 19% no Canadá, 36% na China, entre

4 e 89% em países da Europa e 91% na Índia (PALACIOS; GONZALEZ, 2014; PEREIRA-SANTOS et al., 2019). Alguns fatores como a redução da exposição solar, diminuição da síntese cutânea, obesidade, ingestão dietética e déficit na absorção intestinal tem sido relacionados a hipovitaminose D no idoso (ARABI; EL RASSI; EL-HAJJ FULEIHAN, 2010; CESARI et al., 2011). Além disso, apresentam maiores complicações decorrentes do baixo nível sérico, como problemas no metabolismo ósseo (fraturas, perda óssea), fraqueza muscular, sarcopenia e risco para mortalidade (AMREIN et al., 2020; DUDENKOV et al., 2018; LUO et al., 2018).

No processo de envelhecimento, além de estar relacionado com baixo nível sérico, o aumento de gordura corporal (obesidade) e circunferência abdominal aumentada, tem sido relacionados a depressão no idoso (REPOUSI et al., 2018). O IMC tem sido implicado com uma relação bidirecional com sintoma depressivo em idosos, e alguns estudo tem indicado risco aumentado para aqueles que apresentam obesidade, especialmente em mulheres (DEARBORN; ROBBINS; ELIAS, 2018; GOES et al., 2017; LUPPINO et al., 2010; PAN et al., 2012; SACHS-ERICSSON et al., 2007). Entretanto, poucos estudos investigaram essa relação em amostras representativas em países de renda baixa e média (EVANS-LACKO et al., 2018; KIM; VON DEM KNESEBECK, 2018; PATEL et al., 2018).

Estudos epidemiológicos têm evidenciado uma associação entre o baixo nível sérico de vitamina D e o risco de depressão (JU; LEE; JEONG, 2013; LI et al., 2019). Todavia, é uma relação que não está totalmente elucidada, principalmente pela necessidade de estudos longitudinais na população idosa, e devido a lacuna de estudos provenientes de países de baixo a média renda, nos quais apresenta importante prevalência para as duas condições, e pela grande variação de métodos de avaliação e classificação da vitamina D na base científica existente (CEOLIN et al., 2022a; DE KONING et al., 2018; JORDE; KUBIAK, 2018; SPEDDING, 2014; WONG; IMA-NIRWANA, 2018).

Buscando responder algumas lacunas e contribuir cientificamente com a literatura nacional e internacional, foi elaborada a seguinte pergunta de pesquisa: Quais são os determinantes da concentração sérica de vitamina D e qual é sua associação com sintomas depressivos em idosos de Florianópolis/SC, Brasil?

1.3 RELEVÂNCIA, ORIGINALIDADE E CONTRIBUIÇÃO PARA O CONHECIMENTO

1.3.1 Relevância

A realização deste estudo vai ao encontro de uma das quatro metas do Plano de Ação em Saúde Mental 2013-2020, e da revisão do plano de 2013-2030, da Organização Mundial da Saúde, que consiste no fortalecimento de sistemas de informação, evidências e pesquisas em saúde mental, envolvendo parceria com centros internacionais (WORLD HEALTH ORGANIZATION, 2013, 2021). Segundo o plano, há um desequilíbrio entre as pesquisas em países de alta e baixa/média renda que precisa ser corrigido para garantir que estes tenham estratégias econômica e culturalmente apropriadas às necessidades e prioridades de saúde mental, tendo o foco em verificar a extensão do problema a partir da prevalência e identificação dos principais fatores de risco e fatores de proteção à saúde mental (WORLD HEALTH ORGANIZATION, 2013).

Devido a magnitude do problema já ter sido explorada na seção anterior, enfatiza-se nessa seção a gravidade e as consequências biológicas tanto da depressão, como do baixo nível sérico de vitamina D. A população idosa é considerada um grupo de risco tanto para depressão como para deficiência de vitamina D, por apresentar prevalências importantes e por terem maiores consequências e complicações para as duas condições. Em relação a depressão, é uma doença que causa sofrimento não somente para o idoso, mas também para os familiares e pessoas que auxiliam no cuidado (CHISHOLM et al., 2016). Além disso, a depressão parece ter um maior efeito sobre a piora de escores de saúde em comparação com as doenças crônicas, e há uma piora gradual quando ocorrem concomitantemente, assim como uma piora nos escores de qualidade de vida e associado a mortalidade (BRANDÃO et al., 2019; MOUSSAVI et al., 2007; SIVERTSEN et al., 2015). Por outro lado, os anos vividos sem depressão podem refletir na maior expectativa de vida, com qualidade de vida, menor incapacidade, melhor estado de saúde, e redução de mortes prematuras (ANDRADE et al., 2016; REYNOLDS; HALEY; KOZLENKO, 2008).

A depressão, além de ser uma doença com consequências biológicas e sociais importantes, possui um tratamento dispendioso e novas pesquisas em busca de novas estratégias de prevenção e tratamento têm sido incentivadas (JOHNSTON et al., 2019; OTTE et al., 2016). Há uma lacuna na disponibilidade de tratamento para as pessoas com depressão, sendo que cerca de 76–85% das pessoas em países de baixa e média renda não têm acesso ao tratamento de que precisam, o que é agravado pela subnotificação do diagnóstico (LOPES et al., 2016; WANG et al., 2007; WORLD HEALTH ORGANIZATION, 2020). Além do mais,

uma importante parte das pessoas com depressão não apresentam melhoras com tratamento medicamentoso, cerca de 10 a 30% não respondem a pelo menos dois antidepressivos (AL-HARBI, 2012; JAFFE; RIVE; DENEE, 2019; JOHNSTON et al., 2019; OTTE et al., 2016).

Outro fator importante é em relação aos efeitos adversos causados pelos medicamentos antidepressivos e pela polifarmácia comum em idosos, devido a concomitância de várias patologias. As preocupações com a polifarmácia incluem possibilidades de toxicidade cumulativa, maior vulnerabilidade a eventos adversos e problemas de adesão, e prospectivamente associado a incapacidade funcional (FALCI et al., 2019; KIM; PARISH, 2017; READ et al., 2017). Frente a esses problemas de tratamento, a prevenção tem o potencial de reduzir não apenas as recorrências, mas também os primeiros episódios e, assim, reduzir a prevalência e a incidência de depressão (ORMEL et al., 2020).

Em relação a vitamina D, além dos possíveis benefícios para saúde mental, é importante na manutenção de vários processos biológicos, especialmente o metabolismo ósseo (UMAR; SASTRY; CHOUCHANE, 2018). Por outro lado, o baixo nível sérico, pode apresentar várias complicações como hiperparatireoidismo secundário, perda óssea e aumento do risco de fratura por fragilidade, contribui para a fraqueza muscular relacionada à idade, além de estar associado à sarcopenia (HOLICK, 2006; KESBY et al., 2011; LUO et al., 2018). Alterações no SNC têm sido associados ao baixo nível sérico de vitamina D, como déficit cognitivo, vulnerabilidade a vários transtornos psiquiátricos, incluindo esquizofrenia, transtorno de déficit de atenção, e doenças neurodegenerativas como Alzheimer e demência (MAYNE; BURNE, 2019). Além disso, valores de 25(OH)D <20ng/mL têm sido associados a um maior risco para mortalidade por todas as causas (DUDENKOV et al., 2018).

1.3.2 Originalidade

Para a construção da originalidade, utilizou-se uma busca sistematizada nas bases de dados: *Pubmed, Scopus*, Periódicos Capes, Scielo, *Web of Science, Embase* e Google Acadêmico em abril de 2019, revisada em dezembro de 2022. Foi utilizado os termos de busca do quadro 1, de forma combinada com o auxílio dos operadores boleanos “AND” entre os conjuntos de termos e “OR” entre os termos da mesma categoria.

Quadro 1 - Unitermos para busca de artigos para construção do estado da arte

	Português	**Inglês**
Desfecho	Depressão (termo Decs) Sintomas depressivos (termo Decs)	*Depression (Mesh term)* *Depressive Symptom (*sinônimo no *Mesh term)* *Major Depressive Disorder (Mesh term)* *Depressive Disorder (Mesh term)*
Exposição	Vitamina D 25-hidroxivitamina D 25-hidroxicolecalciferol 25(OH)D	*Vitamin D (Mesh term)* *serum level Vitamin D* *25-hydroxivitamin D (*sinônimo no *Mesh term)* *25-hydroxycholecalciferol* 25(OH)D
População	Idosos (termo Decs) Pessoa Idosa (termo Decs)	*Aged (Mesh term)* *Aging* *Elderly (*sinônimo no *Mesh term)* *Older People* *Older adult*

Fonte: elaborado pelos autores

Os estudos foram pré-selecionados pelo título, após foi realizada a segunda seleção pela leitura do resumo/*abstract,* e por fim a leitura na íntegra. Como critérios de inclusão, o estudo deveria ser observacional, e com participantes adultos e/ou idosos. Como critérios de exclusão, o estudo apresentar distinção em grupos de pessoas com alguma doença específica ou com gestantes. Também foram buscados e incluídos estudos localizados nas referências dos artigos encontrados nas bases, que não tivessem sido localizados anteriormente. Foram selecionados 44 estudos que estão descritos no quadro 2, apresentados por ordem de ano de publicação, iniciando pelo mais recente.

Quadro 2 - Estado da arte sobre o tema Vitamina D e Sintomas Depressivos em idosos

(continua)

Autor/Ano	Tipo de estudo	Local	População/Faixa Etária
(ALBOLUSHI; BOUHAIMED; SPENCER, 2022)	Transversal	Kuwait	65 anos ou mais
(MANZANOS et al., 2022)	Transversal	Argentina	28 a 78 anos
(DI GESSA et al., 2021)	Coorte e de base populacional, com análise longitudinal	Inglaterra	50 anos ou mais
(VAN DEN BERG et al., 2021)	Coorte de depressivos, com análise longitudinal	Amsterdã	60 anos ou mais

Quadro 2 - Estado da arte sobre o tema Vitamina D e Sintomas Depressivos em idosos
(continua)

Autor/Ano	Tipo de estudo	Local	População/Faixa Etária
(MULUGETA; LUMSDEN; HYPPÖNEN, 2021)	Coorte (Biobank) com análise transversal	Reino Unido	37 a 73 anos
(CEOLIN et al., 2020)	Coorte e de base populacional, com análise transversal	Brasil	60 anos ou mais
(SAHASRABUDHE et al., 2020)	Coorte de porto-riquenhos, com análise transversal e longitudinal	Estados Unidos	45 a 75 anos
(KÖHNKE; HERRMANN; BERGER, 2020)	Coorte, com análise transversal	Alemanha	35 a 65 anos
(GRANLUND et al., 2020)	De base populacional, com análise transversal	Suécia	24 a 65 anos
(RHEE; LEE; AHN, 2020)	De base populacional, com análise transversal	Coréia do Sul	19 a 76 anos
(BIGMAN, 2020)	De base populacional, com análise transversal	Estados Unidos	20 a 80 anos
(RONALDSON et al., 2020)	Coorte (Biobank) com análise transversal e longitudinal	Reino Unido	40 a 69 anos
(BRIGGS et al., 2019)	Coorte e de base populacional, com análise longitudinal	Dublin	50 anos ou mais
(ELSTGEEST et al., 2018)	Coorte e de base populacional, com análise longitudinal	Amsterdã	Duas coortes: 55-65 anos e de 65-88 anos
(DE KONING et al., 2018)	Coorte e de base populacional, com análise transversal e Longitudinal	Amsterdã	Duas coortes: 55-65anos e de >65 anos
(SHERCHAND et al., 2018)	Transversal	Nepal	18 anos ou mais
(VIDGREN et al., 2018)	Coorte e de base populacional, com análise transversal	Finlândia	53 a 73 anos
(YAO et al., 2018)	Coorte, com análise transversal	China	100 anos ou mais
(DE OLIVEIRA; HIRANI; BIDDULPH, 2018)	Coorte e de base populacional, com análise transversal	Inglaterra	50 anos ou mais
(JOVANOVA et al., 2017)	Coorte e de base populacional, com análise transversal e longitudinal	Roterdã	55 anos ou mais

Quadro 2 - Estado da arte sobre o tema Vitamina D e Sintomas Depressivos em idosos
(continua)

Autor/Ano	Tipo de estudo	Local	População/Faixa Etária
(COLLIN et al., 2017)	Estudo longitudinal com amostra do estudo SU.VI.MAX (estudo randomizado, duplo-cego, placebo controlado, de prevenção primária, mas não incluía a vitamina D)	França	40 anos ou mais
(LEE et al., 2017)	De base populacional, com análise transversal	Coreia do Sul	20 a 88 anos
(SHIN et al., 2016)	Dados de um centro de exames, com análise transversal	Japão	20 a 70 anos
(RABENBERG et al., 2016)	De base populacional, com análise transversal	Alemanha	18 a 79 anos
(VAN DEN BERG et al., 2016)	Coorte, com análise longitudinal	Amsterdã	Idosos deprimidos de 60 anos ou mais
(SONG et al., 2016)	Coorte, com análise transversal	Coreia do Sul	65 anos ou mais
(BROUWER-BROLSMA et al., 2016)	Análise transversal da linha de base de uma coorte de idosos recrutados do B-PROOF (um ensaio Clínico Randomizado duplo-cego, placebo controlado)	Amsterdã	65 anos ou mais
(ROCHA-LIMA et al., 2016)	Coorte, com análise transversal	Brasil	80 anos ou mais
(HUSEMOEN et al., 2016)	De base populacional, com análise transversal e longitudinal	Dinamarca	18 a 64 anos
(JÄÄSKELÄINEN et al., 2015)	De base populacional, com análise transversal	Finlândia	30 a 79 anos
(ALMEIDA et al., 2015)	Coorte, análise Transversal prospectivo e retrospectivo	Austrália	Homens de 71 a 88 anos
(WILLIAMS et al., 2015)	Coorte, com análise transversal e longitudinal	Pittsburgh, Pensilvânia e Memphis, Tennessee	70 a 79 anos
(IMAI et al., 2015)	Coorte, com análise transversal de base populacional	Islândia	66 a 96 anos
(JÓZEFOWICZ et al., 2014)	Transversal	Polônia	18 a 65 anos
(TOFFANELLO et al., 2014)	Coorte e de base populacional, com análise transversal e longitudinal	Itália	65 anos ou mais
(MILANESCHI et al., 2014)	Coorte, com análise transversal e longitudinal	Amsterdã	18 a 65 anos

Quadro 2 - Estado da arte sobre o tema Vitamina D e Sintomas Depressivos em idosos (conclusão)

Autor/Ano	Tipo de estudo	Local	População/Faixa Etária
(LAPID; CHA; TAKAHASHI, 2013)	Retrospectivo com dados de prontuário	Rochester, Minnesota	60 anos ou mais
(JADDOU et al., 2012)	De base populacional com análise transversal	Jordânia	25 anos ou mais
(CHAN et al., 2011)	Coorte, com análise transversal e longitudinal	Hong Kong	Homens de 65 anos ou mais
(LEE et al., 2011)	Coorte, com análise transversal	Países da Europa	Homens de 40 a 79 anos
(MILANESCHI et al., 2010)	Coorte e de base populacional, com análise longitudinal	Toscana	65 anos ou mais
(STEWART; HIRANI, 2010)	Transversal de base populacional	Inglaterra	65 anos ou mais
(NANRI et al., 2009)	Transversal	Japão	21 a 67 anos
(PAN et al., 2009)	De base populacional, com análise transversal	Pequim e Xangai	50 a 70 anos
(HOOGENDIJK et al., 2008)	Coorte, com análise transversal	Amsterdã	65 anos ou mais
(WILKINS et al., 2006)	Transversal	Estados Unidos	60 anos ou mais

Fonte: elaborado pelos autores

A partir da leitura dos 46 estudos, observa-se que a maioria dos estudos incluiu uma população mista com adultos e idosos (28/46), provenientes de estudos de coorte (28/46) e de países de economias de alta renda (39/46). A maioria das análises realizadas foi transversal (29/46), seguida de transversal e longitudinal no mesmo estudo (10/46) e longitudinal (7/46). Considerando os estudos que incluíram apenas idosos (≥60 anos, 18/46), a maioria tem dados a partir de uma coorte (14/18) e realizou uma análise transversal (11/18), tanto transversal quanto longitudinal (4/18) e apenas análise longitudinal (3/18). Destes, apenas três estudos foram realizados em países de baixa ou média renda e somente uma publicação até o momento foi encontrada com dados provenientes do Brasil (além de um dos produtos desta Tese), entretanto inclui apenas idosos de ≥80 anos, provenientes de um serviço de geriatria.

Dos 18 artigos somente com idosos, 7 estudos são os que mais se aproximam dos estudos que desenvolvemos, sendo cinco com análise transversal (HOOGENDIJK et al., 2008; IMAI et al., 2015; SONG et al., 2016; STEWART; HIRANI, 2010), um combinado transversal e longitudinal (TOFFANELLO et al., 2014); e um com análise longitudinal (MILANESCHI et al., 2010).

Os estudos já realizados apresentam resultados promissores, porém a maioria dos estudos usa amostra combinada com adultos e idosos, havendo necessidade de mais estudos a incluir amostra apenas de idosos, uma vez que o envelhecimento é uma fase distinta e é uma população

de risco para ambas as condições, devido a complicações mais críticas. Além disso, os mecanismos pelos quais a vitamina D atua na depressão, ainda não estão totalmente esclarecidos. Segundo metanálises realizadas até o momento, há associação inversa entre os níveis séricos de 25(OH)D e o risco de depressão, entretanto indicam a necessidade de estudos adicionais (JU; LEE; JEONG, 2013; LI et al., 2019). A atual base de evidências é limitada por limitações metodológicas e há necessidade de mais estudos longitudinais (LI et al., 2019; PARKER; BROTCHIE; GRAHAM, 2017)**.**

Portanto, este estudo é original por utilizar dados de um estudo de coorte de base populacional e domiciliar somente com idosos, e ser o primeiro estudo com essas características no Brasil a avaliar a associação entre vitamina D e sintomas depressivos, por contribuir com a lacuna de estudos provenientes de países de baixa e média renda com idosos. Essa tese tem o potencial de atender às necessidades da ciência, podendo contribuir para a elucidação do tema, que pode auxiliar no preenchimento das lacunas do conhecimento dessa área do saber.

1.3.3 Contribuições para o conhecimento

Com a realização dos estudos desta tese, foi possível fornecer **contribuições teóricas**, pela discussão sobre a prevalência de baixo nível sérico de vitamina D e os fatores relacionados ao nível sérico da vitamina D em idosos, bem como a sua relação transversal e longitudinal com sintomas depressivos, e da adiposidade e sintomas depressivos a partir de dados de uma amostra representativa de Florianópolis-SC. Também, a partir de discussões teóricas e construção de artigos de revisão, aprimoramento das técnicas de análises de dados e parceria com profissionais do meio acadêmico nacional e internacional de diferentes departamentos e instituições buscando um olhar multidisciplinar para os produtos gerados e agregando a literatura nacional e internacional.

A discussão baseada em evidência científica poderá auxiliar no planejamento local, bem como nacional para planejamento de políticas públicas para a prevenção do baixo nível sérico de vitamina D nessa população de risco, além de uma possível estratégia para prevenção de sintomas depressivos. Nessa direção, a presente tese vai ao encontro do Plano de Ação em Saúde Mental 2013-2030 da OMS, conforme mencionado na seção “Relevância” (WORLD HEALTH ORGANIZATION, 2013, 2021). Tem o potencial de auxiliar no fortalecimento de evidências e pesquisas em saúde mental, documentando a prevalência de hipovitaminose D, e prevalência, incidência e um potencial fator de prevenção para sintomas depressivos.

Em relação as **contribuições práticas**, a partir dos achados e da compreensão do tema, espera-se embasar soluções locais para o monitoramento mais frequente do nível sérico de vitamina D nessa população, uma vez que é a população de risco, e apresentou importante prevalência de hipovitaminose D, bem como embasar estratégias para essa população a manter/obter o nível adequado, seja por meio da exposição segura ao sol, alimentação, suplementação e outras práticas que possam promover a prevenção de baixo nível sérico, como a redução da obesidade e estimular a prática de atividade física que apresentaram-se associados a vitamina D.

Por fim, a partir da realização de doutorado sanduíche no *Centre for Neuroscience Studies*, na *Queen's University*, em Kingston/ON, Canadá, almejou-se fornecer contribuições teóricas e práticas, buscando o aumento da rede de pesquisa e educação através da parceria científica firmada entre os grupos de pesquisa, bem como reverter o conhecimento adquirido à Universidade de origem. Também, almejou-se fortalecer o vínculo para futuros intercâmbios para alunos e professores, em busca de aprimoramento no desenvolvimento de trabalhos com rigor científico, quanto desenvolvimento profissional.

Esperou-se poder contribuir com a internacionalização da ciência brasileira, proporcionando maior visibilidade internacional do estudo realizado em conjunto com o grupo de pesquisa do exterior visando o aprimoramento e a qualificação dos estudos, em busca da publicação em revistas que permitam uma alta veiculação do conteúdo, tendo como base a experiência da Prof. Coorientadora do exterior como revisora de revistas internacionais e como integrante do corpo editorial de periódico e a sua parceria com diversos profissionais da área da saúde mental.

1.4 OBJETIVOS

1.4.1 Objetivo geral

Identificar os determinantes das concentrações séricas da vitamina D e avaliar a associação com sintomas depressivos em idosos de Florianópolis-SC.

1.4.2 Objetivos específicos

- Revisar e discutir a relação entre a vitamina D e sintomas depressivos/depressão;
- Identificar os determinantes da concentração sérica de vitamina D;
- Avaliar a associação transversal entre o nível sérico de vitamina D e sintomas depressivos;
- Avaliar a associação longitudinal entre o nível sérico de vitamina D e sintomas depressivos;
- Avaliar a associação longitudinal entre a adiposidade e sintomas depressivos.

2. REVISÃO BIBLIOGRÁFICA

2.1 DEPRESSÃO

Caracterização da depressão

Segundo a Classificação Internacional de Doenças para Estatística de Mortalidade e Morbidade – CID 11 (*International Classification of Diseases for Mortality and Morbidity Statistics – ICD 11*), a depressão compõe os transtornos de humor, na categoria de transtornos mentais, comportamentais e neurológicos. Os transtornos depressivos são caracterizados pelo humor depressivo (triste, irritável, vazio), perda de prazer acompanhada por outros sintomas fisiológicos, comportamentais e cognitivos que afetam significativamente a capacidade de funcionamento do indivíduo (WORLD HEALTH ORGANIZATION, 2019). Para definição do diagnóstico de depressão, são utilizados critérios do Manual Diagnóstico e Estatístico de Transtornos Mentais (*Diagnostic and Satistical Manual of Mental Disorders - DSM-5)* e classificação do CID-11, realizado por profissional da saúde mental, podendo também ser rastreado por ferramentas de triagem de sintomas depressivos por meio de escalas específicas (BARBOSA et al., 2013).

A depressão possui intensidade e duração variável e incluem duas subcategorias principais: 1) Transtorno depressivo maior (TDM), categorizado como episódio único ou recorrente e classificado como leve, moderada ou grave; 2) Transtorno depressivo persistente/Distimia, uma forma persistente ou crônica de depressão leve (WORLD HEALTH ORGANIZATION, 2017). Para o TDM, avalia-se a presença de pelo menos cinco sintomas presentes durante o mesmo período de duas semanas em todos ou quase todos os dias, auto-observada ou observada por outras pessoas, sendo necessário a apresentação de um dos dois sintomas: 1) humor deprimido ou 2) perda de interesse ou prazer. Os demais sintomas avaliados são:

3) Perda ou ganho significativo de peso sem estar fazendo dieta;

4) Insônia ou hipersonia;

5) Agitação ou retardo psicomotor;

6) Fadiga ou perda de energia;

7) Sentimentos de inutilidade ou culpa excessiva ou inapropriada;

8) Capacidade diminuída para pensar ou se concentrar, ou indecisão;

9) Pensamentos recorrentes de morte (não somente medo de morrer), ideação suicida recorrente sem um plano específico, uma tentativa de suicídio ou plano específico para cometer suicídio (AMERICAN PSYCHIATRIC ASSOCIATION, 2014);

Fisiopatologia da depressão

A depressão é heterogênea e etiologicamente complexa, abrangendo um amplo espectro de psicopatologia decorrente de mecanismos fisiopatológicos distintos (BUCH; LISTON, 2021). A interação de fatores ambientais, socioeconômicos, comportamentais e de saúde isoladamente ou interdependente influenciam a fisiopatologia da depressão (KÖHLER et al., 2018; VAN DEN BOSCH; MEYER-LINDENBERG, 2019). Alguns mecanismos neurobiológicos estudados são a genética, os sistemas de neurotransmissores, os sistemas neuroendócrinos, a anatomia cerebral funcional e estrutural e a cognição (KALTENBOECK; HARMER, 2018; OTTE et al., 2016).

A contribuição genética de herdabilidade da depressão tem sido estimado em 37 e 38%, baseado em estudos com famílias e gêmeos homozigotos, e relatado que existem diferenças clínicas e que as pessoas com história familiar de depressão demostraram a doença clinicamente mais grave, com tendência para idade mais precoce e maiores taxas de recorrência (FLINT; KENDLER, 2014). Entretanto, diferentes abordagens metodológicas foram utilizadas, porém não foram confirmadas em estudos de replicação e apenas um pequeno número de genes demonstraram associação, não sendo conclusivo (FLINT; KENDLER, 2014; SHADRINA; BONDARENKO; SLOMINSKY, 2018). Sugere-se a existência de múltiplas vias de risco genéticos, não havendo um gene único que possa contribuir para o desenvolvimento da depressão (KANDEL et al., 2014).

Para os sistemas neurobiológicos, as descobertas mais influentes foram relacionadas a anormalidades nos sistemas de neurotransmissores como as monoaminas (serotonina, noradrenalina e dopamina), sendo o sistema serotoninérgico, o mais estudado pelas funções sobre o humor, emoção, sono e controle das funções comportamentais (FAKHOURY, 2016; KALTENBOECK; HARMER, 2018). De todas as hipóteses, a disfunção da neurotransmissão da serotonina é a mais influente e a mais estudada nas estratégias de tratamento da depressão (FAKHOURY, 2016). A disfunção pode ser dada tanto pelas proteínas receptoras de serotonina (5-HT), pela proteína transportadora de membrana plasmática neuronal (SERT) responsável pela recaptação de 5-HT pela célula pré-sináptica, como também pela baixa disponibilidade de triptofano ou quando há uma baixa expressão da enzima hidroxilase 2 (TPH2) que metaboliza

o triptofano, precursor da serotonina (DOMÍNGUEZ-LÓPEZ; HOWELL; GOBBI, 2012; FAKHOURY, 2016; OGAWA et al., 2014).

Evidências convergentes sugerem que déficits na sinalização do ácido gama-aminobutírico (GABA), neurotransmissor que regula a excitabilidade neuronal através de ciclos de feedback inibitório, e do glutamato, neurotransmissor mediador da transmissão sináptica excitatória, estão envolvidos na fisiopatologia da depressão (CROARKIN; LEVINSON; DASKALAKIS, 2011; DUMAN; SANACORA; KRYSTAL, 2019). Sob condições normais, a transmissão de GABA e glutamato é balanceada e otimizada para fornecer alta relação sinal-ruído e integridade da sinalização neuronal (DUMAN; SANACORA; KRYSTAL, 2019). O GABA também modula a atividade de outros sistemas de neurotransmissores como a inibição de serotonina, a noradrenalina e a liberação de dopamina (CROARKIN; LEVINSON; DASKALAKIS, 2011). No caso da inibição da serotonina, num processo disfuncional o neurotransmissor GABAérgico inibitório aumentado, pode causar um aumento na recaptação de 5-HT.

Na depressão, parece haver um declínio nos neurônios GABAérgicos, que pode ser impulsionado por um aumento na atividade da via de sinalização glutamatérgica (BERRIDGE, 2017). O aumento nos níveis de glutamato aumenta o nível intracelular de cálcio (Ca^{2+}) e o impulso excitatório tônico responsável por regular a atividade neuronal, reduzindo a síntese de proteínas e neurônios GABAérgicos. No estresse crônico, há uma redução nos níveis de GABA, da enzima glutamato descarboxilase (GAD67) no cérebro, da expressão de marcadores de interneurônios GABAérgicos e alterações no nível de receptores (FOGAÇA; DUMAN, 2019). Além do disso, no sistema glutamatérgico, o estresse repetido também diminui a expressão das subunidades dos receptores inotrópicos ácido α-amino-3-hidroxi-5-metil-4-isoxazolpropiônico (AMPA) e N-metil-d-aspartato (NMDA) e aumento ou diminuição dos metabólitos glutamato + glutamina (Glx) (MORIGUCHI et al., 2019).

A depressão, assim como o estresse crônico, pode gerar uma alteração bioquímica, e consequentemente uma atividade persistente no eixo hipotálamo-pituitária-adrenal (HPA). O hormônio liberador de corticotrofina (CRH) é liberado pelos neurônios no hipotálamo e se ligam aos receptores CRH 1 e 2, e a partir disso, a secreção do hormônio adrenocorticotrófico (ACTH) pela hipófise é induzida, e ACTH induz a liberação de glicocorticoides (GC, cortisol) pelas glândulas suprarrenais. Após a ativação do eixo HPA, *loops de feedback* negativo são ativados para restabelecer a homeostase pelos receptores de glicocorticoide (GC) que se ligam ao cortisol inibindo a liberação posterior de CRH (MENKE, 2019; PARIANTE, 2009; THOMPSON et al., 2015). Na depressão, algumas pessoas podem ter a sensibilidade do GR

prejudicada, levando a um mecanismo de *feedback* negativo reduzido e, subsequentemente, a uma hipersecreção central de CRH e um aumento da produção de GCs (MENKE, 2019). Além disso, parece haver uma entrada GABAérgica diminuída para o núcleo paraventricular hipotalâmico, o que também pode contribuir para a hiperatividade eixo HPA, com hipersecreção dos neurônios CRH (GAO et al., 2013). Adultos que na infância sofreram abuso sexual, físico ou emocional têm risco aumentado para depressão e demostram atividade acentuada do eixo HPA e também a função do receptor glicocorticoide é reduzida (resistência aos glicocorticoides) (LI; D'ARCY; MENG, 2016; OTTE et al., 2016; STETLER; MILLER, 2011).

Evidências de uma metanálise indicam que a ativação imune periférica pode estar envolvida na fisiopatologia do transtorno depressivo maior, evidenciando em algumas pessoas, um perfil de citocinas como o nível aumentado de interleucinas (IL-, IL-10 e TNF-α - fator de necrose tumoral alfa) receptor de IL-2, ligantes de IL-13, IL-18 e IL-12, antagonista de receptor IL-1 e receptor de TNF-2 em indivíduos com depressão comparado com controles (KÖHLER et al., 2017). Outros marcadores inflamatórios também foram identificados, como prostaglandina E2 (PGE2) e proteína C reativa reagente de fase aguda (PCR) (ROSENBLAT et al., 2014). A inflamação leva ao aumento da permeabilidade da barreira hematoencefálica, permitindo a entrada mais fácil de moléculas inflamatórias ou células imunes (LEE; GIULIANI, 2019).

A nível celular, foi observado que TNF-α pode induzir a liberação de glutamato pela microglia ativada *in vitro*, levando a danos excitotóxicos nos neurônios (TAKEUCHI et al., 2006). As citocinas, IL-2 e interferon-alfa (IFN-α) mostraram aumentar diretamente a atividade enzimática da indolamina 2,3-dioxigenase (IDO), que aumenta a conversão de triptofano em quinurenina e diminuindo a produção de serotonina já a IL-6 e TNF-α mostraram aumentar a degradação da serotonina por meio da conversão de 5-HT em ácido 5-hidroxiindolacético (5-HIAA) (CAPURON et al., 2001, 2003; ZHANG et al., 2001). Além disso, as citocinas (IL-1, IL-6, TNF-α) podem ativar o eixo HPA, aumentando os níveis de CRH, ACTH e cortisol (ROSENBLAT et al., 2014).

A depressão também tem sido associada a disfunções mitocondriais. Quando ocorre um declínio na função da cadeia de transporte de elétrons responsável pela formação de adenosina trifosfato (ATP), resulta em um aumento na formação de espécies reativas de oxigênio (EROs) que induzem estresse oxidativo (BERRIDGE, 2017). Ocorre extensa oxidação de proteínas e peroxidação lipídica, degeneração celular, como a diminuição da sinalização sináptica e mecanismos de plasticidade cerebral (SALIM, 2017). As EROs desencadeiam uma variedade

de cascatas moleculares que aumentam a permeabilidade da barreira hematoencefálica, permitindo a entrada de citocinas inflamatórias, que têm sido implicadas na diminuição de tetra-hidrobiopterina (BH4), um cofator enzimático chave na síntese de todas as monoaminas e que é altamente sensível ao estresse oxidativo (NEURAUTER et al., 2008). Além disso, o envolvimento da sinalização do receptor de glicocorticoides mediada pelo eixo HPA, toxicidade do glutamato e sistemas de sinalização do receptor NMDA também foi sugerido (SALIM, 2017).

O estresse crônico ligado a fatores ambientais e suscetibilidade genética, podem interagir prejudicando a sinalização de neurotrofinas e isso tem sido relacionado com a depressão. A neurotrofina mais estudada é o fator neurotrófico derivado do cérebro (BDNF), que é responsável pelo crescimento neuronal, diferenciação, conectividade sináptica e reparo neuronal (CHOURBAJI; BRANDWEIN; GASS, 2011; KAREGE et al., 2002; THOMPSON et al., 2015). Alguns possíveis mecanismos implicados nessa sinalização prejudicada têm sido descritos, como a ligação do glutamato aos receptores extra-sinápticos NMDA, induzindo o aumento da excitotoxicidade e à diminuição da produção BDNF (HARDINGHAM; FUKUNAGA; BADING, 2002). Os marcadores inflamatórios IL-1β e TNF e suas vias de sinalização a jusante, incluindo o fator nuclear kappa B (NF-κB) parecem regular negativamente a transcrição de BDNF, em modelos animais de depressão induzida por estresse (GOSHEN et al., 2008; KOO et al., 2010). Além disso, os glicocorticoides parecem inibir a regulação positiva de proteínas sinápticas dependentes de BDNF, suprimindo a ativação das proteínas cinases, diminuindo a sua expressão (NETO et al., 2011).

Em relação a fatores ambientais e de estilo de vida, tem sido sugerido que obesidade, exposição a abuso físico na infância, luto, presença de doença crônica, menor nível educacional, estresse no trabalho, desemprego, menor nível educacional, menor apoio social, ausência de parceiro, uso de álcool, menor atividade física e distúrbios do sono, estão associados a depressão (KÖHLER et al., 2018). Além disso, pesquisas com fatores nutricionais têm mostrado dados promissores, sendo que uma alimentação mais rica em gorduras saturadas e alimentos com alto teor de açúcar têm demostrado maior risco para depressão (CEOLIN et al., 2022b; HUANG et al., 2019). Por outro lado, uma dieta de qualidade, rica em nutrientes como ômega 3 encontrado em peixes, legumes frescos e frutas, e alimentos integrais, parecem reduzir o risco de depressão (FIRTH et al., 2019; HUANG et al., 2019).

Tratamentos para a depressão

Em relação a tratamento, três vias principais têm sido discutidas, como tratamento por antidepressivos, psicoterapia e terapia eletroconvulsiva (KANDEL et al., 2014). Estudos mais recentes têm demostrado que a combinação de antidepressivos e psicoterapia parece ser o meio mais eficaz para tratamento quando comparado essas terapias separadas na população adulta (CUIJPERS et al., 2020).

O tratamento com antidepressivos mais amplamente usados, atuam no sistema monoaminérgico de diferentes maneiras, sendo os principais: inibidores da monoaminoxidase, raramente usados atualmente devido a efeitos adversos; antidepressivos tricíclicos, que promovem efeitos secundários que limitam seu uso (boca seca, sonolência, retenção de urina e hipotensão postural); e inibidores seletivos da recaptação de serotonina, os quais necessitam de várias semanas de tratamento para que a redução dos sintomas clínicos da depressão seja observada (KANDEL et al., 2014). Um tratamento medicamentoso mais recente é o uso de cetamina e esketamina, com atuação no sistema glutamatérgico, indicados para depressão refratária e risco de suicídio (LIPSITZ et al., 2021). Já a terapia eletroconvulsiva (*ECT*, de *electroconvulsive therapy*), uma terapia promissora, é administrada com anestésicos modernos, sendo clinicamente segura e perdura com o a intervenção mais eficiente no tratamento agudo de casos graves de depressão maior (KANDEL et al., 2014).

2.1.1 Depressão no Idoso

Na pessoa idosa, a depressão pode ser desencadeada por uma série de fatores ambientais e comportamentais como limitações nas atividades diárias, cognição e mobilidade, bem como mudanças sociais (como aposentadoria, luto, isolamento social e realocação) que influenciam o humor e a angústia, levando a sintomas depressivos (ANDRADE et al., 2016). Estudos brasileiros evidenciaram maior prevalência de depressão no sexo feminino, nos extremos níveis de instrução, presença de dor crônica, maior dependência nas atividades de vida diária, tabagismo, não ter um companheiro (a), risco de queda e fragilidade, pior saúde bucal e sedentarismo (BORGES et al., 2013; CUNHA; BASTOS; DUCA, 2012; INSTITUTO BRASILEIRO DE GEOGRAFIA E ESTATÍSTICA, 2014; MACIEL; GUERRA, 2006; MENDES-CHILOFF et al., 2018; RAMOS et al., 2015).

No processo de envelhecimento, tem-se identificado uma mudança na composição corporal do idoso, com um aumento de gordura corporal (JAFARINASABIAN et al., 2017; PONTI et al., 2020). O aumento de gordura, classificado como obesidade, tem sido relacionado

a depressão no idoso, além de componentes da síndrome metabólica, como a circunferência abdominal aumentada (REPOUSI et al., 2018). O IMC tem sido implicado com uma relação bidirecional com sintoma depressivo em idosos, e alguns estudo tem indicado risco aumentado para aqueles que apresentam obesidade, especialmente em mulheres (DEARBORN; ROBBINS; ELIAS, 2018; GOES et al., 2017; LUPPINO et al., 2010; PAN et al., 2012; SACHS-ERICSSON et al., 2007). Além disso, para mulheres na fase de transição da menopausa, além da mudança hormonal é um período vulnerável pela perspectiva biológica e social que é associada a um risco aumentado para desfechos diversos, incluindo a depressão (VOEDISCH; DUNSMOOR-SU; KASIRSKY, 2021). Tem sido evidenciado que cerca de 28-31% das mulheres na pré-menopausa e de 45-68% das mulheres na peri-menopausa relatam sintomas depressivos clinicamente relevante podendo influenciar nas idades subsequentes (MAKI et al., 2018).

No envelhecimento, a depressão também é chamada de transtornos de humor tardios (do inglês *late-life mood disorders*), são descritos como produtos de interações complexas entre a psicopatologia e os processos de envelhecimento que afetam a estrutura e a função do cérebro (RUTHERFORD et al., 2017). Alguns processos identificados são o aumento da inflamação de baixo grau, depleção de dopamina, estresse oxidativo, diminuição da neurotransmissão GABAérgica, caracterizados pelo envelhecimento cerebral (do inglês *brain aging)* (LISSEMORE et al., 2018; RUTHERFORD et al., 2017; SMITH et al., 2018). A probabilidade de episódios futuros de TDM no idoso aumenta em 50% após o primeiro episódio (BURCUSA; IACONO, 2007).

Como possíveis desfechos em idosos, a depressão está associada a maior risco de suicídio, hospitalização mais frequente, maior número de consultas para tratamento, bem como um sofrimento e sobrecarga familiares e pessoas próximas que auxiliam no cuidado (AVASTHI; GROVER, 2018; CHISHOLM et al., 2016). Indivíduos com transtornos de humor podem passar por um processo de envelhecimento cerebral acelerado indicando um possível efeito biológico cumulativo da carga de doença, como alterações na cognição, funcionamento, inflamação e neuroanatomia (BALLESTER et al., 2022). Diagnosticar as pessoas idosas com risco de depressão é muito importante, pois é uma estratégia que pode ajudar na prevenção de deficiências graves e outras complicações (KRISHNAMOORTHY; RAJAA; REHMAN, 2020).

Além do diagnóstico convencional, a depressão pode ser rastreada por escalas específicas para população idosa, útil na detecção de quadro depressivo (BRASIL, 2006). As escalas avaliam um conjunto de sintomas de forma rápida e com baixo custo, pode ser útil no

ambiente comunitário para rastrear e encaminhar os idosos com alto risco de depressão para um ambiente de assistência médica mais elevado, pois necessita a confirmação posterior por um profissional da saúde mental (KRISHNAMOORTHY; RAJAA; REHMAN, 2020; MATIAS et al., 2016).

Existem vários instrumentos para avaliação de depressão ou sintomas depressivos, um deles é a Escala de Depressão em Geriatria (do inglês *Geriatric Depression Scale - GDS),* que tem suas versões validadas e utilizadas no Brasil para idoso, sendo a de 15 itens recomendada pelo Ministério da Saúde (BRASIL, 2006). A GDS foi criada em 1982, originalmente composta de 30 questões, possui respostas objetivas (sim ou não) a respeito de como a pessoa idosa tem se sentido durante a última semana, também pode ser usada para medir as mudanças de gravidade da depressão ao longo do tempo (YESAVAGE et al., 1982). Possui versões reduzidas com 1, 4, 10, 15 e 20 questões, para otimizar o tempo na prática clínica, tendo como resultado uma boa validade para as versões de 10 e 15 itens, como uma forma confiável de identificar sintomas depressivos significativos (ALMEIDA; ALMEIDA, 1999). Uma recente revisão sistemática com metanálise identificou que as formas mais curtas de GDS (15 e 10 itens) apresentam maior acurácia quando comparado ao GDS-30 (KRISHNAMOORTHY; RAJAA; REHMAN, 2020).

Em relação a tratamento de depressão em idosos, deve-se considerar todos os fatores envolvidos no distúrbio e deve envolver uma combinação de psicoterapia e farmacoterapia, sendo discutido que muitas vezes essas terapias sozinhas são menos eficazes para remissão da depressão (ALEXOPOULOS et al., 2001; MUKAI; TAMPI, 2009). A diretriz mais recente da APA considera um tratamento com psicoterapeuta e se necessário um tratamento combinado com antidepressivo (AMERICAN PSYCHIATRIC ASSOCIATION, 2019).

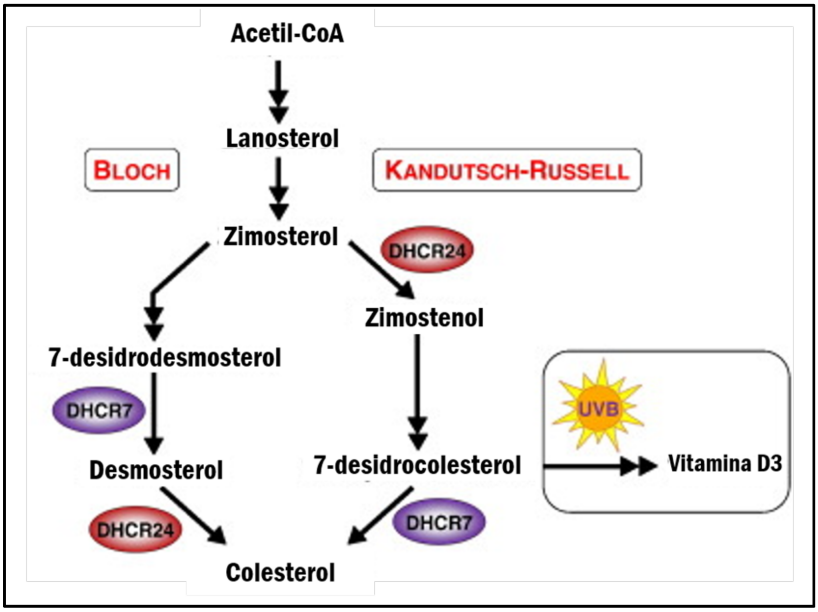
2.2 VITAMINA D

2.2.1 Caracterização e metabolismo

A história da vitamina D tem em torno 350 anos, com as primeiras descrições sobre raquitismo em crianças e osteomalácia em adultos por volta de 1600, e em torno de 100 anos de elucidação sobre o papel da luz solar e estrutura química das principais formas da vitamina D por volta de 1900-1920 e sobre seu metabolismo mais recente, em 1967 (JONES, 2022). Vitamina D é um termo que engloba um grupo de moléculas secosteróides, solúveis em gordura, derivadas do 7-deidrocolesterol (7-DHC), incorporado na bicamada lipídica da membrana plasmática. Se apresenta em duas formas principais, a vitamina D2 ou ergosterol de origem dietética e a vitamina D3 ou colecalciferol de origem dietética ou endógena, a qual é

produzida na pele (BIKLE, 2012; JÄPELT; JAKOBSEN, 2013). O 7-DHC é um derivado do metabolismo do colesterol, que inicia pela acetilcoenzima A (Acetil-CoA) e requer uma série complexa de reações que envolve mais de 20 etapas para o produto colesterol (Figura 2), envolvendo duas vias, a via de *Bloch* e a via de *Kandutsch-Russell.* Para essa segunda via, quando o 7-DHC não é utilizado para produção de vitamina D, pode ser convertido em colesterol agindo como substrato para a enzima 7-desidrocolesterol redutase (DHCR7) (PRABHU et al., 2016).

Figura 2 - Síntese do 7-DHC



Fonte: adaptado de Prabhu et al. (2016)

O processo de síntese da vitamina D pelas células epiteliais da epiderme, inicia pela a incidência da radiação ultravioleta B (UVB, 290-315nm) que promove a transformação não enzimática de 7-DHC ou pró-vitamina D em pré-vitamina D3, por uma quebra fotolítica da ligação entre os carbonos 9 e 10 do anel B do ciclo pentanoperidrofenantreno, formando uma molécula secosteróide, e em seguida sofre uma reação de isomerização induzida pelo calor, transformando em vitamina D3 (ou colecalciferol) (BIKLE; CHRISTAKOS, 2020; CASTRO, 2011; TIAN; HOLICK, 1995). É um processo que leva cerca de 8 horas para a pré-vitamina D3 se converter em vitamina D3 (WACKER; HOLICK, 2013a). O queratinócito é a principal célula da epiderme que possui a maquinaria enzimática para metabolizar a vitamina D produzida em metabólitos ativos e expressar o receptor de vitamina D (VDR, *vitamin D receptor*), envolvidos em ações locais como diferenciação e proliferação epidérmica (BIKLE, 2012; BOUILLON et al., 2019).

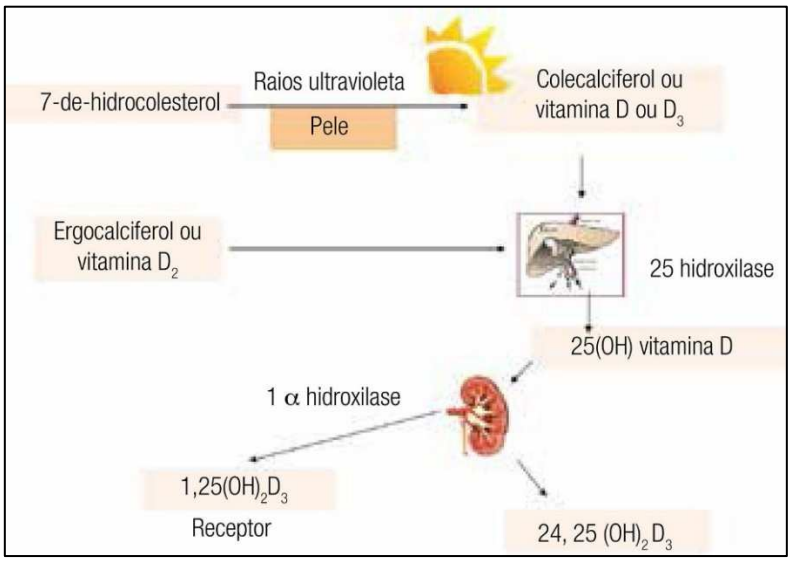
Cerca de 80 a 90% da obtenção da vitamina D é endogenamente pela exposição à radiação UVB ou adquirido pela suplementação dietética, sendo que apenas 10 a 20% das necessidades diárias provém da alimentação (CASTRO, 2011; MAEDA et al., 2014). As fontes alimentares de vitamina D são peixes gordurosos de água fria e profunda como salmão, sardinha, cavala, atum, óleo de fígado de bacalhau, e também são fontes em menor quantidade cogumelos frescos ou secos ao sol, e ainda alimentos fortificados com vitamina D2 como ovos, laticínios e carne bovina (GIUSTINA et al., 2020; HOLICK, 2007). Nas plantas, a vitamina D3 foi identificada em flores, em folhas de tomate, pimentão. Além disso, pode ser encontrada em fitoplâncton e microalgas, o que sugere que consequentemente os peixes que consomem microalgas tem um maior conteúdo natural (BLACK et al., 2017; JÄPELT et al., 2013). Já em fungos e leveduras, a vitamina D2 é produzida a partir da exposição da provitamina D2 aos raios UVB, e pequenas quantidades podem ser encontrados em plantas contaminadas com fungos (JÄPELT; JAKOBSEN, 2013).

A síntese da vitamina D a partir da alimentação/suplementação começa pela incorporação a micelas e é absorvida através da membrana dos enterócitos, por transportadores de membrana apical e também pode ser absorvida por difusão passiva quando a vitamina D é administrada em doses farmacológicas (REBOUL, 2015). Uma fração é incorporada aos quilomícrons, que são transportados para o sistema linfático e, em seguida, para o sistema venoso onde aproximadamente 60% da vitamina D 3 está ligada na proteína ligadora de vitamina D (DBP, *vitamin D binding protein*) (WACKER; HOLICK, 2013a). Uma fração da vitamina D contida no quilomícron pode ser absorvida pelo tecido adiposo e músculo esquelético (GIL; PLAZA-DIAZ; MESA, 2018).

Ambas as vitaminas D2 e D3 são transportadas pelo sangue pela DBP e deve sofrer ativação por meio de 2 reações de hidroxilação enzimática consecutivas que ocorrem no fígado e nos rins, apresentados na Figura 3. No fígado, as vitaminas D2 e D3 são convertidas em 25-hidroxivitamina D (calcidiol ou 25(OH)D), pela ação de 25-hidroxilases que são conhecidas por pertencer ao grupo citocromo P450 (CYP2R1 ou CYP27A1). A 25(OH)D acoplada à DBP é transportada a vários tecidos cujas células contêm a enzima 1-α-hidroxilase (citocromo P450 27B1 ou CYP27B1), como no rim, a onde converte em 1,25-dihidroxivitamina D [calcitriol ou $1,25(OH)_2D$], a forma ativa de vitamina D (HOLICK, 2004; PRABHU et al., 2016; WACKER; HOLICK, 2013b). Ainda, 25(OH)D pode ser transformado em duas formas que não tem afinidade com VDR, a 1,24,25-trihidroxivitamina D [1,24,25(OH3D)] e 24(R),25-dihidroxivitamina D [24,25(OH)2D], pela enzima 24-hidroxilase (CYP24A1, 24-OHase)

responsável por seu catabolismo e posterior excreção na bile (DIRKS et al., 2018; HOLICK, 2007).

Figura 3- Síntese e metabolismo da Vitamina D



Fonte: Maeda, et al (2014).

A conversão de $1,25(OH)_2D$ no rim é regulada por vários fatores, incluindo concentrações circulantes de hormônio da paratireoide (PTH) nas glândulas paratireoides, fósforo sérico, cálcio, fator de crescimento de fibroblasto 23 (FGF-23) no osso, pela sua auto-regulação, onde $1,25(OH)_2D$ diminui a própria síntese por *feedback* negativo, onde diminui a secreção do hormônio da paratireoide e aumenta a expressão 24-hidroxilase (HOLICK, 2007). Essa auto regulação pela expressão de 24-hidroxilase é encontrado na maioria dos tecidos, essencial para o catabolismo de 25OHD e $1,25(OH)_2D$. No rim, a expressão de CYP27B1 é estimulada pelo PTH e inibida pela ação do FGF23 e por feedback negativo de $1,25(OH)_2D$, e como cálcio e o fosfato regulam a secreção de PTH e FGF23, regulam indiretamente a atividade do CYP27b1 (BIKLE; PATZEK; WANG, 2018).

Os efeitos biológicos da $1,25(OH)_2D$ são mediados em grande parte pelo VDR, que é expresso em quase todas as células humanas e parece participar de maneira direta ou indireta da regulação de cerca de 3% do genoma humano (BOUILLON et al., 2008). VDR pertence a uma subfamília de receptores nucleares, que contém dois sítios para ligação ao ligante, chamados de *genomic pocket* (VDR-GP) que se liga numa configuração tipo tigela (*bowl-like)* para transcrição de genes e o *alternative pocket* (VDR-AP), que se liga numa configuração tipo planar (*planar-like*) para respostas rápidas (HAUSSLER et al., 2011). Quando VDR-GP está ligado a $1,25(OH)_2D$, forma um heterodímero receptor retinóide X (RXR), se liga a elementos responsivos à vitamina D (VDRE) nas regiões promotoras dos genes-alvo recrutando

complexos co-ativadores ou co-depressores para regular positiva ou negativamente a transcrição de genes que codificam proteínas que promulgam as funções genômicas tradicionais da vitamina D (GIL; PLAZA-DIAZ; MESA, 2018; HAUSSLER et al., 2011). Um exemplo de ação genômica, é a sinalização intestinal de cálcio e absorção de fosfato para efetuar a homeostase esquelética e de cálcio. Por outro lado, ações não genômicas ocorrem quando $1,25(OH)_2D$ ligado ao VDR-AP localizado em microdomínios de caveolas *lipid-raft* na membrana plasmática, faz a regulação transitória da atividade de canais iônicos (especialmente canais de cloreto e cálcio), quinases e fosfatases (BOUILLON et al., 2019; HAUSSLER et al., 2011).

Outro potencial receptor associado a membrana ligado as respostas rápidas de $1,25(OH)_2D$ e não genômicas, pela ativação de cascatas de sinalização, é a enzima PDIA3, proteína dissulfeto isomerase, família A, membro 3 [*Protein disulfide isomerase family member3*, também conhecido como *endoplasmic reticulum protein* (ERp60, ERp57, Grp58) e *Membrane Associated, Rapid Response Steroid binding receptor* (1,25-MARRS)], que foi associado a fisiologia dos condrócitos, na promoção a produção de proteínas da matriz da cartilagem e dos osteoblastos, na redução de apoptose, e ainda na células musculares, implicada na regulação e proliferação (BOYAN; CHEN; SCHWARTZ, 2012; CHEN et al., 2010).

O PDIA3 é encontrado na membrana plasmática e em vesículas de matriz de condrócitos da placa de crescimento, das células musculoesqueléticas e também está presente nas caveolas (*lipid-raft*), onde interage fisicamente com mediadores a jusante (BOYAN; CHEN; SCHWARTZ, 2012; CHEN et al., 2010). PDIA3 inicia as cascatas de sinalização incluindo a ativação da proteína ativadora de fosfolipase A2 (PLAA), fosfolipase A2 (PLA2), fosfolipase C (PLC) e abertura de canais de Ca^{2+} que resulta na ativação de mensageiros secundários (ZMIJEWSKI; CARLBERG, 2020). PDIA3 e VDR formam separadamente complexos com caveolina-1, ativando seus próprios mediadores a jusante, para obter resultados não genômicos e genômicos. Os complexos interagem de tal forma que a perda do receptor ou da caveolina-1 reduz a resposta dinâmica a $1,25(OH)_2D$ (CHEN et al., 2013).

A ação clássica da vitamina D é no metabolismo ósseo, atuando em 3 órgãos: intestino, rim e osso. A $1,25(OH)_2D$ participa da regulação dos níveis plasmáticos de cálcio ionizado e fosfato, agindo sobre sua absorção intestinal, excreção renal e mobilização óssea de cálcio. A interação da $1,25(OH)_2D$ com o VDR aumenta a eficiência da absorção intestinal do cálcio para 30 a 40% e a absorção do fósforo para aproximadamente 80% (HOLICK, 2007). Quando os níveis de cálcio sérico diminuem, a secreção de PTH é estimulada e ativa a síntese de

$1,25(OH)_2D$, que também estimula a reabsorção renal de cálcio e a mobilização dos ossos (reabsorção óssea) (GIL; PLAZA-DIAZ; MESA, 2018).

A presença do VDR em várias células tem sugerido a existência de funções independentes da regulação da homeostase óssea. Sua presença em tecidos não ósseos sugere sua importância para a regulação da proliferação celular, função imune e muscular, diferenciação da pele e reprodução, além de propriedades vasculares, metabólicas e fisiologia cerebral normal, incluindo a modulação da plasticidade sináptica (BOUILLON et al., 2019; MAYNE; BURNE, 2019). Também tem sido descrito que o tecido adiposo é um importante órgão metabólico e parece ser o principal local de armazenamento da vitamina D, e a já foi relatada a expressão de VDR e CYP27B1 nos adipócitos, que pode ter um papel de regulador na adipogênese e apoptose de adipócitos (ABBAS, 2017; DIX; BARCLAY; WRIGHT, 2018).

2.2.2 Metabolismo Cerebral

As primeiras evidências do papel da vitamina D na função cerebral começaram com achados autorradiográficos da presença de VDR no cérebro de animais em estudos experimentais (STUMPF et al., 1982). O VDR é encontrado em neurônios e células da glia na maioria das regiões do encéfalo, incluindo o córtex (temporal, frontal, parietal e cingulado), substância cinzenta profunda (tálamo, gânglios basais, hipotálamo, hipocampo e amígdala), cerebelo, núcleos do tronco cerebral, substância negra (área rica em neurônios dopaminérgicos), medula espinhal e sistema ventricular (DELUCA et al., 2013).

Em amostra de tecido cerebral humano *post-mortem,* foi evidenciado um mecanismo alternativo onde 25(OH)D pode ser ativada localmente no cérebro por meio da expressão da enzima 1α-hidroxilase, classicamente expressa no rim, que catalisa a conversão em $1,25(OH)_2D$, evidenciando que ambas as formas devem passar a barreira hematoencefálica (EYLES et al., 2005; PARDRIDGE; SAKIYAMA; COTY, 1985). Um estudo com animais sugeriu que há uma maquinaria para essa conversão, encontrando presença de CYP27a1, CYP27b1 e CYP24a1 expressos em neurônios e o CYP27a1 foi expresso em todos os tipos de células, com uma alta expressão nas células endoteliais (LANDEL et al., 2018).

Foi proposto que dentro da unidade neuro-vascular, a metabolização de 25(OH)D3 em $1,25(OH)_2D$ é feita por neurônios e possivelmente pela microglia, e depois é transferida para astrócitos, onde pode se ligar ao VDR e iniciar a transcrição gênica ou ser inativado quando em excesso. A forma ativa da vitamina D desencadeia ações genômicas associadas ao VDR ou ações não genômicas relacionadas ao PDIA3, que é altamente expresso no cérebro, parecendo

ser o principal receptor cerebral de vitamina D. Já o VDR parece ser expresso em maior quantidade em outros tecidos, como fígado e rins e menos expresso no cérebro comparado ao PDIA3 (LANDEL et al., 2018). A vitamina D tem sido chamada de neuroesteróide pelo seu importante papel no SNC, estando ligada a processos como diferenciação celular, produção e liberação neurotrófica, síntese de neurotransmissores, homeostase intracelular de cálcio, prevenção de danos oxidativos, função e metabolismo da estrutura neuronal e funcionamento cognitivo (EYLES et al., 2009; MAYNE; BURNE, 2019).

Devido a vitamina D estar envolvida em diversas funções a nível cerebral, o baixo nível sérico de vitamina D tem sido relacionado a algumas condições, como a esquizofrenia, falhas na plasticidade sináptica relacionada à aprendizagem e à memória, declínio cognitivo e transtornos de humor (BERRIDGE, 2017; CUI et al., 2017; MAYNE; BURNE, 2019). Segundo uma revisão, a forma ativa da vitamina D estimula a síntese do fator de crescimento do nervo (NGF) que atua nos neurônios colinérgicos, regula positivamente a síntese do fator neurotrófico derivado da linha de células gliais (GDNF) que atua nos neurônios dopaminérgicos, e neurotrofina 3 (NT-3) que são chave para a promoção, sobrevivência, diferenciação e plasticidade neuronal (DELUCA et al., 2013).

2.2.3 Mensuração de Níveis Séricos de vitamina D e pontos de corte

Para definição do *status* de vitamina D, a medida do total de 25(OH)D, considerando 25(OH)D3 e 25(OH)D2 é considerado o melhor biomarcador, como medida padrão-ouro, devido à sua meia-vida e estabilidade mais longas de cerca 15 a 25 dias (entre 2 a 3 semanas), e a abundância relativa (isto é, ng/mL; 1 ng/mL = 2.496 nmol/L) no soro (ALTIERI et al., 2020; JONES et al., 2014; LIPS, 2007; SEMPOS et al., 2018). Um estudo demonstrou que a meia vida quando calculado após uma única dose de ataque de 100.000 UI de colecalciferol no início do estudo, seguida por uma dose diária de 4800 UI dos dias 7 a 20, e nenhuma dose a partir do dia 21, a meia-vida de manutenção dos níveis do soro 25(OH)D foi estimado de 82 dias (OLIVERI et al., 2015). Já a forma bioativa di-hidroxilada, $1,25(OH)_2D$ tem meia-vida de 4-6 horas, não sendo um bom parâmetro de avaliação (ALTIERI et al., 2020).

Ainda não foi determinado se o nível livre de 25(OH)D ou 24,25(OH)D oferece mais informações sobre o status da vitamina D e ainda não é recomendado com base na literatura (ALTIERI et al., 2020). A medição de $1,25(OH)_2D$ não reflete a real concentração pois estará dentro da faixa de referência, mesmo quando alguém é considerado deficiente em vitamina D. Entretanto pode ser usado na suspeita de deficiência de 1α-hidroxilase, onde concentrações

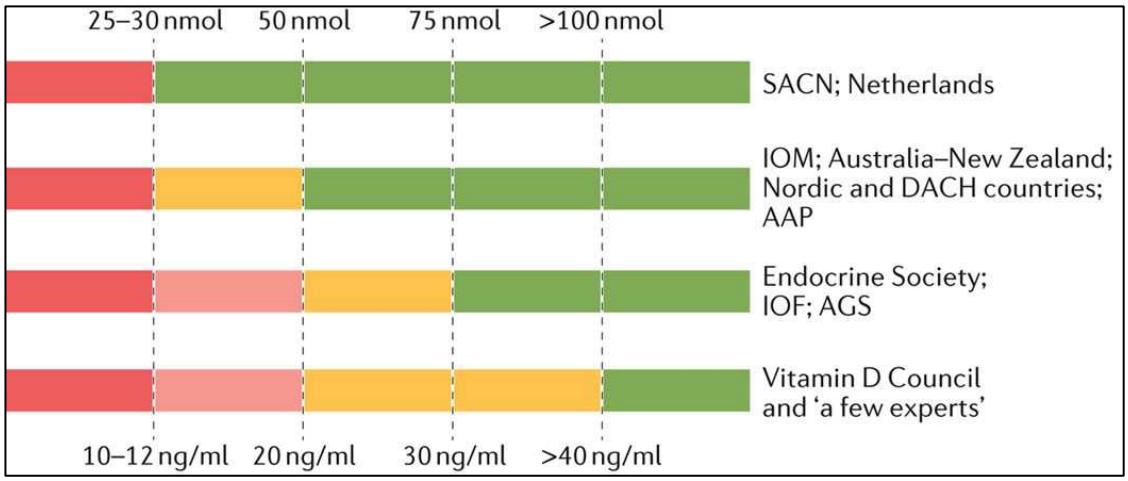
muito baixas de 1,25$(OH)_2$D. Também pode ser útil em síndromes hipofosfatêmicas mediadas por FGF23, marcando concentrações normais a baixas de 1,25$(OH)_2$D e já concentrações muito altas indicam raquitismo hereditário resistente à vitamina D ou a presença de excesso de 1α-hidroxilação extra renal por doenças granulomatosas ou linfoproliferativas (DIRKS et al., 2018).

Ao longo do tempo muitos métodos de mensuração de vitamina D foram sendo estudados e muitos estudos clínicos fornecem a base científica para as recomendações clínicas atuais. Historicamente, a 25(OH)D foi mensurada por um radioimunoensaio manual (RIA) ou um ensaio de proteína de ligação à vitamina D (DBP), com o passar do tempo, laboratórios desenvolveram imunoensaios automatizados e ensaios de imunoabsorção enzimática (ELISA) e também métodos espectrométricos de massa e cromatografia líquida de alta eficiência (ALTIERI et al., 2020). Atualmente, é considerado como padrão ouro o ensaio de cromatografia líquida acoplada à espectrometria de massas em tandem (LC-MS/MS). Este método consegue diferenciar 25(OH)D2 e 25(OH)D3 e outros metabólitos, utilizados em uma variedade de fatores fisiológicos, estados/condições de saúde e também úteis na avaliação da efetividade da suplementação de D2 versus D3 endógena (ALTIERI et al., 2020; SEMPOS et al., 2018). Por outro lado, métodos cromatográficos embora mais precisos são mais trabalhosos e mais caros, e estão disponíveis em laboratórios mais especializados (MAEDA et al., 2014; MINISOLA et al., 2019).

Os estudos de imunoensaios de quimioluminescência (CLIAs), também utilizados na prática clínica e estão prontamente disponíveis na maioria dos laboratórios comerciais e clínicos e são bons o suficiente para avaliar os níveis de 25(OH)D (MINISOLA et al., 2019). Baseiam-se na dissociação de 25(OH)D da VDBP, depois são ligados ao anticorpo de fase específica e depois à adição de partículas magnéticas revestidas com anticorpo contra 25(OH)D, o isolumino traçador (25(OH)D-*isolumino tracer*). Em seguida, o material não ligado é removido com um ciclo de lavagem e os reagentes são adicionados para iniciar a reação quimioluminescente. O sinal de luz é detectado por um fotomultiplicador como unidades de luz relativa, sendo que essa medida é inversamente proporcional à concentração de 25(OH)D (ALTIERI et al., 2020; FOOD & DRUG ADMINISTRATION, 2017). O viés deste teste é que concorrentes comerciais diferem entre si de acordo com a reatividade cruzada com diferentes metabólitos de vitamina D e quando comparados aos métodos cromatográficos (ALTIERI et al., 2020; FULEIHAN et al., 2015). Todavia é reconhecido com um ensaio realizado por laboratórios clínicos, quando o foco permanece no total sérico de 25(OH)D (SEMPOS et al., 2018).

Em relação as diretrizes do nível sérico, há uma divergência em relação definição de hipovitaminose D e *status* 'ótimo' que é baseado na saúde óssea. Em grande parte, isso se deve pelo uso de dosagem por métodos que não são padrão em pesquisas que impede a capacidade de reunir dados de diferentes locais para permitir definições baseadas em evidências (BOUILLON, 2017; SEMPOS et al., 2018). Tem sido discutido que valores abaixo de 12ng/ml são considerados associados a um risco aumentado de raquitismo/osteomalácia, enquanto as concentrações entre 20 ng/ml e 50 ng/ml parecem ser seguras e suficientes na população em geral para a saúde esquelética (SEMPOS et al., 2018). Além disso, uma revisão comparou as divergências entre as recomendações de diferentes agências e países, que são apresentadas na Figura 4 (BOUILLON, 2017).

Figura 4 - Recomendações para a interpretação dos níveis séricos de 25OHD



Fonte: Bouillon (2017)

Legenda: Código de cores: vermelho indica um estado de grave deficiência que deve ser corrigido sem exceção; laranja denota um estado de deficiência leve, em que a intervenção é desejável; verde indica um estado de suprimento suficiente que não se beneficia da suplementação adicional. AAP, Academia Americana de Pediatria; AGS, Sociedade Americana de Geriatria; DACH, *Deutschland (Germany), Austria and Confoederatio Helvetica (Switzerland)*; IOF, Fundação Internacional de Osteoporose; IOM, Instituto de Medicina; SACN, Comitê Científico Consultivo em Nutrição.

Há uma discussão sobre o ponto de corte para os níveis, onde a IOM acredita que o nível de 20 ng/ml reflete um nível que atende às necessidades de quase toda a população em geral. Porém, essas delimitações foram definidas com base na população dos Estados Unidos e Canadá. Além disso, se mostra contrária aos pontos de corte da *Endocrine Society*, em que 30 ng/ml de 25OHD e acima seriam suficientes e que abaixo de 20 ng/ml são deficientes em vitamina D (ROSEN et al., 2012).

Segundo um consenso da 2ª e a 5ª Conferência Internacional sobre Controvérsias em Vitamina D que discutiu os pontos de corte, recomendou que na ausência de dados

convincentes, os valores de 25(OH)D abaixo de 30 nmol/L (12ng/ml) devem ser evitados e considerados associados a um risco aumentado de raquitismo/osteomalácia, enquanto as concentrações de 25 (OH) D entre 50 e 125 nmol/L (20 a 50 ng/ml) parecem ser seguros e suficientes na população em geral para a saúde óssea (GIUSTINA et al., 2020). Para reduzir as fraturas em idosos, são necessários vitamina D para atingir níveis >50 nmol/l (20 ng/ml) e cálcio suficiente (GIUSTINA et al., 2022). No Brasil, a Sociedade Brasileira de Endocrinologia e Metabologia (SBEM), considera como valor de normalidade adequado 20 ng/mL para população saudável até 60 anos, e entre 30 e 60 ng/ml valor recomendado para população de risco, no qual inclui os idosos (FERREIRA et al., 2017; MAEDA et al., 2014).

Da mesma forma, o nível máximo para evitar toxicidade ainda não é definido devido a estudos com humanos serem limitados, entretanto sugere-se que para população saudável doses acima de 10.000 UI/dia e níveis séricos de 25(OH)D em torno de 250 nmol/L (100 ng/ml) podem ser tolerados em curto prazo (FERREIRA et al., 2017; GIUSTINA et al., 2020). Superdosagens com nível sérico de 150 ng/ml, tem sido associado com a toxicidade de vitamina D, demostrando sintomas como confusão, apatia, vômito, dor abdominal, poliúria, polidipsia e desidratação. A toxicidade que tem sido relacionada com a atividade elevada de 1α-hidroxilase ou atividade inibida de 24-hidroxilase, levando ao aumento da concentração de 1,25(OH)D; aumento do número de receptores de vitamina D; e saturação da capacidade da proteína de ligação da vitamina D (MARCINOWSKA-SUCHOWIERSKA et al., 2018).

As recomendações de ingestão diária, indicam que para aqueles que não tem uma exposição solar adequada, tenha um consumo de 5µg/dia [200 UI (1 µg= 40 UI)]; até 50 anos, gestantes e lactantes; 10 µg/dia (400 UI) de 50 a 70 anos; e 15 µg/dia (600 UI) para aqueles com mais de 70 anos (PADOVANI et al., 2006). Para cada 100 UI de vitamina D proveniente de alimentos, a concentração circulante de 25(OH)D pode aumentar em aproximadamente 0,6-1,0 ng/mL (WACKER; HOLICK, 2013a). As fontes alimentares que provem maior conteúdo de vitamina D, são apresentados no Quadro 3.

Quadro 3 – Fontes alimentares de vitamina D

Fonte	Quantidade µg/100g	Quantidade UI/100g
Óleo de fígado de bacalhau e peixes gordurosos	90 a 250	3600 a 10000
Salmão da aquicultura	6 a 10	240 a 400
Cavala selvagem	5 a 8	200 a 320

Salmão selvagem	24	981
Anchova	10	415
Truta de aquicultura	9	371
Peixe-espada	11	447
Bacalhau	2	80
Mexilhões	0,8	33
Atum	4	164
Cogumelo (portobelo exposto a raios ultravioleta)	31	1275
Cogumelo (portobelo)	0,3	14
Cogumelo (Shitake)	0,7	28
Ovo	2	86

Fonte: adaptado de Giustina et al, (2020); Chen et al (2007); USDA (2015).

Em relação a suplementação, estudos têm indicado que a vitamina D3 é mais eficaz em aumentar as concentrações de 25(OH)D no soro do que a vitamina D2 (MO et al., 2019; TRIPKOVIC et al., 2012). Em relação a dose, para idosos acima de 65 anos há uma grande variação na recomendação entre 200 a 2000 UI (BOUILLON, 2017). Segundo um consenso realizado recentemente, as recomendações americanas do *Institute of Medicine*, para adultos com menos de 70 anos, a recomendação diária é de 600 UI (15 µg/dia) e para aqueles com mais de 70 anos, a recomendação diária é de 800 UI (20 µg/dia), e da mesma forma o *International Osteoporosis Foundation* recomenda doses mais altas, de 800 a 1000 UI para idosos (DAWSON-HUGHES et al., 2010, p.; GIUSTINA et al., 2019; ROSS et al., 2011). A *Endocrine Society* recomenda 1500 a 2000 UI, com um aumento de duas a três vezes para indivíduos obesos (3000–6000 IU/dia) (KIMBALL; HOLICK, 2020). No Brasil, a recomendação da Sociedade Brasileira de Endocrinologia vai de encontro a recomendação americana, do *Institute of Medicine*, sendo em pacientes com osteoporose e risco de fraturas aumentado, indica-se 1.000 e 2.000 UI (HOLICK et al., 2011; MAEDA et al., 2014).

Em relação aos protocolos de suplementação de vitamina D para indivíduos com <20 ng/ml são sugeridas as doses de ataque para repor estoques corporais e atingir o nível adequado. O esquema mais utilizado é de 50.000 UI/ semana (ou 7.000 UI/dia) de vitamina D por 6 a 8 semanas (MAEDA et al., 2014). Na atenção primária da saúde do Brasil, para pessoas com doenças ósseas como osteoporose, osteomalácia ou outras condições de redução de massa óssea, os protocolos de: 50.000 UI, 1 vez por semana por 8 semanas; 6.000 UI ao dia, por 8 semanas; ou ainda 3.000 a 5.000 UI ao dia, por 6 a 12 semanas (BRASIL, 2018).

Segundo uma revisão, para gerar vitamina D suficiente através da exposição solar, várias diretrizes recomendam uma exposição solar diária de 7 a 30 minutos (dependendo da latitude, cor da pele e estação do ano) para mãos, braços e rosto (BOUILLON, 2017). É

sugerido que uma exposição diária de 20% do corpo, contando que para cada braço 9%, para cada perna 18% e o abdômen 18%, pode produzir cerca de 1400 a 2000 UI de vitamina D3 nos horários de pico de luz solar (WACKER; HOLICK, 2013a). Tem sido discutido que nos horários antes das 9h e após 15h, que são os horários mais seguros para o risco de câncer de pele, o ângulo do sol se torna mais oblíquo e o ozônio da atmosfera terrestre absorve mais a radiação UVB, diminuindo a quantidade que atinge a superfície terrestre (HOLICK, 2017).

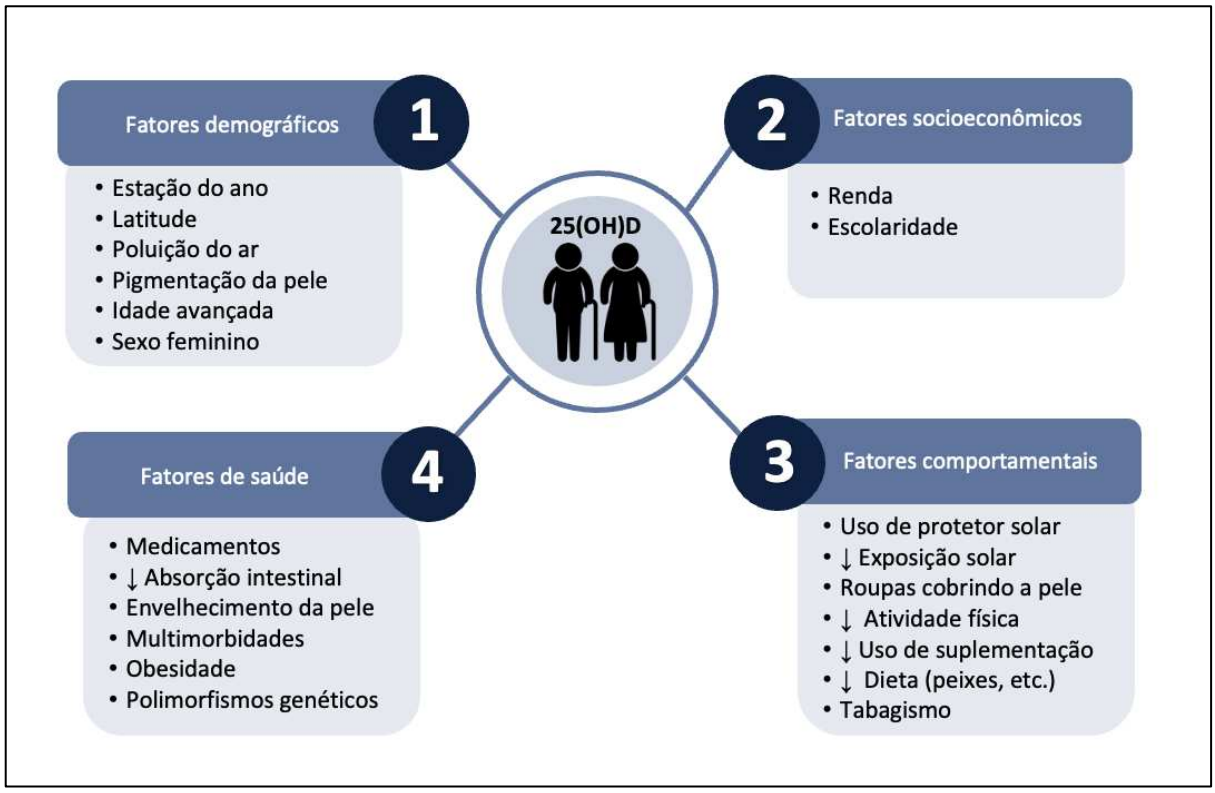
2.3 DETERMINANTES DO NÍVEL SÉRICO DE VITAMINA D

A vitamina D tem sido bastante discutida por seus efeitos no metabolismo ósseo, e vem ganhando espaço em relação a sua ação em outros sistemas. Tem ganhado bastante destaque por apresentar na população uma importante redução a nível sanguíneo sendo relacionada a desfechos importantes em saúde (BOUILLON et al., 2019; HOLICK; CHEN, 2008; MARINO; MISRA, 2019). Entretanto, a mensuração global dos níveis sanguíneos de vitamina D é difícil de realizada precisamente devido à falta de padronização nos métodos laboratoriais, o que também limita a comparações entre estudos ao longo do tempo (ROTH et al., 2018). A heterogeneidade substancial dos estudos pode impedir de tirar conclusões sobre o *status* geral da vitamina D na população mundial (HILGER et al., 2014).

Em 2013, foi realizado um levantamento mundial do baixo nível sérico de vitamina D e foi encontrada uma grande variação entre os continentes, sendo para população adulta, níveis de deficiência estão entre 20 a 90% e população idosa de 4 a 91% (PALACIOS; GONZALEZ, 2014). No Brasil, embora a localização geográfica promove abundância de luz solar, com uma grande extensão territorial próxima ao sol e havendo radiação UVB suficiente para produzir vitamina D na pele durante todo o ano, a insuficiência de vitamina D se mantem prevalente (MENDES et al., 2018). Pesquisadores evidenciaram que um pouco mais de 35% dos adultos e 41% dos idosos apresentam o nível mais baixo de vitamina D, sendo as regiões sul e sudeste as regiões com maior prevalência de deficiência (PEREIRA-SANTOS et al., 2019).

Vários fatores têm sido relacionados com ao baixo nível sérico de vitamina D em idosos e foram sintetizados na figura 5 em quatro dimensões: fatores demográficos, socioeconômicos, comportamentais e de saúde e na figura 6 em forma de nuvem de palavras.

Figura 5 - Fatores associados ao baixo nível sérico de vitamina D



Fonte: Elaborado pelos autores

Figura 6 - Nuvem de palavras relacionadas ao nível sérico de vitamina D

Fonte: Elaborado pelos autores

Entre os fatores demográficos tem sido descrito condições mais relacionadas ao ambiente como poluição do ar, a latitude, estação do ano (inverno e outono) e incidência solar (ARABI; EL RASSI; EL-HAJJ FULEIHAN, 2010; FEIZABAD et al., 2017). A incidência solar parece ser mais influente em países nórdicos, que apresentam baixa incidência solar durante o inverno, e as concentrações de vitamina D podem reduzir de 20 a 30% nesses períodos (JORDE et al., 2010).

Estudos com coortes de idosos tem identificado outros fatores demográficos como a pigmentação da pele mais escura/etnia, idade mais avançada, sexo feminino (ASPELL et al., 2019; CARRILLO-VEGA et al., 2017; LIMA-COSTA et al., 2020). Em relação a cor da pele, indivíduos caucasianos tem um aumento de vitamina D, seis vezes maior do que indivíduos de pele negra, quando expostos ao sol (em 1 dose de eritêmica mínima) (CLEMENS et al., 1982). Em relação a fatores socioeconômicos há uma discussão não muito estabelecida em relação a escolaridade e renda, mas alguns estudos com idosos tem encontrado um risco relacionado a baixa renda e baixa escolaridade (CHENG et al., 2017; LIN et al., 2020). Por outro lado, um estudo outro estudo encontrou proteção para idosos com baixa escolaridade (CARRILLO-VEGA et al., 2017).

Entre os fatores comportamentais encontra-se o uso extensivo de filtro solar, que tem sido usado na prevenção de doenças de pele, em diversos ambientes como na realização de atividades diárias, trabalho, prática de atividade física (PEREIRA-SANTOS et al., 2019). Há uma discussão sobre o bloqueio da ativação cutânea da vitamina D com o uso do protetor solar, sendo evidenciado que o fator de proteção solar 8 pode diminuir a capacidade de fotoprodução em 90% e o fator de proteção dólar 30 pode diminuir em 99%, bem como no inverno as pessoas usam mais camadas de roupas impedindo a exposição solar (HOLICK, 2007; TSIARAS; WEINSTOCK, 2011). Por outro lado, há dados de um estudo que demostram que mesmo utilizando a protetor solar (FPS 15), a vitamina D pode ser produzida na pele (PETERSEN et al., 2012). Segundo um painel de especialistas recente, protetores solares de amplo espectro que previnem o eritema dificilmente comprometem o *status* da vitamina D em populações saudáveis (PASSERON et al., 2019). O hábito de usar roupas que cubram quase a totalidade do corpo também podem limitar a produção epidérmica (ALLALI et al., 2009; ARABI; EL RASSI; EL-HAJJ FULEIHAN, 2010).

Também tem sido discutido a influência de fatores comportamentais como redução da exposição à luz solar, baixa ingestão dietética de alimentos que contenham vitamina D (como peixe e alimentos fortificados) e falta de suplementação (ou a proteção para no caso de quando há suplementação (BEVILACQUA et al., 2021; LAIRD et al., 2018; LIMA-COSTA et al.,

2020; MIGLIACCIO et al., 2019; SHEA et al., 2011). A prática de atividade física também é um fator relacionado, considerado protetivo, entretanto por outro lado a falta prática de atividade física é considerada de risco, possivelmente pela exposição solar (ASPELL et al., 2019; CARRILLO-VEGA et al., 2017; KIM et al., 2018; LAIRD et al., 2018; ROLIZOLA et al., 2022). Ainda, o tabagismo também foi associado aos baixos níveis séricos de vitamina D, entretanto o mecanismo ainda não está estabelecido (CARRILLO-VEGA et al., 2017; KIM, 2020; LAIRD et al., 2018; LIMA-COSTA et al., 2020).

Considerando fatores de saúde, a obesidade tem sido relacionada com baixo nível sérico em idosos (ASPELL et al., 2019; CARRILLO-VEGA et al., 2017; LAIRD et al., 2018). A nível celular, existe uma hipótese de que vitamina D, como é lipossolúvel, é mais facilmente armazenada nas células adiposas (sequestro) antes de estar disponível para posterior metabolismo reduzindo a sua disponibilidade na circulação sanguínea (BOUILLON et al., 2019; WORTSMAN et al., 2000). Há evidências que os adipócitos e seus precursores expressam receptores nucleares envolvidos no metabolismo e na ação dos esteroides. A 1,25-di-hidroxivitamina D3 estimula a adipogênese, potencializando os efeitos dos meios adipogênicos, contendo insulina, dexametasona, 3-isobutil-1-metilxantina e indometacina (BOUILLON et al., 2014).

Além disso, na obesidade, o tecido adiposo é hipertrófico, resultando em desequilíbrio do fluxo sanguíneo, levando à hipóxia, inflamação e infiltração de macrófagos e há um aumento na secreção de interleucinas 6 e 8, TNF-α e a vitamina D3 parece ter uma ação anti-inflamatória sobre os adipócitos, reduzindo a liberação de quimiocinas e citocinas pelos adipócitos (SAVASTANO et al., 2017). Também tem sido discutida a ideia de que pessoas que apresentam marcadores inflamatórios mais elevados, como na obesidade, por exemplo a proteína C reativa, apresentam um menor sérico de vitamina D (DE OLIVEIRA et al., 2017; HAYNES et al., 2013).

Algumas condições de saúde têm sido relacionadas a pacientes em grupo de risco para deficiência da vitamina D, como insuficiência renal, cardíaca e hepática, em particular candidatos e receptores de transplante, doenças gastrointestinais, incluindo doença de Crohn, doença inflamatória intestinal e síndromes de má absorção. Além disso, o uso de alguns medicamentos como os antirretrovirais, antifúngicos, por exemplo, cetoconazol, medicamentos anticonvulsivantes, colestiramina, rifampicina e glicocorticoides também podem reduzir a vitamina D ou afetar a expressão de genes regulados pela vitamina D (AMREIN et al., 2020). O mecanismo proposto é pela ligação ao receptor de esteroide e xenobiótico (SXR) ou receptor ativado por pregnano (PXR), que desempenha um papel importante na desintoxicação de

xenobióticos e drogas, que pode ligar-se a VDRE afetando a transcrição de genes (GRÖBER; KISTERS, 2012). O PXR pode induzir a expressão e 24-hidroxilase, diminuindo assim os níveis de 25(OH)D, e em pacientes expostos ao excesso de glicocorticoides, comum para tratamento de doenças pulmonares, reumáticas e renais crônicas, pode reduzir a expressão do receptor da vitamina D em vários tecidos e células, levando a um estado de resistência à vitamina D (GIUSTINA et al., 2019; SKVERSKY et al., 2011).

Por fim, tem sido discutido que polimorfismos de alguns genes que codificam componentes-chave da via do metabolismo da vitamina D, incluindo DHCR7 (codificando 7-DHC redutase), CYP2R1 (codificando 25-hidroxilase), CYP24A1 (codificando 24-hidroxilase) e GC (que codifica a proteína de ligação da vitamina D) (BEVILACQUA et al., 2021). A produção de vitamina D3 na pele se deve à extensão e qualidade da radiação UVB que atinge a derme, bem como à disponibilidade do 7-DHC e às características da pele (GIL; PLAZA-DIAZ; MESA, 2018). Além disso, outros fatores como a diminuição da produção de vitamina D na pele tem sido relacionada ao envelhecimento, pela diminuição da capacidade da pele de produzir vitamina D, à diminuição do 7-DHC e alterações na morfologia da pele (MACLAUGHLIN; HOLICK, 1985).

2.4 RELAÇÃO ENTRE VITAMINA D E SINTOMAS DEPRESSIVOS

Conforme descrito no capítulo 1, na descrição do estado da arte do tema, estudos transversais e longitudinais têm encontrado associação entre o nível sérico de vitamina D e sintomas depressivos. Resultados de uma metanálise com população mista, com adultos e idosos, evidenciou que um aumento de 10 ng/ml em concentrações séricas de 25(OH)D parece ter um efeito protetor contra a depressão, com diminuição de 4% no risco em estudos transversais e uma diminuição de 8% na incidência em estudos de coorte (JU; LEE; JEONG, 2013). Enquanto que, em estudos envolvendo somente idosos com amostra proveniente de estudos de corte prospectivos, o mesmo aumento de 10 ng/ml de 25(OH)D foi associado a uma redução de 12% no risco de depressão (LI et al., 2019).

Entretanto, metanálises com estudos clínicos têm mostrado dados divergentes em ensaios clínicos com suplementação, onde uma evidência que a vitamina D suplementada (uma dose diária de ≥800 UI) pode ter um efeito na depressão, comparável com o de antidepressivos (SPEDDING, 2014). Devido a variabilidade metodológica dos estudos, a outra metanálise não encontrou nenhuma redução significativa nos sintomas depressivos após a suplementação de vitamina D com diferentes doses (GOWDA et al., 2015).

Apesar de não haver resultados conclusivos ainda, alguns possíveis mecanismos biológicos têm sido descritos. Uma via potencial inclui um desequilíbrio na homeostase do cálcio intracelular e extracelular (Ca^{2+}) é um fator importante responsável pela condução do início da depressão (BERRIDGE, 2017). Quando há uma alteração na atividade neural resultante de um aumento no glutamato, que impulsiona os neurônios excitatórios e pode ser responsável pelo declínio na atividade e no número de neurônios inibidores GABAérgicos. O Glutamato ativa canais NMDA (NMDARs), que é um canal ionotrópico e responde aumentando a entrada de Ca^{2+} externo nos neurônios inibitórios e também há uma ativação da via de sinalização de fosfoinositídeo que gera trifosfato de inositol ($InsP_3$) que libera Ca^{2+} (BERRIDGE, 2017; WARSH; ANDREOPOULOS; LI, 2004; YUAN et al., 2003). A vitamina D entra no núcleo, associa-se ao RXR e depois se liga ao VDRE, induzindo a expressão de proteínas relacionadas à manutenção da homeostase do Ca^{2+}, como calbindina, parvalbumina, trocador cálcio-sódio (NCX1), e membrana plasmática bomba Ca^{2+} ATPase (PMCA). Também regula o Ca^{2+}, reduzindo a expressão do canal de cálcio CaV1.2. (BERRIDGE, 2017; BIVONA et al., 2019). Além disso, GABA também é responsável por modular a atividade de outros sistemas de neurotransmissores como a inibição de serotonina, a noradrenalina e a liberação de dopamina (CROARKIN; LEVINSON; DASKALAKIS, 2011).

Em relação a serotonina, foi proposto que a depressão pode resultar de uma deficiência desse neurotransmissor que é derivado do aminoácido essencial triptofano. Para produzir 5-HT no cérebro, triptofano precisa primeiramente ser transportado e permear a barreira hematoencefálica e então ser metabolizado pela enzima TPH2. A expressão do gene de TPH2 é induzida pela forma hormonal ativa da vitamina D [$1,25(OH)_2D$] juntamente com VDR em neurônios serotonérgicos (KANEKO et al., 2015; PATRICK; AMES, 2015). Além disso, $1,25(OH)_2D$ também pode atuar na repressão do transportador de recaptação de serotonina (*serotonin reuptake transporter*, SERT ou 5-HTT), e a enzima mitocondrial responsável pelo catabolismo das monoaminas, Monoamina Oxidase-A (MAO-A), resultando na potencialização da transmissão nervosa serotoninérgica (SABIR et al., 2018).

No sistema dopaminérgico, a vitamina D tem um papel na maturação de neurônios dopaminérgicos. VDR está presente no núcleo dos neurônios positivos para tirosina hidroxilase (TH), pode estimular a produção fator neurotrófico dos neurônios de dopamina (GDNF), e pode modular o metabolismo por meio da regulação genômica da expressão da catecol-o-metil transferase (COMT), uma das enzimas-chave envolvidas no metabolismo da dopamina (CUI et al., 2013, 2015). Além disso, em estudos experimentais, parece ser semelhante ao tratamento antidepressivo com fluoxetina, e pode melhorar os sintomas anedônicos, provavelmente

regulando o efeito das ações relacionadas à dopamina no núcleo *accumbens* (SEDAGHAT et al., 2019).

Nos mecanismos antioxidantes, a vitamina D estimula a expressão de muitos genes, como o fator relacionado ao fator nuclear eritróide-2 (NRF2), g-glutamil transpeptidase (g-GT), glutamato-cisteína ligase (GCLC), glutationa redutase (GR), glutationa peroxidase (Gpx) (BERRIDGE, 2017). A vitamina D é responsável por regular negativamente a expressão do óxido nítrico sintase induzível em células derivadas de monócitos e por potencializar a produção de γ-Glutamil transpeptidase (γ-GT), uma enzima importante na via da glutationa, em astrócitos expostos a um meio pró - inflamatório (BIVONA et al., 2019; DELUCA et al., 2013). Quando a vitamina D está em déficit, pode causar um desequilíbrio nas EROs, que facilita a liberação de Ca^{2+} aumentando o seu nível. Por outro lado, há um declínio de ATP (adenosina trifosfato), o que reduz a capacidade dos neurônios de liberar Ca^{2+} da célula (BERRIDGE, 2015, 2017; WIMALAWANSA, 2019).

Foi descrito que as citocinas pró-inflamatórias interleucina-1 α e β, fator de necrose tumoral- α (TNF- α) e interleucina-6 têm sido implicadas no início da depressão (BERK et al., 2013; SWARDFAGER et al., 2016; TICINESI et al., 2016). A vitamina D modula a resposta imune ao interagir com as células do sistema imune inato e adaptativo, regulando a expressão de citocinas, uma vez que macrófagos, células dendríticas e linfócitos B e T ativados expressam 1α-hidroxilase e VDR (CALTON et al., 2015; TICINESI et al., 2016). A atividade do NF-kB, um fator de transcrição envolvido na síntese de citocinas pró-inflamatórias é inibida por $1,25(OH)_2D$,e mantem o equilíbrio das células T auxiliares (T helper, Th), inibindo a produção de citocinas Th1 e Th17 (IFN-γ, TNF-α, IL-1, etc) e aumenta síntese de citocinas Th2 (IL-10, IL-4) (BIVONA et al., 2019).

Em relação a estrutura e funcionalidade cerebral, estudos encontraram uma associação entre depleção de vitamina D com menor volume cerebral em adultos e volume de matéria cinzenta em idosos (ANNWEILER et al., 2014; KARAKIS et al., 2016; PLÓZER et al., 2015). O volume intracraniano mediou a relação entre sintomas depressivos em pessoas com TDM e vitamina D (ZHU et al., 2019). Em um estudo recente, foi proposto que a vitamina D pode atuar no sistema de conectividade neuronal. A partir de imagem por ressonância magnética funcional (fMRI, do inglês *Functional Magnetic Ressonance Imaging*), avaliando conectividade de rede funcional, foi identificado que mulheres adultas apresentaram alteração da cognitividade relacionada a TDM, e foi correlacionada com ambos: sintomas depressivos e com menor concentração sérica de vitamina D, não sendo evidente em homens (ZHU et al., 2022).

3. MÉTODOS

Neste capítulo são descritas a caracterização e procedimentos de coleta de dados do estudo EpiFloripa Idoso, bem como a amostra que compôs os estudos desta tese. O modelo de análise estatística dos artigos originais e outros detalhes dos estudos de revisão são apresentados na sessão de resultados em cada manuscrito desenvolvido, facilitando a compreensão.

3.1 CARACTERIZAÇÃO DO ESTUDO

Caracteriza-se como um estudo multimétodos, que incluiu estudo de revisão narrativa, e estudo empírico longitudinal, observacional, de base populacional e domiciliar, oriundo do estudo: "Condições de saúde de Idosos de Florianópolis - EpiFloripa Idoso", o qual teve sua primeira onda de coleta (linha de base) desenvolvido em 2009-2010, segunda onda de coleta em 2013-2014, a qual também contemplou a coleta de exames laboratoriais e testes físicos, intitulada "Perfil lipídico, marcadores inflamatórios, composição corporal, condições de saúde e hábitos de vida em idosos: estudo longitudinal de base populacional em Florianópolis, SC, EpiFloripa 2013" entre 2014-2015, e a terceira onda de coleta realizada em 2017-2019, caracterizada como uma coorte aberta, na qual foram entrevistados novamente os idosos do acompanhamento (estudo longitudinal) e incluídos novos idosos para adequar o tamanho da amostra.

3.2 DESCRIÇÃO DO LOCAL E POPULAÇÃO EM ESTUDO

O estudo EpiFloripa Idoso é um estudo desenvolvido na região urbana da cidade de Florianópolis, capital do estado de Santa Catarina. A população estimada no município em 2021 era de 516.524 habitantes e que no momento da coleta da primeira onda do estudo do EpiFloripa, segundo o último Censo Demográfico de 2010, era de 421.239 habitantes, sendo 11,4% equivalendo a população idosa, com 60 anos ou mais (INSTITUTO BRASILEIRO DE GEOGRAFIA E ESTATÍSTICA, 2011, 2021).

A amostra da presente tese foi composta por todos os idosos de 60 anos ou mais, de ambos os sexos, entrevistados na onda 1 (2009-2010), na onda 2 (2013-2014) e na onda 3 de seguimento (2017/2019), com dados válidos para as variáveis de interesse, e sendo excluídos aqueles que não faziam parte da onda 3 (novos entrevistados).

3.3 CÁLCULO DO TAMANHO DE AMOSTRA E PROCESSO DE AMOSTRAGEM

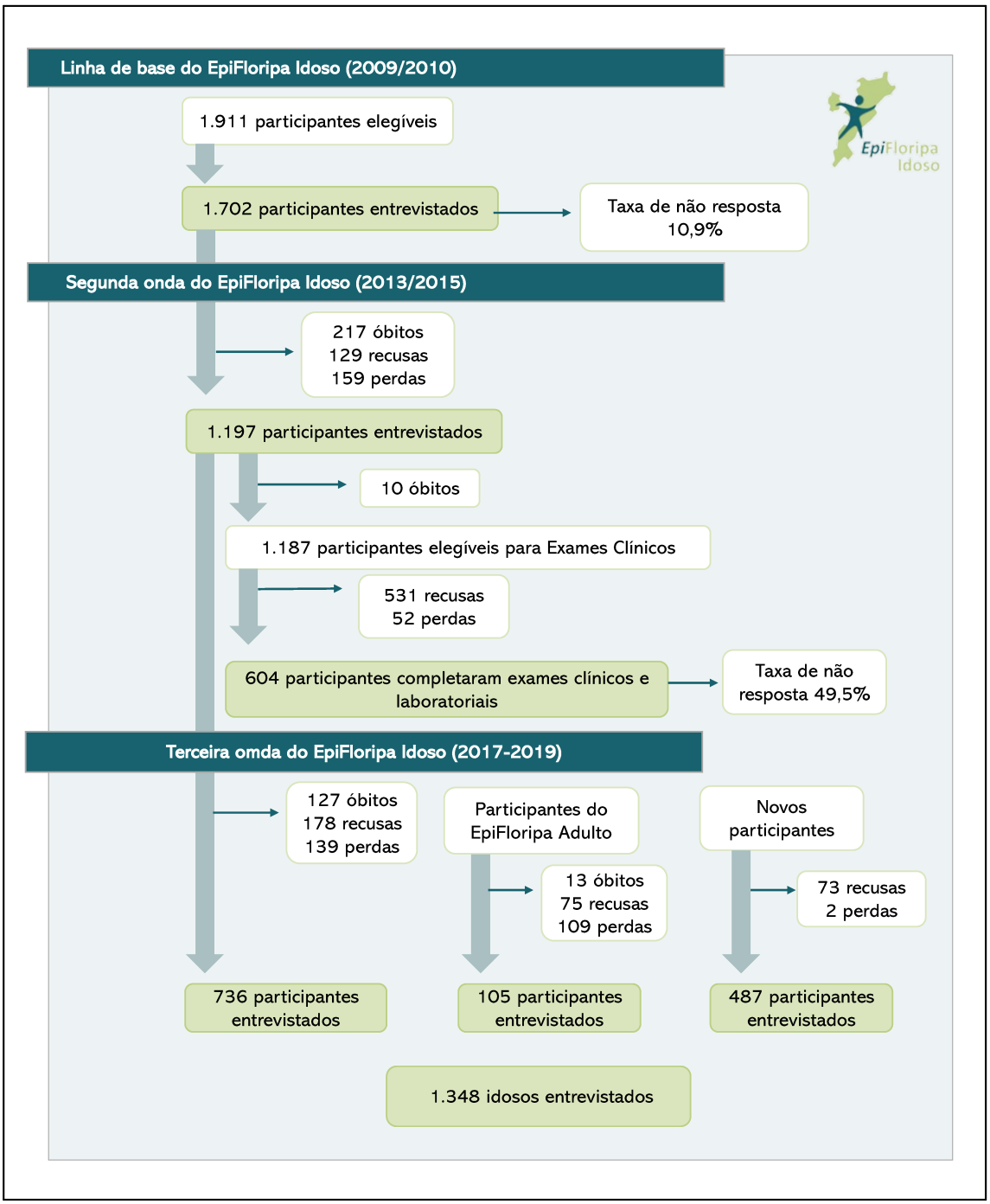
O cálculo da amostra da linha de base do EpiFloripa Idoso, foi realizada com o auxílio do programa Epi Info versão 6.04, com base no cálculo de prevalência, referente à estimativa populacional para o ano de 2009 para a população de 60 anos ou mais (44.460 hab.), com um nível de significância de 95%, prevalência desconhecida do fenômeno de 50%, erro amostral de 4%, efeito do delineamento amostral 2%, sendo acrescidos 20% para perdas estimadas e 15% para estudos de associação, resultando em um tamanho amostral de mínimo 1.599 idosos (SCHNEIDER et al., 2017). O processo de amostragem foi realizado por conglomerados, em dois estágios: primeiro o sorteio de setores censitários dos 420 setores censitários urbanos de Florianópolis, 80 foram sorteados sistematicamente, e após sorteio de domicílios (CONFORTIN et al., 2017). Em virtude da disponibilidade de recursos financeiros, a amostra final foi estimada em 1.911 idosos elegíveis (SCHNEIDER et al., 2017).

A amostra da linha de base foi composta por 1.705 idosos efetivamente entrevistados, de ambos os sexos, com 60 anos ou mais completos até o momento da entrevista, considerando o critério de exclusão, para idosos que estivessem institucionalizados (domiciliados em Instituições de Longa Permanência de Idosos - ILPIs, hospitais, presídios) (SCHNEIDER et al., 2017). Para a onda de seguimento 2013-2014, primeiramente foram identificados os óbitos no Sistema de Informações sobre Mortalidade (SIM), do Ministério da Saúde (MS) e após foi realizada busca ativa dos entrevistados em 2009/2010, utilizando o banco de dados existente para captação e atualização dos dados, identificando os elegíveis e realizado o contato para realização do inquérito, resultando num total de 1.197 idosos entrevistados (SCHNEIDER et al., 2017). Todos os idosos foram convidados a participar da segunda etapa, de exames complementares laboratoriais, de imagem, avaliação corporal e teste físicos, nas dependências da Centro de Ciências da Saúde da Universidade Federal de Santa Catarina (CONFORTIN et al., 2019).

Para a onda de seguimento de 2017-2019, da mesma forma que na segunda onda, foram identificados os óbitos no SIM/MS e após foi realizada busca ativa dos entrevistados, resultando em 736 entrevistas do acompanhamento. Devido ao número reduzido de participantes, foram incluídos novos idosos provenientes do estudo EpiFloripa Adulto que completaram 60 anos e foram sorteados novos domicílios para recompor a amostra representativa, totalizando em 1348 entrevistas (CONFORTIN et al., 2022). Em relação as perdas e recusas, foram consideradas perdas as pessoas não localizadas após quatros visitas ao domicílio, mínimo uma final de semana e uma à noite, mudança de cidade ou hospitalização e

a recusa considerada a resposta de não interesse em participar (SCHNEIDER et al., 2017). Um fluxograma da composição da amostra de cada onda do inquérito EpiFloripa Idoso é representado na figura 7.

Figura 7 - Fluxograma da composição da amostra do estudo EpiFloripa Idoso



Fonte: adaptado de d'Orsi et al., (2020)

A amostra que compôs a presente tese, incluiu idosos participantes das três ondas de pesquisa, sendo que da terceira onda (2017/2019), foram incluídos apenas os idosos do acompanhamento (736 participantes).

3.4 PROCEDIMENTOS ÉTICOS DA PESQUISA

O EpiFloripa Idoso atendeu os preceitos éticos, conforme a Resolução nº 466 de 2012, do Conselho Nacional de Saúde, aprovado pelo Comitê de Ética em Pesquisa com Seres Humanos (CEPSH) da UFSC, em 2009-2010 pelo protocolo número 352/2008 (Anexo 1); em 2013-2014 pelo CAAE 16731313.0.0000.0121 e parecer número 526.126 e; e em 2017-2019 pela emenda sob o parecer número 1.957.977.

Em cada entrevista, o entrevistador explicou os objetivos da pesquisa, os procedimentos a serem realizados e as dúvidas foram esclarecidas. O entrevistado consentiu a participação através da assinatura do Termo de Consentimento Livre e Esclarecido-TCLE (Anexo 2) em todas as ondas, sendo entregue uma cópia ao entrevistado e outra com arquivada na sede do estudo. Em caso de vulnerabilidade, o responsável legal assinou o termo. O TCLE garantiu a confidencialidade das informações, participação voluntária e a possibilidade de deixar o estudo a qualquer momento, sem necessidade de justificativa.

3.5 PROCESSO DE COLETA DE DADOS

A coleta de dados do EpiFloripa Idoso da primeira onda foi realizada no período de setembro de 2009 a junho de 2010, a segunda onda foi realizada no período de dezembro de 2013 a outubro de 2014, sendo a coleta de exames no período de março de 2014 a março de 2015, e ainda a coleta de dados da terceira onda foi realizada entre outubro de 2017 a dezembro de 2019.

O questionário para coleta de dados foi elaborado em 2009-2010 e reestruturado para as ondas de seguimento pela equipe de trabalho do EpiFloripa Idoso. É estruturado em blocos de questões, contemplando diversas áreas do conhecimento e de acordo com o interesse dos pesquisadores participantes e permitindo a avaliação e acompanhamento longitudinal dos entrevistados (disponíveis em: https://epifloripaidoso.paginas.ufsc.br/). Para cada estudo/produto da tese foram descritas no método correspondente, as variáveis, a forma de operacionalização e análise de acordo com o objetivo definido, na seção de resultados.

Equipe de trabalho

A equipe de trabalho do EpiFloripa Idoso foi variável ao longo dos anos de coleta, porém é composta por estudantes de Pós-Doutorado, Doutorado, Mestrado, alunos da Graduação, dos Departamentos de Saúde Coletiva, Ciências Médicas, Educação Física,

Nutrição e Fonoaudiologia da Universidade Federal de Santa Catarina, bem como uma equipe de entrevistadores composta preferencialmente por profissionais da saúde.

O Grupo de Pesquisa é coordenado pela Professora Doutora Eleonora d'Orsi, do Departamento de Saúde Pública da UFSC e sub foi coordenado pelo Professor Cassiano Ricardo Rech, do Departamento de Educação Física durante a terceira onda. Contudo, a equipe de pesquisa também é composta por professores colaboradores dos Departamentos de Saúde Coletiva, Nutrição e Educação Física da UFSC, da Universidade do Sul de Santa Catarina, da Universidade de São Paulo e da *University College London*.

Treinamento e realização do inquérito

A etapa de treinamento para a equipe de entrevistadores para ambas as ondas de coleta foi realizada por uma equipe de supervisores, composta por mestrandos e doutorandos, juntamente com coordenadora de pesquisa. Para onda 3 foi construído um manual do entrevistador, com o intuito de orientar os entrevistadores em relação às características gerais da pesquisa, postura profissional, material de trabalho, bem como apoiar as atividades de coleta de dados (D'ORSI et al., 2017). Primeiramente foram divulgadas as vagas para entrevistadores e feita uma seleção por meio de entrevista, depois realizada a apresentação geral do projeto, trabalho de campo, instrumento e manual de instruções, e após um treinamento prático com mensuração de medidas, instruções sobre cuidado do preenchimento do questionário e manuseio dos equipamentos. Ao final do treinamento foi aplicado um teste para seleção dos entrevistadores para realizarem a harmonização de medidas antropométricas. A harmonização foi realizada pela equipe, guiada por um profissional com experiência em medidas, sendo designado como padrão ouro. Os entrevistadores foram treinados e a para a harmonização foi avaliado a diferença de medidas do entrevistador em relação a próprias medidas repetidas e em relação ao padrão ouro.

Os entrevistadores receberam uma balança digital, com uma precisão de 100 gramas, calibrada antes do trabalho de campo e a cada seis meses pelo INMETRO, para mensurar o peso, a ser posicionada em uma superfície lisa e plana. O avaliado foi posicionado em posição ortostática e olhando para um ponto fixo a frente, descalço, com roupas leves, sem adornos. Para a medida da estatura foi utilizado um estadiômetro portátil, desenvolvido especificamente para o estudo, com graduação de 1mm, em duplicata, onde o avaliado foi posicionado em posição ortostática (em pé, posição ereta, pés afastados à largura do quadril, em equilíbrio, distribuindo igualmente a sua massa corporal sobre seus membros inferiores, posicionando a cabeça no Plano Horizontal de Frankfurt, braços livremente soltos ao longo do tronco, com as

palmas das mãos voltadas para as coxas). Para as medida de circunferência da cintura utilizou-se uma fita flexível e inextensível de 160 cm de comprimento, com o participante em posição ereta, olhar no horizonte, com os pés levemente separados na largura dos quadris e os braços cruzados à frente do corpo, preferencialmente no peito, mensurando o ponto médio entre a última costela e a crista ilíaca (LOHMANN; ROCHE; MARTORELL, 1988).

Também como parte do treinamento, os entrevistadores realizaram uma entrevista supervisionada com idosos não participantes da pesquisa, a fim de testar o programa desenvolvido para aplicação do instrumento, a compreensão das questões por parte dos entrevistados, a qualidade das informações coletadas, padronização da coleta de dados, e minimização de possíveis erros e ações que pudessem comprometer a coleta. Para a onda de 2013-2014 foi realizado um estudo piloto com idosos não pertencentes a amostra, a fim de testar o inquérito e realizar possíveis modificações no questionário.

A pesquisa foi amplamente divulgada para a população, as entrevistas foram agendadas previamente e cada entrevistador recebeu um kit com materiais e instrumentos para aferição das medidas e um *netbook/notebook* com o questionário em programação. Cada entrevistador foi designado a um supervisor a fim de auxiliar e coordenar o trabalho de campo, a conferência e a transferência dos dados coletados para a central. Ao final de cada entrevistas, os entrevistadores revisavam o processo de salvamento dos dados (*netbook/notebook*, pasta compartilhada do *dropbox* e *pendrive*).

Em relação ao controle de qualidade, o questionário incluiu instrumentos validados, preferencialmente entrevistadores estudantes ou formados da área da saúde e com experiência em pesquisa. Para o recebimento de entrevistas foi criada uma equipe de recebimento de dados, realizando a verificação das inconsistências previamente a consolidação do banco de dados. Os dados eram entregues e analisados semanalmente, sendo que dados faltantes ou respostas incongruentes foram verificadas pelos pesquisadores juntamente com os entrevistadores realizando as modificações necessárias. Por fim, foi realizada uma aplicação da versão resumida do instrumento de coleta por telefone, em aproximadamente 10% da mostra de forma aleatória pelos supervisores, buscando verificar possíveis erros, respostas falsas, concordância nas respostas, postura do entrevistador e a reprodutibilidade das questões.

Coleta de exames complementares

Os exames complementares foram realizados na segunda etapa da segunda onda de pesquisa (2014-2015). Os idosos foram contatados por telefone para agendamento da coleta,

sendo que a ordem das ligações obedeceu à sequência de realização das entrevistas e ao interesse demonstrado pelos idosos em participarem desta etapa.

Os idosos foram orientados em relação ao local de realização e horário, foi fornecido transporte até a universidade e houve a necessidade de jejum de 8 a 10 horas e apresentação de documento oficial de identificação com foto (CONFORTIN et al., 2019). A coleta iniciou pelo material biológico devido o jejum e logo após cada idoso recebeu um café da manhã para o andamento dos próximos exames. A coleta foi realizada no Centro de Ciências da Saúde da Universidade Federal de Santa Catarina (CONFORTIN et al., 2019). Foram colhidas amostras de 30 mL de sangue venoso periférico e as amostras foram imediatamente armazenadas em tubos criogênicos (alíquotas de soro e plasma) em ultra freezer a -80 °C, sendo analisadas entre novembro de 2016 a abril de 2017. Para analisar a vitamina D (25-hidroxivitamina D), foi utilizado o método de Quimioluminescência por Micropartículas - (CMIA)/Liaison (BIANCHI et al., 2012; CONFORTIN et al., 2019; ERSFELD et al., 2004).

Para a avaliação da composição corporal, utilizou-se a densitometria por dupla emissão de raios X (do inglês *Dual Energy X-ray Absorptiometry* - DXA), Modelo Lunar *Prodigy Advance* da *General Electric*, seguindo as recomendações do aparelho/fabricante. A avaliação da atividade física objetiva foi coletada pelo uso do acelerômetro (GT3X e GT3X+, *ActiGraph LLC, Pensacola, FL, EUA*) durante o período de vigília em 7 dias consecutivos no lado direito do quadril com uma cinta elástica, exceto para banho e atividades aquáticas e exceto aqueles com baixa mobilidade (cadeirantes, acamados, com problemas de mobilidade), pescadores (pela realização de atividades aquáticas) e aquele com provável déficit cognitivo (CONFORTIN et al., 2019). Os dados foram analisados por meio do software *ActiLife (ActiGraph*).

Fontes de financiamento

Todas as ondas de coleta de dados do EpiFloripa foram financiadas por órgãos de fomento, sendo para a linha de base (2009-10), pelo Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), sob processo número 69834/20082. Para a onda 2 (2013-15), a coleta de exames recebeu financiamento do CNPq, processo número 475.904/2013-3. E a onda 3 (2017-19), foi viabilizada por financiamento do *Economic and Social Research Council* do Reino Unido, pelo processo número 75/2017.

4. RESULTADOS

Os resultados da tese são apresentados em forma de capítulos, subdivididos em três itens:

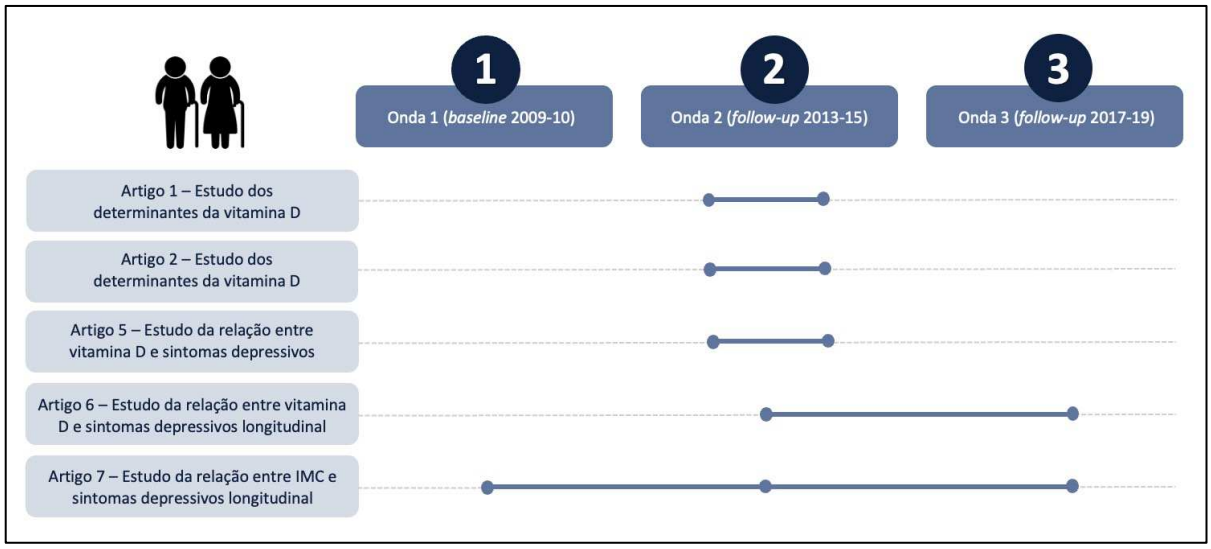
1) Estudo dos determinantes do nível sérico de vitamina D, que gerou a produção de dois artigos;

2) Estudo da associação entre o nível sérico de vitamina D e sintomas depressivos que gerou a produção de três artigos;

3) Estágio de doutorado de sanduíche, no qual são apresentados os dois artigos produzidos na *Queen's University*, em Kingston, ON, Canadá, supervisionado pela Prof. Dra. Elisa Brietzke.

Os artigos com dados provenientes do estudo de coorte EpiFloripa Idoso, utilizaram dados das três ondas de pesquisa de acordo com cada objetivo delineado, conforme apresentado da figura 8:

Figura 8 - Estudos desenvolvidos com dados do EpiFloripa Idoso



Fonte: elaborado pelos autores

Para divulgação dos resultados e devolutiva aos participantes, foram criados a Nota de Imprensa (Apêndice A), Carta aos participantes do EpiFloripa Idoso (Apêndice B) e Post para mídias sociais (Apêndice C).

4.1. CAPÍTULO 1 - ESTUDOS DOS DETERMINANTES DO NÍVEL SÉRICO DA VITAMINA D

Neste capítulo são apresentados os artigos:

Artigo 1 - "*Adiposity and physical activity are among the main determinants of serum vitamin D concentrations in older adults: the EpiFloripa Aging cohort study"* (páginas 68 a 95).
Artigo em apreciação: *Nutrition Research* (Qualis Capes A2, Fator de impacto 3.876).

Artigo 2 - "*The association between physical activity and vitamin D is partially mediated by adiposity in older adults: EpiFloripa Aging Cohort Study*" (páginas 96 a 127).
Artigo publicado: CEOLIN, G. et al. The association between physical activity and vitamin D is partially mediated by adiposity in older adults: EpiFloripa Aging Cohort Study. **Nutrition Research**, p. 1–63, mar. 2022.

4.1.1 Artigo 1

Adiposity and physical activity are among the main determinants of serum vitamin D concentrations in older adults: the EpiFloripa Aging cohort study

Gilciane Ceolin[1,2], Luísa Harumi Matsuo[1], Guilherme Ocker[3], Mateus Grellert[3], Eleonora d'Orsi[4], Débora Kurrle Rieger Venske[2,5], Júlia Dubois Moreira[2,5]

1 Postgraduate Program in Nutrition, Federal University of Santa Catarina, Florianópolis, Brazil.

2 Translational Nutritional Neuroscience Working Group, Federal University of Santa Catarina, Florianopolis, Brazil.

3 Graduate Program in Computer Science (PPGCC), Federal University of Santa Catarina, Florianopolis, Brazil.

4 Department of Public Health, Federal University of Santa Catarina, Florianópolis, Brazil.

5 Postgraduate Program in Nutrition, Department of Nutrition, Federal University of Santa Catarina, Florianopolis, Brazil.

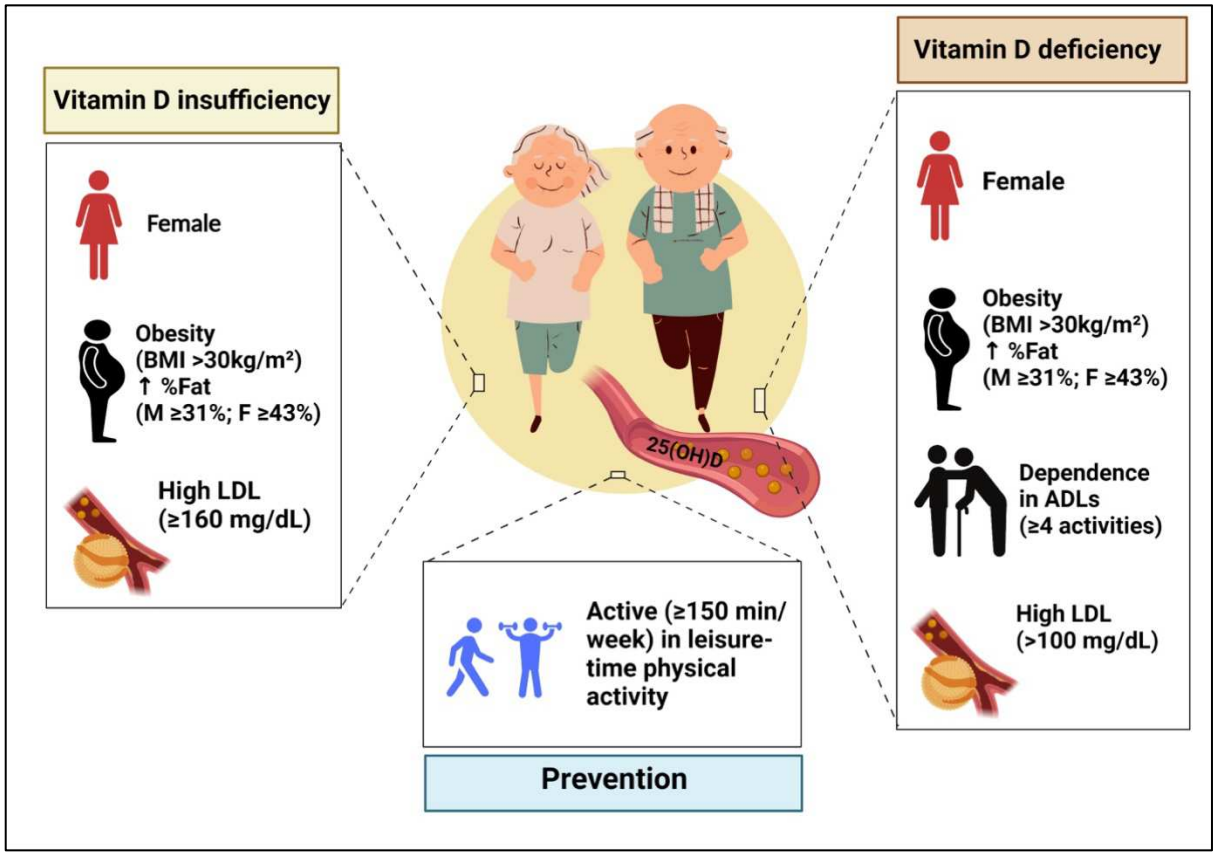
Highlights

- Hypovitaminoses D (≤ 30 ng/ml) was prevalent in more than half of the participants (67.2%)
- Leisure-time physical activity was protective to hypovitaminoses D
- Female had more risk to have hypovitaminoses D compared to Male
- Higher low-density lipoprotein cholesterol and obesity were risk factors for hypovitaminoses D

Abbreviations

%fat, body fat percentage; 25(OH)D, 25-hydroxyvitamin D concentration; 95% CI, 95% confidence interval; ADL, activities of daily living; BMI, body mass index; CRP, C-reactive protein; DXA, dual-energy x-ray absorptiometry; F, female; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PA, physical activity; M, male; MICe, maximum information coefficient; N-3, omega-3; RRR, relative risk ratio; UFSC, Federal University of Santa Catarina.

Graphical Abstract



The multinomial analysis revealed a possible intervention to prevent hypovitaminosis D in older adults. The risk factors to Insufficiency were to be female, obesity (BMI > 30 kg/m2; %Fat to male ≥ 31; female ≥ 43%), and high levels of low-density lipoprotein cholesterol (LDL-C ≥ 160mg/dl). To deficiency, were to be female, obesity (BMI > 30 kg/m2; %Fat to male ≥ 31; female ≥ 43 %), all categories of LDL (>100mg/dL), dependence in activities of daily life (ADL, ≥ 4 activities). Regarding protective factor, being active in leisure-time physical activity (≥ 150 minutes /week) presented less risk to both insufficiency and deficiency.

Abstract

The identification of factors associated with low 25-hydroxycholecalciferol (25(OH)D) concentration can help to suggest more specific interventions for older adults. In this cross-sectional study of older adults from southern Brazil, we hypothesized that some sociodemographic, behavioral, and health factors positively or negatively influence the 25(OH)D concentration in this population. The analysis was performed using data from the second wave of the EpiFloripa Aging Cohort Study (2013–2015). Serum 25(OH)D were classified according to the guidelines of the Endocrine Society. Multinomial logistic regression

was performed to evaluate the relative risks of sociodemographic, behavioral, and health factors in each 25(OH)D category. A total of 574 older adults participated in this study. The prevalence of insufficiency was 43.7%, and that of deficiency was 23.5%. In the adjusted analysis, female sex, higher levels of low-density lipoprotein cholesterol (LDL-C ≥160mg/dL), obesity in body mass index (BMI), and obesity in body fat percentage (%fat) presented higher relative risks for insufficiency than for sufficiency. For those with deficiency, the associated factors were female sex, moderate/severe dependence on activities of daily living (ADLs), all categories of LDL-C, obesity in BMI, and obesity in %fat. A protective factor against insufficiency and deficiency was active leisure-time physical activity (PA). Our results demonstrated that being female and having modifiable factors, such as high levels of LDL-C, obesity, and a higher dependence on ADLs, were negatively associated with hypovitaminosis D. On the other hand, leisure-time PA was positively associated with the adequate serum vitamin D concentration.

Key Words: vitamin D; aging; cross-sectional studies; protective factors; risk factors.

1. Introduction

The importance of vitamin D has been recognized not only for its function in bone homeostasis and skeletal health but also for its involvement in several other extra-skeletal biological mechanisms in the human body [1]. Vitamin D receptors and their metabolic enzymes are widely expressed, and evidence suggests that vitamin D exerts effects in the regulation of cell proliferation, immune system and muscle function, skin differentiation and reproduction, properties of the vascular system, and mental health [1,2].

Due to the importance of vitamin D, low concentration of 25(OH)D (<20 ng/mL) have been implicated in several health conditions and unfavorable skeletal outcomes, especially in older adults, including fractures and bone loss, age-related muscle weakness and sarcopenia, and more recently, an increased risk of mortality and unfavorable respiratory outcomes related to coronavirus 2019 (COVID-19) [3–6]. Since there is evidence of a worldwide prevalence of low 25(OH)D, especially in the older adult population, which is considered an age group at risk for vitamin D deficiency, it has become a critical issue in public health [7].

Previous studies have investigated factors associated with 25(OH)D, but the relative contribution of individual differences in socioeconomic status, behavior, physiological characteristics, and diet to vitamin D status is still not fully understood [8]. Some evidence has indicated that low concentrations of vitamin D have been linked to sunscreen use, air pollution,

dark skin pigmentation, obesity, age, poor socioeconomic status, and seasons leading to less sun exposure [9–11]. Aging can decrease the capacity of the human skin to synthesize 25(OH)D and reduce sun exposure owing to mobility issues [9,12]. In Nordic countries, a low solar incidence during the winter may decrease the concentration of 25(OH)D [13]. Nevertheless, vitamin D insufficiency is also prevalent in Brazil, which is a country with abundant sunlight, and this not support the common assumption that the level of solar radiation in the country ensures an adequate level of vitamin D, suggesting that there may be other factors associated with the level of vitamin D [8,14].

Moreover, there is a lack of data from population-based studies in low- and middle-income countries, which are known to have a higher prevalence of deficiency, requiring the development of further studies [15]. The present study aimed to test the hypothesis that sociodemographic, behavioral, and health factors positively or negatively influence the serum 25(OH)D concentration in older adults. We also aimed to describe the prevalence of the serum 25(OH)D concentrations in older adults from a population-based sample living in an urban community in southern Brazil. Identifying the determinants of 25(OH)D concentration could add to the literature by identifying those at risk of deficiency and developing support strategies to improve the status of vitamin D in older adults.

2. Methods and Material

2.1 Population sample and data collection

This is a cross-sectional study that was carried out with data from the second wave of the study titled, "Conditions of the health of the older adults in Florianopolis - EpiFloripa Aging Cohort Study". It is a population-based, home-based cohort study that evaluates older adults of both sexes aged 60 years and older who are living in the urban area of Florianopolis/Santa Catarina in southern Brazil. Those living in residential aged care facilities, hospitals, and prisons were excluded from the data collection. Further detail regarding the methodology can be found in previous publications [16,17]. Domiciliary data collection was carried out by trained interviewers (face-to-face) using a structured instrument, and the data were recorded using a netbook. Consistency analysis and quality control were conducted by telephone interview through a reduced questionnaire application in 10% of the interviews (selected randomly) [17].

The baseline occurred in 2009/2010, resulting in a sample of 1705 interviews **(Figure 1)**. Follow-up data were collected in 2013–2014, resulting in 1197 interviews (retention rate of

70.2%). All older adults who participated in the second follow-up were invited to undergo physical tests and complementary examinations, including biochemical blood analysis, collected between 2014–2015, at the *Universidade Federal de Santa Catarina* (UFSC) [16]. This resulted in a sample size of 604 participants (retention rate of 50.5%). For the analysis of the present study, we excluded 28 individuals who did not present complete data for the measurement of 25-hydroxy-cholecalciferol and two who presented outlier results in a sample of 574 individuals.

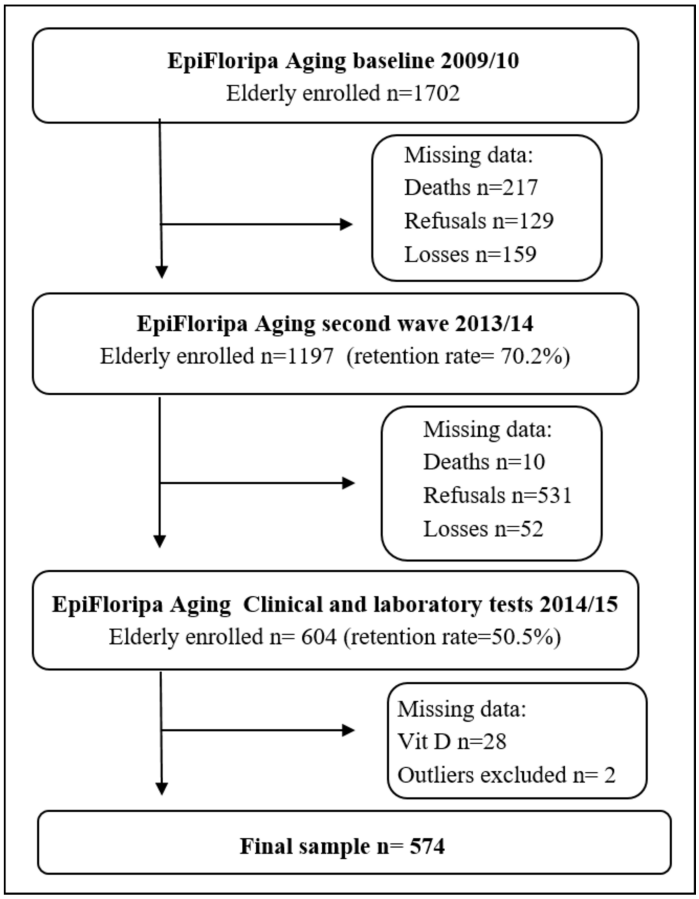


Figure 1. Flowchart sample of EpiFloripa Aging study 2013–2015.

EpiFloripa Aging Study baseline started in 2009–2010. There was a second wave in 2013–2014. All participants were invited to participate in the collection of clinical and laboratory tests in 2014–2015.

2.2 Measurements

Vitamin D

Blood samples were collected at the Laboratory of Metabolism and Dietetics of the UFSC and analyzed at the Laboratory of Clinical Analysis of the University Hospital [16]. Each participant was asked to fast for 8–10 h before blood collection was performed, during which 30 mL of peripheral venous blood was collected. The serum 25(OH)D concentrations

were measured using a Microparticle Chemiluminescence LIAISON® (DiaSorin, São Paulo, SP, Brazil) [18]. LIAISON® is a rapid, accurate, and precise assay (functional sensitivity, ≤2.0 ng/mL; inter-assay imprecision, <20%) [19]. Since 2014, LIAISON® has received certification for total 25-hydroxyvitamin D assays from the Vitamin D Standardization Certification Program by the Centers for Disease Control and Prevention (CDC/VDSCP) [20].

Blood samples were centrifuged at 3,500 rpm for 10 min. The serum samples were immediately processed according to the manufacturer's instructions [19]. In this method, an antibody specific to vitamin D was coated with magnetic particles, and 25(OH)D was conjugated to an isoluminol derivative and diluted in phosphate buffer (pH 7.4). In the first incubation period, 25(OH)D dissociated from the binding protein and interacted with the antibody. In the second incubation, which was performed with the tracer reagent, the microplate was washed with the buffer, and starter reagents were added to generate the chemiluminescent signal, which was measured by a photomultiplier [19].

25(OH)D was categorized according to the Endocrine Society reference values as follows [21]: sufficiency (≥30 ng/mL), insufficiency (21–29 ng/mL), and deficiency (≤ 20 ng/mL).

Covariates

The covariates included sociodemographic, behavior-modified, and health status variables. Sociodemographic covariates were sex (male/female), skin color (white/others), season during blood collection (summer, spring, autumn, and winter), age range (60–69; 70–79; ≥80 years), education (0–8; 9–11; ≥ 12 years), and per capita family income in minimum wages according to the values in 2013 and 2014 (R$ 678 and R$ 724, respectively) (≤1 and >1; ≤3 and >3; ≤5 and >5; ≤10 minimum wages).

Behavioral modified factors included smoking habit (no; yes), alcohol consumption (no; yes) collected by the Alcohol Use Disorder Identification Test [22]; leisure-time PA (inactive, <10; insufficiently active, <150; sufficiently active, ≥150 minutes) collected by the International Physical Activity Questionnaire [23,24]; N-3 rich-fish weekly consumption (none; once or more) was collected by a frequency questionnaire created and based on a food composition table and studies conducted at the national and regional levels [25–27]. The list of fish included salmon, tuna, sardines, anchovies, trout, corvina*, cascudo, pintado,* and *traíra*. Vitamin D supplement intake was collected at the conference of all boxes of medicines prescribed and used by the participants. Anatomical Therapeutic Chemical Classification codes from the World Health Organization Collaborating Centre for Drug Statistic Methodology were applied for classification in the database [28].

Information related to health status included dependence on ADLs [no disability; low disability (any level of disability in one to three activities), and moderate/severe disability (any level of disability in four or more activities)], which were collected by the scale of daily personal and instrumental activities [29]. The metabolic variable include low-density lipoprotein cholesterol (LDL-C: optimal, <100 mg/dL; near optimal/above optimal, 100/129 mg/dL; borderline high, 130/159 mg/dL; high, 160/189 mg/dL; very high, ≥190 mg/dL), high-density lipoprotein cholesterol (HDL-C: low, <40 mg/dL; borderline high, 40/60 mg/dL; desirable, >60 mg/dL), cholesterol (desirable, <200 mg/dL; borderline high, 200/239 mg/dL; high, ≥240 mg/dL), triglycerides (optimal, <150 mg/dL; borderline high, 150/200 mg/dL; high, 201/499 mg/dL; very high, ≥500 mg/dL), and C-reactive protein (CRP: low risk, <1.0 mg/L; average risk, 1.0/3.0 mg/L; high risk, >3.0 mg/L) [30,31].

Body mass index (BMI) was calculated using the measured body weight (kg) and height (m), and it was classified by the World Health Organization guidelines: underweight, <18.5 kg/m²; normal weight, 18.5/24.9 kg/m²; overweight, 25/29.9 kg/m²; and obesity, ≥30 kg/m² [32]. Body composition was assessed to determine relative body fat percentage (% fat) using a dual emission densitometer with x-rays (DXA, Lunar Prodigy Advance, General Electric, Madison, WI, USA) following the manufacturer's instructions [33]. Body fat percentage (% fat) was categorized based on fat mass (kg) following the classification of 60 years or over to male (M) and female (F): underweight, M <13, F <25; normal weight, M 13–24.9, F 25–37.9; overweight, M 25–30.9, F 38–42.9; obesity, M ≥31, F ≥43 [16,34].

2.3 Statistical analyses

A descriptive analysis of the data is presented as the absolute and relative frequencies for the total sample. The distribution of covariates was determined using the chi-squared test and Fisher's exact test. To verify the mean differences in serum 25(OH)D concentrations between sexes and depressive symptoms, we performed Student's t-test. To assess the correlation between the independent (input) variables and the 25(OH)D outcome, three metrics were used: Pearson, Spearman's rank, and maximum information coefficient (MICe). The MICe is a metric that measures the dependency between two variables and is capable of modeling nonlinear relationships (e.g., periodic and logarithmic), even when they are not monotonic. Therefore, MICe can detect a broader range of dependencies than Pearson and Spearman [35].

Logistic multinomial regression was used to evaluate the relative risks (RR) for the 25(OH)D category and the respective 95% confidence intervals (CI) in the unadjusted and adjusted models. The covariates presenting a *P*-value of <0.25 in the univariate regression following a hierarchical model (socioeconomic covariates, followed by behavioral covariates and health covariates) were included in the adjusted analysis. Using the backward method, the covariates that obtained a *P*-value of <0.20 were kept in the model. Model 1 was adjusted for demographic and socioeconomic variables (season, sex, skin color, age range, and family income). Model 2 included demographic, socioeconomic, and behavioral variables (leisure-time physical activities, vitamin D supplementation, and consumption of n-3-rich fish). Model 3 included demographic, socioeconomic, behavioral, health variables, and metabolic/inflammatory markers (dependence on ADLs, BMI, %fat, and LDL-C). We excluded supplement intake and underweight category in BMI and %fat from the analysis because, in the deficiency category of 25(OH)D, there were few observations (only vitamin D, n = 3; calcium combined with vitamin D, n = 4), BMI underweight category (n = 7), and %fat underweight category (n = 6).

The analysis was performed using the Stata 14.0 software (StataCorp, College Station, TX, USA). We considered the effect of the sample design by conglomerates and the sample weight using the command "*svy"*. A significance level of 5% was considered for all analyses. Correlation and MICe analyses were performed using Python 3 on the Google Compute Engine backend (Google Colab). The libraries used were scipy stats (pearsonr, spearmanr) [36] and minepy Maximal Information-based Nonparametric Exploration (MINE) for the MICe analisys [37]. For the MICe analysis, alpha = 0.65, c = 15 were used as the parameters, and "mic_approx" was used as an estimator [38].

2.4 Ethical approval

All procedures in the EpiFloripa Aging Cohort Study were conducted in accordance with the Declaration of Helsinki. The human research ethics committee of the *Universidade Federal de Santa Catarina* (approval protocol numbers: 329.650 and 526.126) approved the data collection for the second wave of follow-up. The voluntary participation of the individuals consented through the signing of the Informed Consent Term after explanation of the study objectives and collection procedures.

3. Results

The characteristics of the cohort are listed in **Table 1**. In the total sample of 574 older adults, the prevalence of insufficiency was 43.7%, the prevalence of deficiency was 23.5%, and blood samples were collected during winter (48.9%). We observed a statistically significant difference in each category of 25(OH)D for season, sex, per capita family income, supplementation, leisure-time PA, dependence on ADLs, cholesterol, LDL-C, supplementation use, smoking habits, BMI, and %fat ($p < 0.05$).

Table 1. Sample characterization according to demographic, socioeconomic, behavioral, and health variables and metabolic/inflammatory markers stratified by 25(OH)D. EpiFloripa Aging study, Florianopolis, Santa Catarina, Brazil, 2013–2015.

			Serum 25(OH)D						
	Total		Sufficiency		Insufficiency		Deficiency		
	n	%	n	%	n	%	n	%	*P*
Season									<0.001
Summer	37	7.7	12	7.7	15	8.0	10	7.3	
Spring	86	16.4	24	12.9	36	16.8	26	20.4	
Winter	303	48.9	127	64.6	131	47.2	45	30.0	
Autumn	148	27.0	28	14.8	67	28.0	53	42.3	
Sex									<0.001
Male	199	33.2	90	45.9	69	27.1	40	26.9	
Female	375	66.8	101	54.2	180	72.9	94	73.1	
Age range (years)									0.115
60-69	243	42.0	85	43.7	110	42.7	48	36.6	
70-79	239	41.6	81	40.6	103	44.4	55	39.7	
≥ 80	92	16.4	25	15.7	36	12.9	31	23.7	
Skin Color									0.195
White	469	83.4	166	87.3	200	80.5	103	83.5	
No white	90	16.6	23	12.7	44	19.5	23	16.5	
Education (years)									0,057
0-8	348	61,1	107	57,0	152	59,2	89	70,5	
9-11	87	14,9	26	12,2	38	17,0	23	14,5	
≥ 12	138	24,0	58	30,8	59	23,8	21	15,0	
Per capita family income (mw)									0,010
≤ 1	44	7,6	10	4,4	19	7,4	15	12,8	
>1 and ≤ 3	159	29,1	47	23,7	73	31,6	39	32,4	
>3 and ≤ 5	113	21,1	37	21,8	56	23,6	20	15,1	
>5 and ≤ 10	138	23,9	45	23,1	54	20,9	39	30,7	

>10	100	18,3	48	26,9	38	16,5	14	9,0	
Vitamin D supplement use									0.011*
None	518	90.4	165	87.9	226	90.0	127	94.7	
Yes (only vit D)	35	6.2	21	9.8	11	5.5	3	2.4	
Yes (calcium+vit D)	20	3.4	5	2.4	11	4.4	4	2.9	
Alcohol Consumption									0.485
No	332	59.7	106	56.8	142	58.6	84	66.0	
Moderate	158	27.0	51	27.3	73	27.9	34	24.8	
High	84	13.3	34	16.0	34	13.5	16	9.1	
Smoking									0.042
Never	363	63.5	113	59.5	167	66.5	83	63.3	
Smoked and stopped	171	30.1	69	35.7	66	27.4	36	27.2	
currently smokes	40	6.4	9	4.8	16	6.1	15	9.5	
Leisure-time PA									<0.001
Inactive	311	55.2	84	43.4	145	58.7	82	65.5	
Insufficiently active	100	17.5	30	16.1	44	18.2	26	18.2	
Active	162	27.3	76	40.5	60	23.2	26	16.3	
Weekly consumption of n-3 rich fish									0.425
No	279	48.2	88	44.5	118	46.6	73	56.5	
Once	153	27.7	51	26.9	66	27.8	36	28.5	
Twice or more	141	24.1	52	28.6	64	25.5	25	15.0	
Dependence in ADLs									<0.001
None	207	35.8	83	44.1	96	38.3	28	19.3	
Low (1-3)	218	37.6	67	33.7	98	39.1	53	40.3	
Moderate/severe (4+)	146	26.7	40	22.2	55	22.7	51	40.4	
Cholesterol (mg/dL)									<0.001
Desirable <200	378	65.0	145	75.8	162	61.7	71	55.7	
Borderline high 200-239	136	24.5	31	16.5	58	26.2	47	32.6	
High >240	60	10.6	15	7.6	29	12.1	16	11.7	
HDL-C (mg/dL)									0.608
Desirable >60	122	21.0	38	20.0	60	23.3	24	18.0	
Low <39	151	26.0	53	27.9	60	23.2	38	28.4	
Borderline high 40-60	301	53.0	100	52.1	129	53.5	72	53.6	
LDL-C (mg/dL)									0.001

Optimal <100	180	31.5	77	42.5	77	28.2	26	22.2	
Near optimal 100-129	189	32.7	63	31.6	82	33.9	44	32.0	
Borderline high 130-159	133	23.6	36	19.7	53	22.7	44	30.6	
High/very high ≥160	72	12.2	15	6.2	37	15.1	20	15.3	
Triglycerides (mg/dL)									
Optimal <150	421	73.0	148	76.7	183	73.5	90	67.0	0.355
Borderline high 150-200	98	16.8	29	14.4	43	16.9	26	20.1	
High ≥201	54	10.2	14	9.0	23	9.6	17	12.9	
CRP (mg/L)									0.616
Low risk <1	172	33.2	63	37.8	75	34.3	34	24.9	
Average risk 1-3	204	37.9	65	34.9	87	39.1	52	39.9	
High risk >3	155	28.8	48	27.3	67	26.6	40	35.2	
BMI by WHO (kg/m²)									0.013*
Underweight <18.4	7	1.1	2	1.4	3	0.5	2	1.7	
Normal 18.4-24.9	155	27.7	64	35.1	56	23.6	35	24.9	
Overweight 25-29.9	230	41.2	82	43.9	105	42.1	43	35.5	
Obesity >30	175	30.0	42	19.6	84	33.7	49	37.8	
BMI by NSI (kg/m²)									0.001
Underweight <22	49	8,6	17	10,4	16	05,6	16	10,9	
Normal 22-27	259	46,5	107	57,1	113	45,8	39	34,0	
Overweight >27	259	44,9	66	32,5	119	48,6	74	55,1	
%fat									0.009
Underweight M <13; F <25	18	2.8	6	3.9	6	0.8	6	0.5	
Normal M 13-24.9; F 25-37.9	144	25.7	59	34.0	59	24.3	26	16.2	
Overweight M 25-30.9; F 38-42.9	163	30.4	65	33.9	68	29.7	30	26.5	
Obesity M ≥31; F ≥43	242	41.0	61	28.0	144	45.1	67	52.2	
Serum 25(OH)D (ng/mL)	-	-	191	32.9	249	43.7	134	23.5	

Sufficiency (≥ 30 ng/mL), Insufficiency (21–29 ng/mL), Deficiency (≤ 20 ng/mL). PA, physical activity; ADLs, activities of daily living; BMI, Body Mass Index; CRP, C-reactive protein; LDL-C; low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; %fat, body fat percentage; M, male; F, female; CI confidence interval; *P*-value, statistical significance; * *P*-value of Fisher's exact test.

In **Figure 2** (also see **Supplementary Table 1**), we present the correlation between the 25(OH)D levels and sociodemographic, behavioral, and health factors. All variables presented a weak correlation with the serum 25(OH)D concentration. However, the MICe method detected a higher correlation than did the other methods.

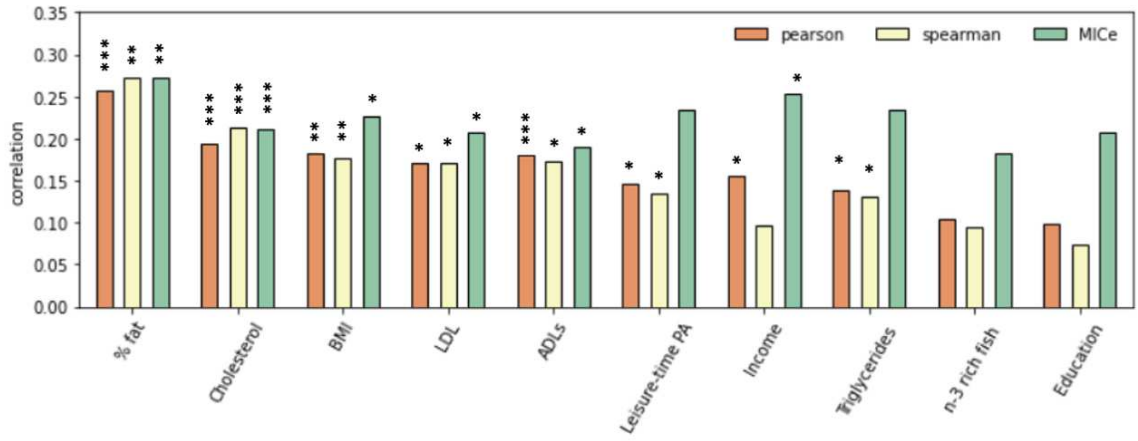


Figure 2. Correlation between Vitamin D and the socio-demographic, behavioral, and health factors, using different methods.

To assess the correlation between the factors and Vitamin D [25(OH)D], the Pearson, Spearman's correlation, and maximum information coefficient (MICe) were used. %Fat, body fat percentage; BMI, body mass index; LDL-C, low-density lipoprotein cholesterol; ADLs, activities of daily life; PA, physical activity; n-3, omega-3; * P > 0.05; **P = 0.001; ***P > 0.001.

Table 2 presents the crude analysis for each 25(OH)D category. We observed a statistically significant higher relative risk ($p < 0.005$) for both insufficiency and deficiency in 25(OH)D for females, to those with higher LDL-C levels, those with obesity by BMI, and those with obesity by %fat. In the deficiency category, the variables that presented a higher relative risk were the autumn season, a borderline high cholesterol, and all categories of LDL-C and ADLs. On the other hand, the variable that presented a low relative risk (protective factor) to vitamin deficiency, the consumption of n-3-rich fish to those that have a consumption of twice a week or more, and for both insufficiency and deficiency of vitamin D, those that were active in leisure-time PA and in those that had a per capita family income in the category of >3 and ≤5 and >10 minimum wages ($p > 0.006$) and 12 or more years of education.

Table 2. Unadjusted Multinomial Logistic Regression of determinants of 25(OH)D in older adults of EpiFloripa Aging. Florianopolis, Southern Brazil, 2013-2015.

Variables	Serum 25(OH)D						
	Sufficiency	Insufficiency			Deficiency		
		RR	95%CI	P	RR	95%CI	P
Model 1							
Season							
Summer	1	-	-	-	-	-	-
Spring	-	1.24	0.39;3.93		1.67	0.50;5.52	
Winter	-	0.70	0.26;1.92	0,294	0.49	0.16;1.50	0.038
Autumn	-	1.82	0.68;4.86		3.03	1.11;8.29	
Sex							
Male	1	-	-	-	-	-	-
Female	-	2.28	1.49;3.48	<0.001	2.30	1.42;3.72	0.001
Age range (years)							
60-69	1	-	-	-	-	-	-
70-79	-	1.12	0.68;1.83	0.822	1.17	0.68;2.00	0.122
≥ 80	-	0.84	0.43;1.65		1.80	0.85;3.83	
Skin Color							
White	1	-	-	-	-	-	-
No white	-	1.67	0.82;3.37	0.152	1.36	0.55;3.37	0.497
Education (years)							
0-8	1	-	-	-	-	-	-
9-11	-	1.34	0.70;2.57	0.281	0.96	0.44;2.08	0.010
≥ 12	-	0.74	0.46;1.19		0.39	0.19;0.80	
Per capita family income (mw)							
≤ 1	1	-	-	-	-	-	-
>1 and ≤ 3	-	0.80	0.32;2.00		0.47	0.17;1.33	
>3 and ≤ 5	-	0.65	0.26;1.63	0.007	0.24	0.08;0.75	0.006
>5 and ≤ 10	-	0.54	0.21;1.39		0.46	0.15;1.39	
>10	-	0.37	0.13;1.02		0.12	0.03;0.47	
Model 2							
Alcohol Consumption							
None	1	-	-	-	-	-	-
Moderate	-	0.99	0.64;1.53	0.569	0.78	0.47;1.30	0.096
High	-	0.82	0.46;1.49		0.49	0.21;1.17	
Smoking							
Never	1	-	-	-	-	-	-
Smoked and stopped	-	0.69	0.40;1.13	0.360	0.71	0.41;1.24	0.897
currently smokes	-	1.14	0.46;2.78		1.85	0.70;4.89	
Leisure-time PA							
Inactive	1	-	-	-	-	-	-
Insufficiently active	-	0.83	0.47;1.47	0.001	0.75	0.40;1.42	<0.001
Active	-	0.42	0.26;0.68		0.27	0.16;0.46	

Weekly consumption of n-3 rich fish							
No	1	-	-	-	-	-	-
Once	-	0.99	0.58;1.67	0.605	0.83	0.44;1.59	0.023
Twice or more	-	0.85	0.47;1.53		0.41	0.20;0.84	
Model 3							
Dependence in ADLs							
None	1	-	-	-	-	-	-
Low (1-3)	-	1.34	0.80;2.23	0.459	2.74	1.17;6.42	0.000
Moderate/severe (4+)	-	1.18	0.66;2.11		4.16	1.91;9.06	
Cholesterol (mg/dl)							
Desirable <200	1	-	-	-	-	-	-
Borderline high 200-239	-	1.94	0.99;3.80	0.024	2.68	1.44;4.99	0.004
High >240	-	1.95	0.86;4.44		2.08	0.87;4.97	
HDC (mg/dL)							
Desirable >60	1	-	-	-	-	-	-
Low <39	-	0.71	0.34;1.50	0.826	1.13	0.51;2.50	0.755
Borderline high 40-60	-	0.88	0.50;1.55		1.14	0.53;2.47	
LDL-C (mg/dL)							
Optimal <100	1	-	-	-	-	-	-
Near optimal 100-129	-	1.61	0.89;2.93	0.005	1.94	1.10;3.41	<0.001
Borderline high 130-159	-	1.74	0.84;3.62		2.99	1.59;5.63	
High/very high ≥160	-	3.70	1.54;8.86		4.76	2.05;11.06	
Triglycerides (mg/dL)							
Optimal <150	1	-	-	-	-	-	-
Borderline high 150-200	-	1.22	0.65;2.29	0.596	1.60	0.83;3.10	0.039
High ≥201	-	1.12	0.49;2.54		1.65	0.86;3.18	
CRP (mg/dl)							
Low risk <1	1	-	-	-	-	-	-
Average risk 1-3	-	1.24	0.72;2.13	0.769	1.74	0.95;3.12	0.065
High risk >3	-	1.08	0.57;2.02		1.96	0.96;4.02	
BMI by WHO (kg/m^2)							
Normal 18.4-24.9	1	-	-	-	-	-	-
Overweight 25-29.9	-	1.43	0.87;2.34	0.004	1.14	0.59;2.17	0.004
Obesity >30	-	2.57	1.38;4.80		2.72	1.42;5.23	
% fat							
Normal M 13 to 24.9; F 25 to 37.9	1	-	-	-	-	-	-

Overweight (M 25 to 30.9; F 38 to 42.9)	-	1.22	0.76;1.97	0.002	1.63	0.92;2.89	<0.001
Obesity (M 31≥; F 43≥)	-	2.25	1.32;3.83		3.90	2.07;7.33	

Sufficiency (≥ 30 ng/mL), Insufficiency (21–29 ng/mL), Deficiency (≤ 20 ng/mL). MW, minimum wage; PA, physical activity; ADLs, activities of daily living; BMI, Body Mass Index; LDL-C; low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; %fat, body fat percentage; M, male; F, female; 96%CI confidence interval; *P*-value, statistical significance.

The results of the adjusted analysis are presented in **Table 3**. The association was maintained in both insufficiency and deficiency categories, presenting a higher relative risk for females for the higher level of LDL-C (≥160) and obesity in %fat compared with the reference category; for those in the deficiency category, a moderate/severe dependence for ADLs, all categories for LDL-C, and obesity in BMI. The variables that maintained a protective factor for all 25(OH)D categories were active leisure-time PA. Although the consumption of n-3-rich fish twice a week or more presented a low risk to those in the deficiency category according to the significant 95% confidence interval, the *P*-value was not statistically significant (95% CI: 0.19, 0.87; p = 0.086).

Table 3. Adjusted Multinomial Logistic Regression of determinants of 25(OH)D in older adults of EpiFloripa Aging. Florianopolis, Southern Brazil, 2013-2015.

Variables	**Serum 25(OH)D**						
	Sufficiency	**Insufficiency**			**Deficiency**		
		RR	IC95%	p	RR	95%CI	p
Model 1							
Season							
Summer	1	-	-	-	-	-	-
Spring	-	1.74	0.58;5.23		1.94	0.52;7.23	
Winter	-	0.87	0.32;2.33	0.330	0.57	0.17;1.89	0.052
Autumn	-	2.13	0.84;5.36		3.41	1.16;10.04	
Sex							
Male	1	-	-	-	-	-	-
Female	-	2.20	1.42;3.43	0.001	2.32	1.31;4.09	0.004
Age range (years)							
60-69	1	-	-	-	-	-	-
70-79	-	1.30	0.76;2.20	0.928	1.40	0.73;2.66	0.386
≥ 80	-	0.82	0.38;1.75		1.29	0.56;2.96	
Per capita family income (mw)							
≤ 1	1	-	-	-	-	-	-
>1 and ≤ 3	-	0.95	0.39;2.29	0.162	0.65	0.19;2.15	0.210

>3 and ≤ 5	-	0.79	0.33;1.85		0.32	0.09;1.15	
>5 and ≤ 10	-	0.63	0.25;1.62		0.66	0.20;2.24	
>10	-	0.62	0.22;1.74		0.25	0.05;1.21	
Skin Color							
White	1	-	-	-	-	-	-
No white	-	1.81	0.87;3.77	0.112	1.29	0.53;3.14	0.573
Model 2							
Leisure-time PA							
Inative	1	-	-	-	-	-	-
Insufficiently active	-	0.76	0.44;1.48	0.001	0.73	0.34;1.54	<0.001
Active	-	0.38	0.22;0.65		0.29	0.17;0.54	
Weekly consumption of n-3 rich fish							
No	1	-	-	-	-	-	-
Once	-	1.33	0.76;2.33	0.670	1.31	0.59;2.49	0.086
Twice or more	-	1.21	0.42;1.37		0.41	0.19;0.87	
Model 3							
Dependence in ADLs							
None	1	-	-	-	-	-	-
Low (1-3)	-	0.82	0.44;1.53	0.445	2.73	0.85;5.70	0.033
Moderate/severe(≥4)	-	0.80	0.41;1.47		2.73	1.09;6.82	
LDL-C (mg/dL)							
Optimal <100	1	-	-	-	-	-	-
Near optimal 100-129	-	1.70	0.86;3.36		2.96	1.48;5.91	
Borderline high 130-159	-	1.61	0.73;3.52	0.025	4.56	2.18;9.52	<0.001
High/very high ≥160	-	3.49	1.25;9.74		7.94	3.18;19.82	
BMI by WHO (kg/m²)							
Normal (18.4 - 24.9)	1	-	-	-	-	-	-
Overweight (25 - 29.9)	-	1.62	0.97;2.71	0.013	1.19	0.53;2.63	0.027
Obesity (>30)	-	2.37	1.21;4.64		2.25	1.08;4.71	
%fat							
Normal (M 13 to 24.9; F 25 to 37.9)	1	-	-	-	-	-	-
Overweight (M 25 to 30.9; F 38 to 42.9)	-	1.10	0.62;1.96	0.020	1.48	0.71;3.06	0.002
Obesity (M ≥31; F ≥43)	-	2.10	1.15;3.82		3.62	1.79;7.33	

Sufficiency (≥ 30 ng/mL), Insufficiency (21–29 ng/mL), Deficiency (≤ 20 ng/mL). MW, minimum wage; PA, physical activity; ADLs, activities of daily living; BMI, Body Mass Index; LDL-C; low-density lipoprotein cholesterol; %fat, body fat percentage; M, male; F, female; 96%CI confidence interval; *P*-value, statistical significance.

4. Discussion

This study demonstrated that hypovitaminosis D (deficiency + insufficiency) was prevalent in more than half of the participants (67.2%). Although we observed a weak correlation between 25(OH)D and the continuous variables, the MICe produced a higher correlation than did the other methods. The adjusted analysis demonstrated that females, those with higher levels of LDL-C (≥160 mg/dL), and obesity in %fat were more likely to be at risk for both 25(OH)D deficiency and insufficiency. A moderate/severe dependence for ADLs, all categories for LDL-C, and obesity in BMI demonstrated an association with the risk of deficiency. Being active in leisure-time PA demonstrated a lower risk for both 25(OH)D insufficiency and deficiency.

Data from a meta-analysis of studies with older Brazilian adults also observed a high prevalence of hypovitaminosis that is similar to insufficiency (45.8%) and lower than our study for deficiency (41.5%) [14]. Other studies with representative samples have found variation in the prevalence of deficiency, which is 19.0% in Canada, 34.0% in the United States, 86.0% in Spain, and 52.0% in England [7]. Nevertheless, according to a recent review, trends in 25(OH)D status have improved in the older population in the United States due to dairy fortification and declined in the Inuit population in Canada due to changes in traditional fish intake to a Western diet [11]. Vitamin D food fortification is widely used as a strategy to achieve homeostasis levels; however, in Brazil, this kind of product is expensive, which limits the acquisition of these foods [39].

In addition to the low serum vitamin D level, we observed low use of vitamin D supplements in the sample (6.2%). This is an important fact because there is a high prevalence of hypovitaminosis, and older adults are considered one of the risk groups for low vitamin D levels and its consequences. Indeed, it can lead to low screening, diagnosis, and treatment supplementation. Unfortunately, we were unable to perform a regression analysis of supplement use because of the low number of observations in the sample.

The consumption of n-3-rich fish (twice a week or more) showed a lower risk of deficiency. However, this was not maintained in the adjusted model ($p = 0.05$). The positive association between fish consumption and vitamin D is supported by previous findings in the literature [40,41]. A possible explanation is that n-3-rich fish also have vitamin D content. The fish listed in our questionnaire, such as salmon, tuna, sardines, anchovies, and trout, also have a vitamin D content [42,43]. However, this type of food may be more expensive to purchase on a supermarket shelf and has a high cost in Brazil. Although it was not statistically significant,

we observed a decreasing tendency for the risk of insufficiency and risk of deficiency with an increasing family income.

Another factor that demonstrated a lower risk of hypovitaminosis was leisure-time PA (>150 min/week). This finding is supported by a previous study of our research group that analyzed the same sample; PA was measured by an accelerometer, and moderate and vigorous PA demonstrated a direct and total positive effect on 25(OH)D ($\beta = 0.12$; $p < 0.05$) and was partially mediated by %fat [44]. In addition, other studies have demonstrated either a protective factor from the practice of PA [45,46] or a risk factor from sedentary lifestyle and insufficient PA to 25(OH)D [47,48]. Although we did not investigate whether PA was practiced indoors or outdoors, a possible explanation is that sun exposure in outdoor PA can facilitate 25(OH)D synthesis in the skin. In addition, a decrease in PA or reduction in mobility is usually associated with less time spent outdoors [11], which can be related to a higher risk of deficiency in those with moderate/severe dependence in ADLs in our data. It was postulated that daily exposure to 20% of the body surface is considered sufficient to increase 25(OH)D levels [49].

It is important to note that obesity, measured by both BMI and % fat, demonstrated an increased risk of both insufficiency and deficiency. We also observed this finding in a previous study with a different statistical approach [44], and this also was supported by previous studies in which obesity is associated with lower 25(OH)D in older adults [11,46,48,50]. Some possible explanations have been discussed as a common hypothesis in that adipose tissue storage 25(OH)D decreases the bioavailability in the blood circulation [51] and can also be used for local metabolism [52,53]. The dilution of 25(OH)D according to body size, in that a large fat mass could explain the low concentrations [54]; people with obesity can spend less time outdoors and reduce the skin synthesis of 25(OH)D [11]; and that obesity could reduce the capacity of hepatic conversion of vitamin D due to a decrease in the expression of the main hepatic vitamin D hydroxylase [55].

It was observed that females presented higher prevalence of insufficiency and deficiency, and it was confirmed in the regression that they had a higher risk, by slightly more than two times, than that of insufficiency (RR = 2.28, 95% CI: 1.49, 3.48) and deficiency (RR = 2.30, 95% CI: 1.42, 3.72) compared to males. These findings are consistent with previously reported results [40,45,46]. One hypothesis is that females have a higher prevalence of obesity, which is associated with a lower 25(OH)D [56]. In our sample, females had a higher prevalence (data not shown) of overweight and obesity than the males (61.5% and 77.8%, respectively, $p > 0.001$).

Some studies have investigated the relationship between 25(OH)D and LDL-C; however, the mechanisms underlying this relationship have not yet been established [60]. Cross-sectional studies have demonstrated an inverse association between 25(OH)D and serum lipid levels [61,62], while in a meta-analysis of clinical trials with vitamin D supplementation, it remains controversial because some studies demonstrated an increase in LDL-C [63], whereas others demonstrated a decrease in LDL-C [64]. Interestingly, it was identified an interaction between two key genes in the vitamin D pathway (retinoid X receptor gamma gene [RXRG] and vitamin D-binding protein gene [GC]) and LDL-C levels, linking vitamin D circulating levels to the lipid profile [67]. RXRG is located in a chromosomal region closely related to familial combined hyperlipidemia (FCHL) and is characterized by several hyperlipidemic phenotypes [68]. Also, some authors have been discussing that vitamin D metabolites could regulate positively statin activity due to inducing the enzyme CYP3A4 and CYP2C9, and it could be one of the keys [60].

It is important to mention that our study has some limitations. A possible limitation is the logistics of data collection of blood samples, which were not collected at the same time as the interviews were conducted at the participant's home and were carried out mostly in winter and autumn, which can limit the comparability between the seasons. Blood tests were performed with a part of the total EpiFloripa study sample, and this may have limited some of the analyses, such as the inclusion of supplement use in the regression. Clinical and biochemical examinations were conducted at the university to select individuals with relatively better health conditions than those from the general population. Although we used a technique certified by the CDC/VDSCP for total 25-hydroxyvitamin D assays to measure 25(OH)D, it is wise to consider that it differs from the gold standard [69]. Finally, cross-sectional analyses should be considered with caution because of the methodological limitations inherent to data collection.

Similarly, we need to highlight the strengths of our study. We consider that the sample includes only the elderly since it is a population at risk for low levels of vitamin D and is quite different considering metabolic changes and aspects of the life cycle. The study followed a highly accurate method of data quality, including trained and supervised interviewers, conducting a pilot study, face-to-face interviews, and quality control of the interviews. The method of assessing body fat composition is considered to be the gold standard.

In summary, our study highlights potential risk factors for vitamin D deficiency. We observed that being female and having modifiable factors such as higher levels of LDL-C and obesity to have dependence in more ADLs were positively associated with hypovitaminosis D.

On the other hand, modifiable factors, such as leisure-time PA, were positively associated with adequate concentrations of vitamin D. Despite being an important topic, few studies have investigated the older population and need to be better understood for planning proper protective interventions that help maintain an adequate vitamin D status. Further studies should be encouraged, especially in low- and middle-income countries.

Acknowledgment

The authors have no acknowledgments to declare.

Sources of Support

This study was supported by partnerships with the Federal University of Santa Catarina (UFSC), other research projects, and assistance from students and teachers involved in the research. All infrastructure and instruments needed to carry out the research were made available by the UFSC, with the exception of the netbooks used for data collection, which were provided by the Oswaldo Cruz Foundation in Rio de Janeiro. The stage of collecting clinical and laboratory examinations were financed by the *Conselho Nacional de Desenvolvimento Científico e Tecnológico* (process number 475.904 / 2013-3) and were developed within the scope of the postgraduate program in collective health at UFSC. This study was financed in part by the *Coordenação de Aperfeiçoamento de Pessoal de Nível Superior*/Brazil (finance code 001).

Author Contributions

All authors contributed to the study conception and design and take full responsibility for the integrity of the data and the accuracy of the data analysis. **Gilciane Ceolin**, conceptualization, methodology, formal analysis, writing – original draft, visualization, and validation; **Luísa Harumi Matsuo**, conceptualization, methodology, writing – review and editing, and validation; **Guilherme Ocker**, formal analysis, writing – review and editing, and validation; **Mateus Grellert**, formal analysis, writing – review and editing, and validation; **Eleonora d'Orsi**, funding acquisition, project administration, conceptualization, methodology, investigation, writing – review and editing, and validation; **Débora Kurrle Rieger**, supervision, conceptualization, writing – review and editing, and validation; and **Júlia Dubois Moreira**, supervision, conceptualization, methodology, writing – review and editing, and validation. All authors have read and approved the final manuscript.

Author Declarations

The authors declare no financial support or relationships that may represent any conflicts of interest.

References

[1] Bouillon R, Marcocci C, Carmeliet G, Bikle D, White JH, Dawson-Hughes B, et al. Skeletal and extraskeletal actions of vitamin D: current evidence and outstanding questions. Endocr Rev 2019;40:1109–51. doi: 10.1210/er.2018-00126.

[2] Landel V, Stephan D, Cui X, Eyles D, Feron F. Differential expression of vitamin D-associated enzymes and receptors in brain cell subtypes. J Steroid Biochem Mol Biol 2018;177:129–34. doi: 10.1016/j.jsbmb.2017.09.008.

[3] Luo J, Quan Z, Lin S, Cui L. The association between blood concentration of 25-hydroxyvitamin D and sarcopenia: a meta-analysis. Asia Pac J Clin Nutr 2018;27:1258–70. doi: 10.6133/apjcn.201811_27(6).0013.

[4] Dudenkov DV, Mara KC, Petterson TM, Maxson JA, Thacher TD. Serum 25-hydroxyvitamin D values and risk of all-cause and cause-specific mortality: a population-based cohort study. Mayo Clin Proc 2018;93:721–30. doi: 10.1016/j.mayocp.2018.03.006.

[5] Cesari M, Incalzi RA, Zamboni V, Pahor M. Vitamin D hormone: a multitude of actions potentially influencing the physical function decline in older persons. Geriatr Gerontol Int 2011;11:133–42. doi: 10.1111/j.1447-0594.2010.00668.x.

[6] Dissanayake HA, de Silva NL, Sumanatilleke M, de Silva SDN, Gamage KKK, Dematapitiya C, et al. Prognostic and therapeutic role of vitamin D in COVID-19: systematic review and meta-analysis. J Clin Endocrinol Metab 2022;107:1484–502. doi: 10.1210/clinem/dgab892.

[7] Palacios C, Gonzalez L. Is vitamin D deficiency a major global public health problem? J Steroid Biochem Mol Biol 2014;144 Pt A:138–45. doi: 10.1016/j.jsbmb.2013.11.003.

[8] Mendes MM, Hart KH, Botelho PB, Lanham-New SA. Vitamin D status in the tropics: Is sunlight exposure the main determinant? Nutr Bull 2018;43:428–34. doi: 10.1111/nbu.12349.

[9] Arabi A, El Rassi R, El-Hajj Fuleihan G. Hypovitaminosis D in developing countries—prevalence, risk factors and outcomes. Nat Rev Endocrinol 2010;6:550–61. doi: 10.1038/nrendo.2010.146.

[10] Feizabad E, Hossein-Nezhad A, Maghbooli Z, Ramezani M, Hashemian R, Moattari S. Impact of air pollution on vitamin D deficiency and bone health in adolescents. Arch Osteoporos 2017;12:34. doi: 10.1007/s11657-017-0323-6.

[11] Lips P, de Jongh RT, van Schoor NM. Trends in vitamin D status around the world. JBMR Plus 2021;5:e10585. doi: 10.1002/jbm4.10585.

[12] MacLaughlin J, Holick MF. Aging decreases the capacity of human skin to produce vitamin D3. J Clin Invest 1985;76:1536–8.

[13] Jorde R, Sneve M, Hutchinson M, Emaus N, Figenschau Y, Grimnes G. Tracking of serum 25-hydroxyvitamin D levels during 14 years in a population-based study and during 12 months in an intervention study. Am J Epidemiol 2010;171:903–8. doi: 10.1093/aje/kwq005.

[14] Pereira-Santos M, Santos JYG dos, Carvalho GQ, Santos DB dos, Oliveira AM. Epidemiology of vitamin D insufficiency and deficiency in a population in a sunny country: Geospatial meta-analysis in Brazil. Crit Rev Food Sci Nutr 2019;59:2102–9. doi: 10.1080/10408398.2018.1437711.

[15] Roth DE, Abrams SA, Aloia J, Bergeron G, Bourassa MW, Brown KH, et al. Global prevalence and disease burden of vitamin D deficiency: a roadmap for action in low- and middle-income countries. Ann N Y Acad Sci 2018;1430:44–79. doi: 10.1111/nyas.13968.

[16] Confortin SC, Schneider IJC, Danielewicz AL, Fassula AS, Souza BB de, Santos CES dos, et al. Estudo Longitudinal EpiFloripa Idoso – Rotinas de organização e protocolos referentes à coleta, análise e armazenamento de material biológico, exames de imagem e capacidade físico-funcional. Cad Saúde Coletiva 2019;27:210–24. doi: 10.1590/1414-462x201900020169.

[17] Schneider IJC, Confortin SC, Bernardo C de O, Bolsoni CC, Antes DL, Pereira KG, et al. EpiFloripa Aging cohort study: methods, operational aspects, and follow-up strategies. Rev Saúde Pública 2017;51. doi: 10.11606/s1518-8787.2017051006776.

[18] Bianchi S, Maffei S, Prontera C, Battaglia D, Vassalle C. Preanalytical, analytical (DiaSorin LIAISON) and clinical variables potentially affecting the 25-OH Vitamin D estimation. Clin Biochem 2012;45:1652–7. doi: 10.1016/j.clinbiochem.2012.08.003.

[19] Ersfeld DL, Rao DS, Body J-J, Sackrison JL, Miller AB, Parikh N, et al. Analytical and clinical validation of the 25 OH vitamin D assay for the LIAISON® automated analyzer. Clin Biochem 2004;37:867–74. doi: 10.1016/j.clinbiochem.2004.06.006.

[20] Centers for Disease Control and Prevention. Laboratory quality assurance and standardization programs 2021. https://www.cdc.gov/labstandards/hs_certified_participants.html (accessed March 8, 2021).

[21] Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society

clinical practice guideline. J Clin Endocrinol Metab 2011;96:1911–30. doi: 10.1210/jc.2011-0385.

[22] Babor TF, Higgins-Biddle JC, Saunders JB, Monteiro MG. The alcohol use disorders identification test: guidelines for use in primary care 2001:41.

[23] Benedetti TB, Mazo GZ, Barros MVG de. Application of the International Physical Activity Questionnaire (IPAQ) for evaluation of elderly women: concurrent validity and test-retest reprodutibility. Rev Bras Ciênc Mov 2004;12:25–34.

[24] Benedetti TRB, Antunes P de C, Rodriguez-Añez CR, Mazo GZ, Petroski ÉL. Reproducibility and validity of the International Physical Activity Questionnaire (IPAQ) in elderly men. Rev Bras Med Esporte 2007;13:11–6. doi: 10.1590/S1517-86922007000100004.

[25] Andrade AD (University of M, Rubira AF, Matsushita M, Souza NE. The omega 3 fatty acids in freshwater fish from south Brazil. J Am Oil Chem Soc USA 1995.

[26] Scherr C, Gagliardi ACM, Miname MH, Santos RD, Scherr C, Gagliardi ACM, et al. Fatty acid and cholesterol concentrations in usually consumed fish in brazil. Arq Bras Cardiol 2015;104:152–8. doi: 10.5935/abc.20140176.

[27] Universidade Estadual de Campinas. Brazilian Table of Food Composition (TACO). 4th ed. Campinas: 2011.

[28] World Health Organization. WHOCC - ATC/DDD Index 2022. https://www.whocc.no/atc_ddd_index/ (accessed December 20, 2019).

[29] Rosa TE da C, Benício MHD, Latorre M do RD de O, Ramos LR. Determinant factors of functional status among the elderly. Rev Saúde Pública 2003;37:40–8. doi: 10.1590/S0034-89102003000100008.

[30] Xavier HT, Izar MC, Faria Neto JR, Assad MH, Rocha VZ, Sposito AC, et al. V Diretriz brasileira de dislipidemias e prevenção da aterosclerose. Arq Bras Cardiol 2013;101:1–20. doi: 10.5935/abc.2013S010.

[31] Pearson T. A., Mensah George A., Alexander R. Wayne, Anderson Jeffrey L., Cannon Richard O., Criqui Michael, et al. Markers of inflammation and cardiovascular disease. circulation 2003;107:499–511. doi: 10.1161/01.CIR.0000052939.59093.45.

[32] World Health Organization. Obesity: preventing and managing the global epidemic: report of a WHO Consultation on Obesity 1998.

[33] Genton L, Hans D, Kyle UG, Pichard C. Dual-Energy X-ray absorptiometry and body composition: differences between devices and comparison with reference methods. Nutrition 2002;18:66–70. doi: 10.1016/S0899-9007(01)00700-6.

[34] Gallagher D, Heymsfield SB, Heo M, Jebb SA, Murgatroyd PR, Sakamoto Y. Healthy percentage body fat ranges: an approach for developing guidelines based on body mass index. Am J Clin Nutr 2000;72:694–701. doi: 10.1093/ajcn/72.3.694.

[35] Reshef DN, Reshef YA, Finucane HK, Grossman SR, McVean G, Turnbaugh PJ, et al. Detecting novel associations in large data sets. Science 2011;334:1518–24. doi: 10.1126/science.1205438.

[36] Virtanen P, Gommers R, Oliphant TE, Haberland M, Reddy T, Cournapeau D, et al. SciPy 1.0: fundamental algorithms for scientific computing in Python. Nat Methods 2020;17:261–72. doi: 10.1038/s41592-019-0686-2.

[37] Reshef YA, Reshef DN, Finucane HK, Sabeti PC, Mitzenmacher MM. Measuring dependence powerfully and equitably 2021. doi: 10.48550/arXiv.1505.02213.

[38] Albanese D. A practical tool for Maximal Information Coefficient (MIC) analysis. minepy - Maximal Information-based Nonparametric Exploration (MINE) in C and Python; 2022.

[39] Kimball SM, Holick MF. Official recommendations for vitamin D through the life stages in developed countries. Eur J Clin Nutr 2020;74:1514–8. doi: 10.1038/s41430-020-00706-3.

[40] Lima-Costa MF, Mambrini JVM, de Souza-Junior PRB, de Andrade FB, Peixoto SV, Vidigal CM, et al. Nationwide vitamin D status in older brazilian adults and its determinants: The Brazilian Longitudinal Study of Aging (ELSI). Sci Rep 2020;10:13521. doi: 10.1038/s41598-020-70329-y.

[41] Adebayo FA, Itkonen ST, Lilja E, Jääskeläinen T, Lundqvist A, Laatikainen T, et al. Prevalence and determinants of vitamin D deficiency and insufficiency among three immigrant groups in Finland: evidence from a population-based study using standardised 25-hydroxyvitamin D data. Public Health Nutr 2020;23:1254–65. doi: 10.1017/S1368980019004312.

[42] Giustina A, Adler RA, Binkley N, Bollerslev J, Bouillon R, Dawson-Hughes B, et al. Consensus statement from 2nd International Conference on Controversies in Vitamin D. Rev Endocr Metab Disord 2020;21:89–116. doi: 10.1007/s11154-019-09532-w.

[43] Chen TaiC, Chimeh F, Lu Z, Mathieu J, Person KS, Zhang A, et al. Factors that influence the cutaneous synthesis and dietary sources of vitamin d. arch biochem biophys 2007;460:213–7. doi: 10.1016/j.abb.2006.12.017.

[44] Ceolin G, Confortin SC, da Silva AAM, Rech CR, d'Orsi E, Rieger DK, et al. Association between physical activity and vitamin d is partially mediated by adiposity in

older adults: EpiFloripa Aging cohort study. Nutr Res 2022. doi: 10.1016/j.nutres.2022.03.001.

[45] Duarte C, Carvalheiro H, Rodrigues AM, Dias SS, Marques A, Santiago T, et al. Prevalence of vitamin D deficiency and its predictors in the portuguese population: a nationwide population-based study. Arch Osteoporos 2020;15:36. doi: 10.1007/s11657-020-0695-x.

[46] Aspell N, Laird E, Healy M, Shannon T, Lawlor B, O'Sullivan M. The prevalence and determinants of vitamin d status in community-dwelling older adults: results from the English Longitudinal Study of Ageing (ELSA). Nutrients 2019;11. doi: 10.3390/nu11061253.

[47] Wanner M, Richard A, Martin B, Linseisen J, Rohrmann S. Associations between objective and self-reported physical activity and vitamin D serum levels in the US population. Cancer Causes Control CCC 2015;26:881–91. doi: 10.1007/s10552-015-0563-y.

[48] Brock K, Huang W-Y, Fraser DR, Ke L, Tseng M, Stolzenberg-Solomon R, et al. Low vitamin D status is associated with physical inactivity, obesity and low vitamin D intake in a large US sample of healthy middle-aged men and women. J Steroid Biochem Mol Biol 2010;121:462–6. doi: 10.1016/j.jsbmb.2010.03.091.

[49] Wacker M, Holick MF. Sunlight and vitamin D: A global perspective for health. Dermatoendocrinol 2013;5:51–108. doi: 10.4161/derm.24494.

[50] Pereira-Santos M, Costa PRF, Assis AMO, Santos C a. ST, Santos DB. Obesity and vitamin D deficiency: a systematic review and meta-analysis. Obes Rev Off J Int Assoc Study Obes 2015;16:341–9. doi: 10.1111/obr.12239.

[51] Wortsman J, Matsuoka LY, Chen TC, Lu Z, Holick MF. Decreased bioavailability of vitamin D in obesity. Am J Clin Nutr 2000;72:690–3. doi: 10.1093/ajcn/72.3.690.

[52] Nimitphong H, Park E, Lee M-J. Vitamin D regulation of adipogenesis and adipose tissue functions. Nutr Res Pract 2020;14:553–67. doi: 10.4162/nrp.2020.14.6.553.

[53] Wamberg L, Christiansen T, Paulsen SK, Fisker S, Rask P, Rejnmark L, et al. Expression of vitamin D-metabolizing enzymes in human adipose tissue—the effect of obesity and diet-induced weight loss. Int J Obes 2013;37:651–7. doi: 10.1038/ijo.2012.112.

[54] Drincic AT, Armas LAG, Diest EE van, Heaney RP. Volumetric dilution, rather than sequestration best explains the low vitamin D status of obesity. Obesity 2012;20:1444–8. doi: 10.1038/oby.2011.404.

[55] Roizen JD, Long C, Casella A, O'Lear L, Caplan I, Lai M, et al. Obesity decreases hepatic 25-hydroxylase activity causing low serum 25-hydroxyvitamin D. J Bone Miner Res 2019;34:1068–73. doi: 10.1002/jbmr.3686.

[56] Muscogiuri G, Barrea L, Somma CD, Laudisio D, Salzano C, Pugliese G, et al. Sex differences of vitamin D status across BMI classes: an observational prospective cohort study. Nutrients 2019;11:3034. doi: 10.3390/nu11123034.

[57] Eloi M, Horvath DV, Szejnfeld VL, Ortega JC, Rocha D a. C, Szejnfeld J, et al. Vitamin D deficiency and seasonal variation over the years in São Paulo, Brazil. Osteoporos Int J Establ Result Coop Eur Found Osteoporos Natl Osteoporos Found USA 2016;27:3449–56. doi: 10.1007/s00198-016-3670-z.

[58] van Schoor NM, Knol DL, Deeg DJH, Peters FPAMN, Heijboer AC, Lips P. Longitudinal changes and seasonal variations in serum 25-hydroxyvitamin D levels in different age groups: results of the Longitudinal Aging Study Amsterdam. Osteoporos Int 2014;25:1483–91. doi: 10.1007/s00198-014-2651-3.

[59] Greene-Finestone LS, Berger C, de Groh M, Hanley DA, Hidiroglou N, Sarafin K, et al. 25-Hydroxyvitamin D in Canadian adults: biological, environmental, and behavioral correlates. Osteoporos Int J Establ Result Coop Eur Found Osteoporos Natl Osteoporos Found USA 2011;22:1389–99. doi: 10.1007/s00198-010-1362-7.

[60] Warren T, McAllister R, Morgan A, Rai TS, McGilligan V, Ennis M, et al. The Interdependency and Co-Regulation of the Vitamin D and Cholesterol Metabolism. Cells 2021;10:2007. doi: 10.3390/cells10082007.

[61] Dziedzic EA, Przychodzeń S, Dąbrowski M. The effects of vitamin D on severity of coronary artery atherosclerosis and lipid profile of cardiac patients. Arch Med Sci AMS 2016;12:1199–206. doi: 10.5114/aoms.2016.60640.

[62] Jeenduang N, Sangkaew B. The association between serum 25-hydroxyvitamin D concentrations and serum lipids in the Southern Thai population. Arch Med Sci 2022;18:11–7. doi: 10.5114/aoms.2020.101100.

[63] Manousopoulou A, Al-Daghri NM, Garbis SD, Chrousos GP. Vitamin D and cardiovascular risk among adults with obesity: a systematic review and meta-analysis. Eur J Clin Invest 2015;45:1113–26. doi: 10.1111/eci.12510.

[64] Mirhosseini N, Rainsbury J, Kimball SM. Vitamin D supplementation, serum 25(OH)D concentrations and cardiovascular disease risk factors: a systematic review and meta-analysis. Front Cardiovasc Med 2018;5:87. doi: 10.3389/fcvm.2018.00087.

[65] Christensen R, Lorenzen JK, Svith CR, Bartels EM, Melanson EL, Saris WH, et al. Effect of calcium from dairy and dietary supplements on faecal fat excretion: a meta-analysis of randomized controlled trials. Obes Rev Off J Int Assoc Study Obes 2009;10:475–86. doi: 10.1111/j.1467-789X.2009.00599.x.

[66] asbaghi O, Kashkooli S, Choghakhori R, Hasanvand A, Abbasnezhad A. Effect of calcium and vitamin D co-supplementation on lipid profile of overweight/obese subjects: a systematic review and meta-analysis of the randomized clinical trials. Obes Med 2019;15:100124. doi: 10.1016/j.obmed.2019.100124.

[67] Grave N, Tovo-Rodrigues L, da Silveira J, Rovaris DL, Dal Bosco SM, Contini V, et al. A vitamin D pathway gene–gene interaction affects low-density lipoprotein cholesterol levels. J Nutr Biochem 2016;38:12–7. doi: 10.1016/j.jnutbio.2016.08.002.

[68] Sentinelli F, Minicocci I, Montali A, Nanni L, Romeo S, Incani M, et al. Association of RXR-Gamma Gene variants with familial combined hyperlipidemia: genotype and haplotype analysis. J Lipids 2013;2013:e517943. doi: 10.1155/2013/517943.

[69] Elsenberg EHAM, ten Boekel E, Huijgen H, Heijboer AC. Standardization of automated 25-hydroxyvitamin D assays: how successful is it? Clin Biochem 2017;50:1126–30. doi: 10.1016/j.clinbiochem.2017.06.011.

Supplementary material

Supporting Information

Table S1. Correlation between continuous socio-demographic, behavioral and health variables, and vitamin D.

	Vitamin D		
	Pearson	**Spearman**	**MICe**
Age	0.00	0.00	0.20
Education	0.10	0.07	0.21
Income	0.16*	0.10	0.25*
n-3 rich fish	0.11	0.09	0.18
Leisure-time PA	0.14*	0.14*	0.23*
ADLs	0.18***	0.17*	0.19*
Cholesterol	0.19***	0.21***	0.21***
HDL-C	0.20	0.00	0.21
LDL-C	0.17*	0.17*	0.20*
Triglicerydes	0.14*	0.13*	0.23
CRP	0.08	0.07	0.21*
BMI	0.18**	0.18**	0.23*
%Fat	0.26***	0.27**	0.27**

PA, physical activity; ADLs, activities of daily life; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; CRP C-reactive protein; BMI, body mass index; %Fat, body fat percentage; MICe, Maximum Information Coefficient; * P>0.05; **P=0.001; ***P>0.001.

4.1.2 Artigo 2

CEOLIN, G. et al. The association between physical activity and vitamin D is partially mediated by adiposity in older adults: EpiFloripa Aging Cohort Study. **Nutrition Research**, p. 1–63, mar. 2022.

The association Between Physical Activity and Vitamin D is Partially Mediated by Adiposity in Older Adults: EpiFloripa Aging Cohort Study

Gilciane Ceolin[1,6], Susana Cararo Confortin[2], Antônio Augusto Moura da Silva[2], Cassiano Ricardo Rech[3], Eleonora d'Orsi[4], Débora Kurrle Rieger[5,6], Júlia Dubois Moreira[5,6]

1 Postgraduate Program in Nutrition. Federal University of Santa Catarina, Florianopolis, Brazil.
2 Postgraduation Program of Collective Health. Department of Public Health. Federal University of Maranhão, São Luís, Brazil.
3 Physical Education Department. Federal University of Santa Catarina, Florianopolis, Brazil.
4 Postgraduate Program in Public Health. Department of Public Health. Federal University of Santa Catarina, Florianopolis, Brazil.
5 Department of Nutrition. Federal University of Santa Catarina, Florianopolis, Brazil
6 Translational Nutritional Neuroscience working group. Federal University of Santa Catarina, Florianopolis, Brazil.

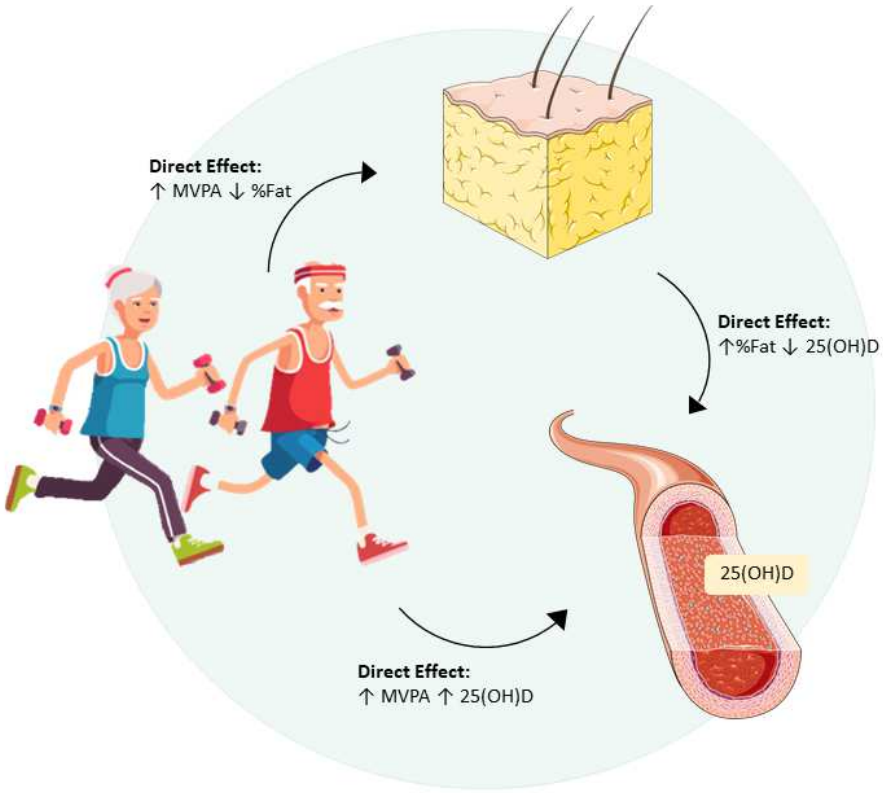
Highlights

- Moderate-to-vigorous physical activity (MVPA) could elevate 25-hydroxyvitamin D (25(OH)D)
- MVPA could decrease the body fat percentage (%fat)
- The reduction in %fat contributes to the elevation in 25(OH)D
- The impact of MVPA on 25(OH)D is partially explained by a decrease in %fat

Abbreviations

%fat, body fat percentage; 25(OH)D, 25-hydroxyvitamin D concentration; 95% CI,; Confidence interval of 95%; ADLs, activities of daily living; BMI, Body Mass Index; CFI, Comparative Fit Index; DAG, directed acyclic graph; DXA, Dual Energy X-ray Absorptiometry; FMI, Fat Mass Index; LPA, light physical activity ; MVPA, moderate and

vigorous physical activity; PA, physical activity; RMSEA, Root Mean Square Error of Approximation; SD, standard deviation; SEM, Structural Equation Modeling; TLI, Tucker Lewis Index; TPA, total physical activity; UFSC, Federal University of Santa Catarina; VDR, Vitamin D Receptor; WLSMV, Weighted Least Squares Mean and Variance Adjusted.



Graphical Abstract

The Structural Equation Modeling analysis revealed a possible intervention to prevent hypovitaminosis D in older adults. The increase in the practice of moderate and vigorous physical activity (MVPA) had a direct effect on both the decrease of body fat percentage (%fat) and increase of 25-hydroxycholecalciferol (25(OH)D) concentration. The increase in %fat had a direct effect on the decrease of 25(OH)D. Therefore, strategies to increase MVPA and decrease %fat could help prevent low 25(OH)

Abstract

Studies have found that physical activity (PA) could be a protective factor and adiposity a risk factor, for low serum 25-hydroxycholecalciferol (25(OH)D) concentration. This cross-sectional study hypothesized that PA could have a direct effect on 25(OH)D, and adiposity could be a mediating factor. Data from the second wave of the EpiFloripa Aging longitudinal study, collected during 2013–2014 (n=1,197) in Florianopolis, Santa Catarina, Brazil, was

used. PA was measured using an accelerometer and classified as light PA (LPA), moderate and vigorous PA (MVPA), and total PA (TPA); 25(OH)D levels were measured using the microparticle chemiluminescence method. Body fat composition (%fat) was assessed using dual-energy X-ray absorptiometry (DXA). Structural equation modeling was performed to analyze the total, direct, and indirect effects of PA on %fat and 25(OH)D levels, presented using the standardized coefficient (β). Participants with complete data were included in the analysis (n=574, 66.7% female). MVPA showed a direct (β=0.11; P<0.05) and total positive effect on 25(OH)D (β=0.12; P<0.05). All models of PA had a direct negative effect on %fat. Additionally, a direct negative effect of %fat on 25(OH)D was observed in all models. A marginal and partial effect of %fat as a mediator of the relationship between MVPA and 25(OH)D was noted (β=0.01, P=0.09). Our results show that PA presents a direct effect on serum 25(OH)D. %fat has a small contribution as a mediator of this relationship. These data suggest that an increase in MVPA and a decrease in %fat could be strategies to increase 25(OH)D levels in older adults.

Keywords: Vitamin D; Aging; Physical activity; Adipose tissue; Structural equation modeling.

1. Introduction

Evidence suggests a high prevalence of 25-hydroxycholecalciferol [25(OH)D] deficiency worldwide [1,2]. Older adults are at risk of 25(OH)D deficiency. Considering deficiency of 25(OH)D (<50 nmol/L or <20 ng/mL, cutoff point based on bone health), the prevalence has been estimated to be 34% in the United States, 19% in Canada, 36% in China, and 4–89% in European countries [1]. Furthermore, the prevalence can be higher in low- and middle-income countries; for example, 41% in Brazil [3], 91% in India, and 46% in Guatemala [1].

Several conditions can lead to complications related to 25(OH)D deficiency (<20 ng/mL), such as the risk of fractures due to fragility and bone loss, age-related muscle weakness, and sarcopenia [4,5]. The serum 25(OH)D concentration depends on synthesis by the skin and intestinal absorption, and it is influenced by various factors such as skin pigmentation, latitude, season, age, obesity, and inflammatory bowel diseases [6,7]. In addition to aging, other factors such as reduced exposure to the sun; decreased synthesis by the skin and dietary intake; intestinal malabsorption; certain diseases such as kidney, heart, and liver failure; and the use of some medications can influence 25(OH)D concentrations [5,6].

Observational studies have revealed that individuals with obesity could present lower circulating 25(OH)D concentrations [8]. In addition, due to its fat-soluble characteristic,

vitamin D appears to be more easily stored in fat cells before becoming available for further metabolism, reducing its availability in the bloodstream [9]. Therefore, adipose tissue, especially in individuals who have overweight and obesity, in which fatty mass is increased, can accumulate a substantial amount of vitamin D [10]. The vitamin D-metabolizing enzymes, such as 25-hydroxylase and 1α-hydroxylase, are responsible for converting both the inactive to the active form of vitamin D (1,25-dihydroxyvitamin D3) and the catabolic 24-hydroxylase, found in adipose tissue [11,12]. In addition, adipose tissue can express vitamin D receptors (VDR) involved in steroid metabolism and activities [12]. Moreover, vitamin D has been shown to affect adipocyte development and metabolic and endocrine functions [12,13].
People with obesity have hypertrophic adipose tissues, resulting in blood flow imbalance, which in turn leads to hypoxia, inflammation, and macrophage infiltration. Increased secretion of interleukins 6 and 8 and tumor necrosis factor-alpha is observed. These inflammatory markers induce the expression of VDR in adipose tissue, and vitamin D appears to exhibit an anti-inflammatory action on adipocytes [12,14]. Older adults with higher inflammatory markers have been found to have lower 25(OH)D concentrations [15].

Researchers have identified that, compared with normal weight, obesity and overweight can decrease the effect of vitamin D supplementation, and higher doses of vitamin D are required to increase 25(OH)D concentrations [16]. Conversely, weight loss seems to be a potential factor for elevation in 25(OH)D concentrations [17]. Moreover, a recent review discussed the possible role of physical activity (PA) in mobilizing vitamin D from adipose tissue [10]. PA is a potent stimulus for lipid mobilization from adipose tissue and for weight loss [18]. Additionally, outdoor PA has been associated with an increase in 25(OH)D concentrations resulting from exposure to the sun [19–22].

Few studies have investigated the relationship of PA and adiposity or body mass index (BMI) with serum 25(OH)D [20,23]. Furthermore, data from population-based studies in low- and middle-income countries are lacking, and further studies are needed [2]. This study aimed to test the hypothesis that PA could have a positive and direct effect on 25(OH)D, helping to elevate the blood concentration, and a positive indirect effect mediated by adiposity, in which the PA could reduce the body fat percentage (%fat) and indirectly help elevate 25(OH)D concentration in older adults. It can be postulated that 25(OH)D, a fat-soluble vitamin, could be stored (sequestered) in the adipose tissue when the individual has an increased %fat. When performing PA, the process of fat mobilization from the adipose tissue could release the 25(OH)D into the bloodstream. Thus, PA and %fat could have direct or indirect effects on the serum 25(OH)D concentration, and %fat could act as a mediator of this relationship. This

analysis could add to the literature and suggest a possible strategy to prevent low 25(OH)D concentrations in older adults.

2. Methods and Materials

2.1 Population sample and data collection

This cross-sectional analysis was carried out with data from the second wave of the cohort of the "Conditions of the health of the older adults in the Florianopolis - EpiFloripa Aging Cohort study," a population-based, home-based, longitudinal cohort study. The inclusion criteria at baseline (2009–2010) were as follows: men and women aged ≥60 years and living in an urban area in southern Brazil (Florianopolis/Santa Catarina). The exclusion criteria were: living in long-term care institutions, hospitals, and prisons [24,25].

Previous publications present the details of the study sample and methodology [24,25]. Briefly, the face-to-face home interview for data collection was carried out by trained interviewers using a structured questionnaire, and data were recorded using a netbook. In addition, consistency analysis and quality control were carried out by telephone through a reduced questionnaire version application in 10% of the interviews (selected randomly) [25].

All older adults who initially participated in the study were invited to participate in the second wave of the study, which enrolled 1,197 individuals (**Figure 1**). Participants at the second follow-up were invited to undergo tests and complementary examinations, which included biochemical blood sample analysis (n=574), body composition assessment (n=564), and objective assessment of PA (n=405) [24]. This resulted in a sample of 574 participants. The power of the sample size ($1 - \beta$ error probability) was calculated a posteriori (post hoc) using G*Power (version 3.1.9.7, Düsseldorf, Germany) [26], establishing as parameters the quadratic regression coefficient of 0.17 and the number of predictor variables of 13 (power=0.99).

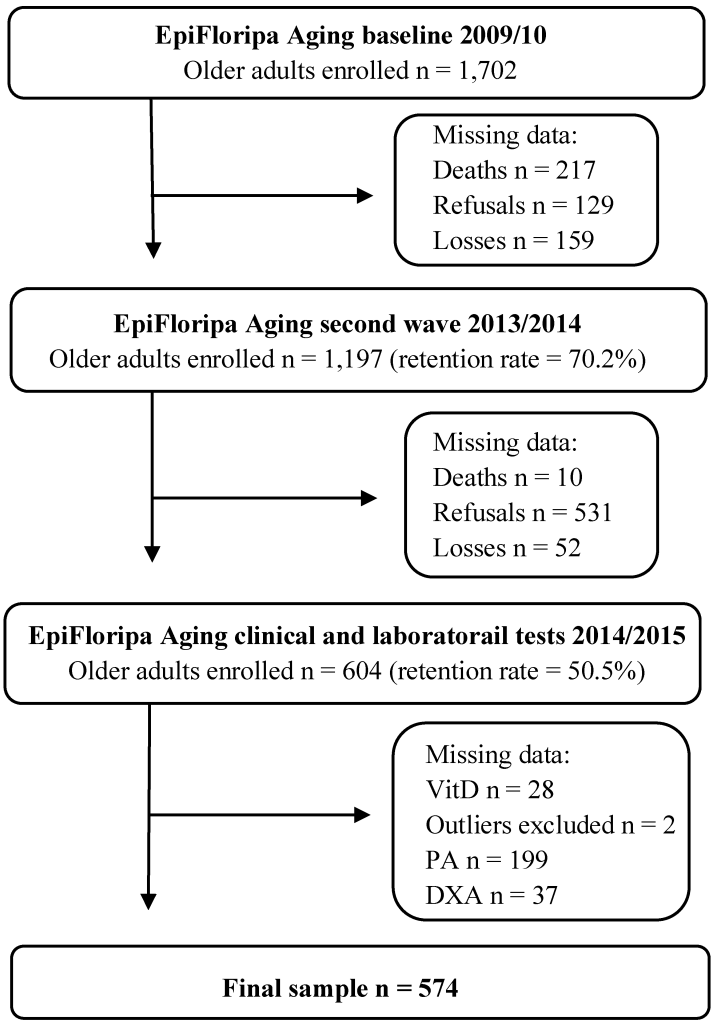


Figure 1. Flowchart of the EpiFloripa Aging study sample

EpiFloripa Aging Study baseline started in 2009–2010. There was a second wave in 2013–2014. All participants were invited to participate in the collection of clinical and laboratory tests in 2014–2015.

2.2 Measurements

Vitamin D

Participant were asked to fast for 8–10 h before blood collection, and 30 mL of peripheral venous blood was collected from each participant. Blood samples were collected at the Laboratory for Metabolism and Dietetics of the Federal University of Santa Catarina (UFSC) and analyzed at the laboratory of clinical analysis of the *Polydoro Ernani de São Thiago* University Hospital [24].

Serum 25(OH)D concentrations (ng/mL) were measured using the microparticle chemiluminescence method [27]. The blood samples were centrifuged at 3,500 rpm for 10 min

to collect serum. Serum samples used to detect 25(OH)D were immediately processed according to the manufacturer's instructions using LIAISON® (DiaSorin, São Paulo, SP, Brazil)[28]. In this method, an antibody specific to vitamin D was coated with magnetic particles, and 25(OH)D was conjugated to an isoluminol derivative and diluted in phosphate buffer (pH 7.4). In the first incubation period, 25(OH)D was dissociated from the binding protein and interacted with the antibody. During the second incubation period with the tracer reagent, the microplate was washed with the buffer, and starter reagents were added to generate the chemiluminescent signal, measured using a photomultiplier [28].

The LIAISON® is a rapid, accurate, and precise assay (functional sensitivity, ≤ 2.0 ng/mL; inter-assay imprecision, < 20%) [28]. Since 2014, the LIAISON® has received certification for total 25-hydroxyvitamin D assays from the Vitamin D Standardization Certification Program by the Center for Disease Control and Prevention [29].

Body composition

Assessment of body composition to determine relative body fat (%fat) and fat mass (kg) was performed using Dual Energy X-ray Absorptiometry (DXA, Lunar Prodigy Advance, General Electric, Madison, WI, USA) following the manufacturer's instructions [30]. The %fat was calculated based on fat mass (kg). The fat mass index (FMI) was also calculated based on the ratio of fat mass (kg) to height squared (m^2). The indices were chosen to correct the fat mass distribution in the body by height [31]. BMI was also calculated to classify nutritional status based on the ratio of weight (kg) to height squared (m^2) [32].

Physical activity

All participants who underwent complementary examinations were invited to complete the PA measurements using an accelerometer for 7 consecutive days, except those with decreased mobility (in wheelchairs, bedridden, and mobility problems), fishermen (engaging in water activities), and those with probable cognitive deficits. The participants were instructed to use the accelerometer only during the waking period and not use it during bathing and water activities [24]. In addition, the participants were asked to attach the accelerometer to the right side of the hip with an elastic belt. Using the accelerometer for a minimum number of records over 4 days during the week (10 h/day), including 1 day on the weekend (8 h/day), was considered valid.

The objectively measured PA was obtained using GT3X and GT3X+accelerometers (ActiGraph LLC, Pensacola, FL, USA), and data were analyzed using ActiLife software (ActiGraph). It is a valid and reliable instrument that provides information on the volume and

intensity of activities performed, expressed in counts [33–35]. Light PA (LPA) (<1,041 counts/min), moderate and vigorous PA (MVPA) (≥1,041 counts/min), and total PA (TPA), using a combination of LPA and MVPA, were assessed in min per day to adjust for the number of days the device was used [36]. In addition, for the best fit of the analyses, PA in h/week was evaluated.

Covariates

A directed acyclic graph (DAG, or causal Bayesian networks) was constructed to represent the theoretical model and elucidate the involvement of covariates in the association between PA and 25(OH)D (**Supplementary Figure 1**). The DAG was built using DAGitty software (version 3.0; Nijmegen, GE, The Netherlands) [37]. The graphical criteria for selecting the adjusted covariates were used to define the minimum set of covariates and reduce variable selection bias [38,39].

The covariates selected using DAG were sociodemographic variables, such as sex (men/women), skin color (white/others), the season of blood sample collection (summer, spring, autumn, winter), age (years), education (years), and per capita family income in minimal wages (categories: ≤1; >1 and ≤3; >3 and ≤5; >5 and ≤10; >10 minimal wages) according to the values in 2013 (R$ 678.00) and 2014 (R$ 724.00). In addition, education (years of study) and family income were used to create a latent variable to represent socioeconomic status.

Behavioral modified factors, such as smoking habit (no/ex-smoker/yes) and alcohol consumption (no/moderate/severe) collected using the Alcohol Use Disorder Identification Test [40], were included in the analysis. Information on health status included dependence in activities of daily living (ADLs) collected using the Scale of Daily Personal and Instrumental Activities [41] and the number of morbidities (sum of diagnosed diseases: spine or back disorders, arthritis, cancer, diabetes, bronchitis, cardiovascular disease, renal disease, tuberculosis, cirrhosis, stroke, osteoporosis, hypertension, and depression).

2.3 Statistical analysis

Descriptive analysis of the data are presented as absolute and relative frequencies and the mean and standard deviation (SD). The minimum set of adjusted covariates indicated by applying the back-door criterion to the DAG was composed of season, sex, age, education, family income, skin color, alcohol intake, smoking habit, ADLs, and morbidities. Structural equation modeling (SEM) was performed to analyze the total, direct, and indirect effects of PA

(LPA, MVPA, and TPA) on 25(OH)D and the mediation by adiposity (%fat, FMI, and BMI) using standardized coefficients.

The robust weighted least squares mean and variance adjusted (WLSMV) and THETA parameterization were used to control for differences in residual variances. The "mod indices" command was used to indicate new paths in the initial theoretical model that would better fit the model. When the proposed modification suggestions were considered plausible from a theoretical point of view, a new model was developed and analyzed if the modification index value was >10 [42]. To determine whether the model presented a good fit, the following fit indices were considered: P >0.05 for the chi-square test ($\chi 2$) [43], P <0.05 and an upper limit of the 90% confidence interval <0.08 for the root mean square error of approximation (RMSEA) [42], values >0.90 for the comparative fit index (CFI), and the Tucker–Lewis Index (TLI) [44], values <0.05 for the standardized root mean square residual (SRMR), and P <0.05 for factor loading >0.5, as a good indicator of convergent validity, indicative of a correlation of moderately high magnitude between the observed variables and construct [43].

The analysis was performed using Stata 14.0 software (StataCorp, College Station, TX, USA), considering the sample weights. To perform SEM, the MPlus 8.4 software (Muthen & Muthen, Los Angeles, CA, USA) was used for all analyses, and a P-value <0.05 was considered statistically significant. To facilitate clinical interpretation, the effect of MVPA and %fat on the 25(OH)D, the original metric, was obtained by multiplying the value of the standardized coefficient of the total effect by the SD of the variable.

2.4 Ethical Approval

The EpiFloripa Aging cohort study was conducted in accordance with the Declaration of Helsinki. The second wave of follow-up was approved by the Human Research Ethics Committee of the UFSC (approval numbers 329.650 and 526.126). After explaining the study objectives and collection procedures, all participants voluntarily agreed to participate in the study and signed the informed consent form.

3. Results

Of the total number of participants included in the analysis (n=574), 66.7% were women. The mean 25(OH)D concentration was approximately 26.2 SD ± 8.5 ng/mL (48.9% of the blood samples were collected in the winter). The mean LPA was 29.4 SD ± 9.8 h/week,

and MVPA was 5.6 SD ± 4.1 h/week. The mean fat body percentage was 36.8 SD ± 9.4 (**Table 1**).

Table 1. Sample characterization according to demographic, socioeconomic, and health characteristics. EpiFloripa Aging study, Florianopolis, Santa Catarina, Brazil, 2013–2015

Participants' characteristics	**n**	**%**	**95% CI**
Season of the year in which blood sample was collected (n=574)			
Summer	37	7.7	5.3; 11.2
Spring	86	16.4	12.4; 21.3
Autumn	148	27.0	20.4; 34.7
Winter	303	48.9	40.5; 57.3
Sex (n=574)			
Men	199	33.2	29.0; 37.7
Women	375	66.7	62.3; 71.0
Skin color (n=574)			
White	469	83.4	77.5; 88.1
Others	90	16.6	11.9; 22.5
Family income (n=554)			
≤1 minimum wage	44	7.6	5.4; 10.6
>1 and ≤3 minimum wages	159	29.1	24.6; 34.1
>3 and ≤5 minimum wages	113	21.1	17.1; 34.1
>5 and ≤10 minimum wages	138	23.9	19.9; 28.4
>10 minimum wages	100	18.3	12.9; 25.3
Smoking habit (n=574)			
No	363	63.4	58.9; 67.7
Ex-smoker	171	30.1	25.8; 34.7
Yes	40	6.4	4.1; 10.1
Alcohol consumption (n=574)			
No	332	59.7	53.4; 65.7
Moderate	158	27.0	21.9; 32.7
Severe	84	13.3	10.3; 17.0
	Mean	**SD**	

Age (years; n=574)	72.3	6.4	–
Education (years; n=573)	7.9	5.7	–
ADLs (n=571)	2.4	3.1	–
Number of morbidities (n=574)	3.1	1.8	–
LPA (h/week; n=405)	29.4	9.8	–
MVPA (h/week; n=405)	5.6	4.1	–
TPA (h/week; n=405)	35.0	12.2	–
BMI (kg/m²; n=567)	28.2	5.1	–
FMI (kg/m²; n=564)	10.6	4.1	–
% fat (n=567)	36.8	9.4	–
25(OH)D (ng/mL; n=574)	26.2	8.5	–

N, number of participants; 95% CI, 95% confidence interval; SD, standard deviation; ADLs, activities of daily living; LPA, light physical activity; MVPA, moderate and vigorous physical activity; TPA, total physical activity; BMI, body mass index; FMI, fat mass index; 25(OH)D, and concentration of 25-hydroxycholecalciferol.

The simplified theoretical model is presented in **Figure 2**, and the standardized coefficients of the total, direct, and indirect effects of PA and %fat on 25(OH)D are listed in **Table 2**. The three models of PA were presented: LPA, MVPA, and TPA. Only MVPA presented a direct (β=0.11; P<0.05) and total positive effect on 25(OH)D (β=0.12; P<0.05) (also see **Supplementary Figure 2**). The increase of 1 SD in the MVPA model resulted in an increase of 0.11 SD in 25(OH)D [in the original metric, for each 4.1 h/week (SD) increase in MVPA, there was a 1.02 ng/mL increase in 25(OH)D].

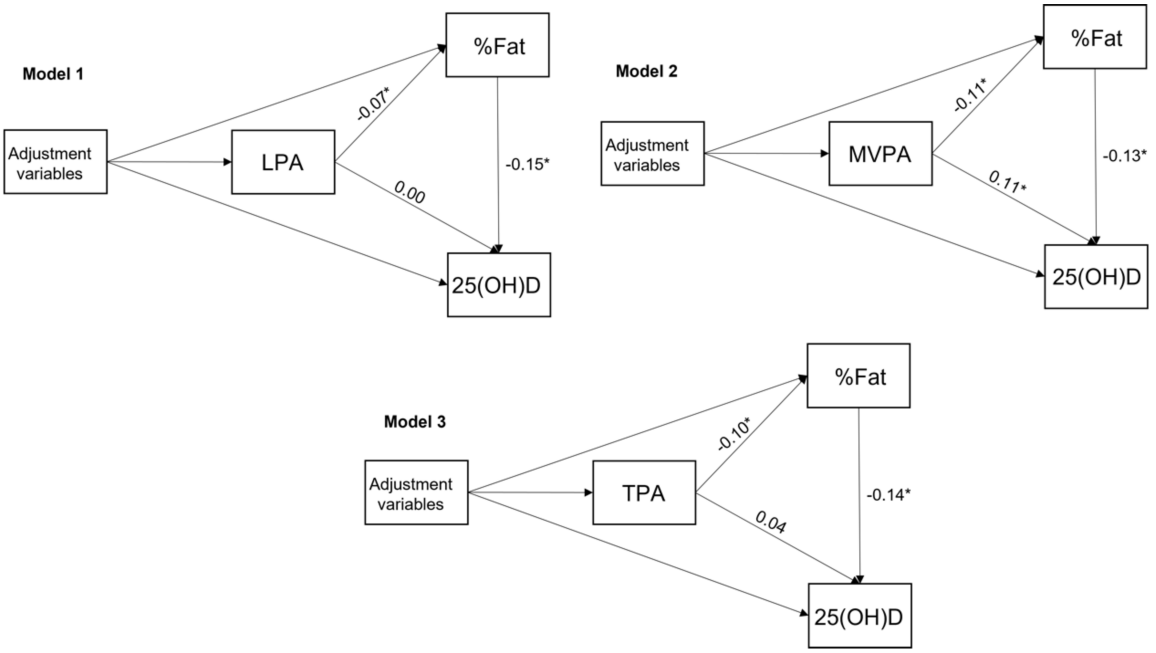


Figure 2. Simplified theoretical model of the direct effects of physical activity on %fat and 25(OH)D

The structural modeling equation (SEM) analysis was applied and presented using standardized coefficients. All models are adjusted by season, socioeconomic status, sex, age, skin color, smoking habit, alcohol intake, activities of daily living, and the number of morbidities. In all models, the increase of all intensities of physical activity showed a direct effect on body fat percentage (%fat). In all models, the increase %fat presented a direct effect on the decrease of 25-hydroxycholecalciferol [25(OH)D] concentration. Only in model 2, the increase of moderate and vigorous physical activity (MVPA) presented a direct effect on 25(OH)D. *P < 0.05. LPA: light physical activity; TPA: total physical activity.

Table 2. Direct, indirect, and total effects of PA on %fat and 25(OH)D (n=559). EpiFloripa Aging cohort study, Florianopolis, Santa Catarina, Brazil, 2013-2015.

Pathways and estimates	**Standardized coefficient**	**Standard error**	***P*-value**
Direct effects			
Model 1			
LPA → %fat	-0.07	0.03	<0.05
LPA → 25(OH)D	0.001	0.04	0.97
%fat → 25(OH)D	-0.15	0.05	<0.05
Model 2			
MVPA → %fat	-0.11	0.04	<0.05

MVPA → 25(OH)D	0.11	0.05	<0.05
%fat → 25(OH)D	-0.13	0.05	<0.05
Model 3			
TPA → %fat	-0.10	0.04	<0.05
TPA → 25(OH)D	0.04	0.05	0.48
%fat → 25(OH)D	-0.14	0.05	<0.05
Indirect effects			
LPA → %fat → 25(OH)D	0.01	0.01	0.08
MVPA → %fat → 25(OH)D	0.01	0.01	0.09
TPA → %fat → 25(OH)D	0.01	0.01	0.06
Total effects			
LPA (Model 1)	0.01	0.05	0.79
MVPA (Model 2)	0.12	0.05	<0.05
TPA (Model 3)	0.05	0.05	0.33

SEM analysis results of the direct, indirect, and total effect of Physical Activity (PA) on body fat percentage (%fat), and on concentration of 25-hydroxycholecalciferol [25(OH)D]. Model 1: Light Physical Activity (LPA), %fat, and 25(OH)D. Model 2: Moderate and Vigorous Physical Activity (MVPA), %fat, and 25(OH)D. Model 3: Total Physical Activity (TPA), %fat, and 25(OH)D. The arrows represent the direct effect. Models are adjusted by season, socioeconomic status, sex, age, skin color, smoking habit, alcohol intake, activities of daily living, and the number of morbidities. Adjustment parameters that validated the models: **Model 1**: X^2=0.10, RMSEA=0.02, 90% CI superior=0.04, probability=0.99, CFI=0.99, TLI=0.98, and SRMR=0.04. **Model 2**: X^2=0.10, RMSEA=0.02, 90% CI superior=0.04, probability=0.99, CFI=0.99, TLI=0.98, and SRMR=0.04. **Model 3**: X^2=0.10, RMSEA=0.02, 90% CI superior=0.04, probability=0.99, CFI=0.99, TLI=0.98, and SRMR=0.04.

All the models of PA had a direct negative effect on %fat. In addition, in all the models, %fat had a direct negative effect on the 25(OH)D. The increase of 1 SD in %fat in the MVPA model resulted in a decrease of 0.13 SD in 25(OH)D (in the original metric, for each 9.4% [SD] increase in %fat, there was a 1.10 ng/mL decrease in 25(OH)D). There was a marginal and partial effect of %fat as a mediator of the relationship between MVPA and 25(OH)D (β=0.01, P=0.09).

The effects in the models using BMI and FMI were also analyzed (**Supplementary Table 1**). In the models using BMI, the LPA (β=0.02; P<0.05) and MVPA (β=0.12; P<0.05) had a direct positive effect on the 25(OH)D, but only the MVPA model presented a total effect (β=0.12; P<0.05). None of the PA models had a significant effect on BMI. In contrast, all the

models using BMI had a direct negative effect on 25(OH)D. In the models using FMI, only MVPA presented a direct (β =0.11; P<0.05) and total (β=0.12; P<0.05) positive effect on 25(OH)D. None of the PA models had a significant effect on FMI. All the models using FMI had a direct negative effect on 25(OH)D. Details of the direct effect of the adjustment variables in each model can be found in **supplementary tables 2, 3, and 4**.

4. Discussion

Using SEM analysis, our findings showed that the practice of MVPA had a direct positive effect on 25(OH)D (β=0.11; P<0.05) and a direct negative effect on %fat (β=-0.11; P<0.05). In addition, %fat had a direct negative effect on 25(OH)D (β=-0.13; P<0.05) after adjusting for confounding variables. Moreover, in the models using BMI or FMI, MVPA showed a direct positive effect on 25(OH)D. %fat, BMI, and FMI had a direct negative effect on 25(OH)D in all the models. Overall, the results indicated that an increase in MVPA practice could increase 25(OH)D and decrease %fat, and an increase in %fat can decrease 25(OH)D. A marginal effect of MVPA on 25(OH)D mediated by %fat was detected (P=0.09), which was partially in line with our initial hypothesis.

To the best of our knowledge, this is the first study to investigate the total, direct, and indirect effects of PA on 25(OH)D, mediated by adiposity using SEM. Few studies have investigated the association between PA and adiposity with 25(OH)D [20,23]. A previous study using longitudinal data in adults and older adults from the United Kingdom (n=1,853) investigated adiposity as an outcome using SEM. However, similar results were observed: PA affects visceral adiposity (β=-0.23; P<0.001) and 25(OH)D (β=0.15; P<0.001) [20]. A study in Iceland (n=229) showed that PA is associated with a higher concentration of 25(OH)D only in normal/overweight participants (β=1.27; P=0.001) and not with obesity, using linear regression [23].

Studies investigating the determinants of 25(OH)D in adults and older adults have found an association with PA as a protective factor for low 25(OH)D and BMI as a risk factor for low 25(OH)D [45,46]. In contrast, a sedentary lifestyle or insufficient PA is associated with an increased risk of low 25(OH)D [19,47].

Our data showed that for a 4.1 h/week increase in MVPA, there was a 1.02 ng/mL increase in 25(OH)D. Despite causing only a marginal increase, MVPA may affect 25(OH)D, contributing to maintenance of adequate serum status in the older adult

population. In addition, PA 4.1 h/week would be equivalent to a pattern of 35 min/day, which is the recommended PA for older adults according to the Physical Activity Guidelines for Americans [48]. Accordingly, for substantial health benefits, older adults should achieve at least 150 min (2 h and 30 min) to 300 min (5 h) a week of moderate PA, or 75 min (1 h and 15 min) to 150 min (2 h 30 min) a week of vigorous PA, and a combination of both (MVPA) [48].

Although indoor or outdoor PA practice has not been investigated, some studies have found a difference between outdoor PA and 25(OH)D [21,22], whereas no significant difference was found in another study [19]. For instance, in adults (≥20 years old) from the United States (n=15,148), the practice of outdoor PA presented a higher mean 25(OH)D concentration (11.5 nmol/L or 4.6 ng/mL, $P<0.001$) than that in inactive individuals [22]. In addition, in a population of older adults from Italy (n=2,349), those who practice outdoor activities (cycling or gardening) presented a significantly higher 25(OH)D than those who did not [68 vs. 51 nmol/L (27.2 vs. 20.4 ng/mL in women and 101 vs. 73 nmol/L in men); $P<0.001$] and are less likely to be 25(OH)D deficient [<50 nmol/L; cycling odds ratio (OR)=0.51; 95% confidence interval (CI), 0.37, 0.69 in women; OR=0.50; 95% CI, 0.29, 0.87 in men; and gardeners OR=0.62; 95% CI, 0.47, 0.83 in women; OR=0.46; 95% CI, 0.26, 0.80 in men] but not for brisk walkers [21].

A possible explanation for the different results with outdoor activities is that sun exposure can enhance the synthesis of vitamin D by the skin [49]. Daily exposure to 20% of the body surface is considered sufficient to increase 25(OH)D levels [50]. In contrast, other factors can also influence the production of vitamin D in the skin, such as incidence of the sun according to the season of the year [6], the availability of 7-dehydrocholesterol (7-DHC, the precursor of vitamin D3) [51], aging-related skin characteristics such as decreased skin capacity to synthesize vitamin D [52], dark skin pigmentation [53], and the habit of wearing clothes that cover almost the entire body [6].

Our results showed that MVPA had a direct negative effect on %fat, in line with a recent meta-analysis of studies on exercise interventions, moderate-to-vigorous intensity four times per week, 50 min per session (2 h and 20 min/week), reduced weight (d=-0.58; 95% CI, -0.84, -0.31), BMI (d=-0.50; 95% CI, -0.78, -0.21), and accumulated visceral fat (d=-1.08, 95% CI, -1.60, -0.57) [18]. Previous studies have shown that an increase in PA can promote loss of adiposity and a rise in 25(OH)D [54,55]. Furthermore, PA has a possible role in mobilizing vitamin D stored in adipose tissue [10]. However, a meta-analysis indicated a minor increase in 25(OH)D than expected from the direct

mobilization of stores into the circulation, indicating possible local use of its metabolites [55].

Independent of the method used to evaluate adiposity, %fat, BMI, and FMI presented a direct negative effect on 25(OH)D concentrations in all the models. This supports previous findings in the literature in which obesity is associated with lower 25(OH)D in adults and older adults [8,46,47]. Although this association's underlying mechanisms and direction are not fully understood, some hypotheses have been proposed. The most common hypothesis is that adipose tissue decreases the bioavailability of 25(OH)D owing to storage [56]. In addition, there is a discussion regarding the dilution of vitamin D according to body size, and a large fat mass could explain the low 25(OH)D concentrations [57]. Finally, an alternative proposed mechanism suggests that obesity could reduce the capacity of hepatic conversion of vitamin D owing to a decrease in the expression of the principal hepatic vitamin D 25-hydroxylase [58].

Some studies have shown that vitamin D is not only stored in adipose tissue but can also play a role in the expression of vitamin D-metabolizing enzymes in the adipose tissue [12,59]. Furthermore, vitamin D has been demonstrated to act through VDR and decrease adipose tissue inflammation by inhibiting inflammatory pathways such as adipokine expression (leptin, interleukin 6, and nuclear factor-κB) in human adipocytes [12]. In addition, vitamin D regulates human adipose tissue growth and remodeling [13].

Our study had some limitations. First, the sample size was reduced from the original sample of the EpiFloripa Aging study because only a few participants accepted and could complete the additional evaluations of objective PA, body composition, and blood sample collection, which may have limited some of the analyses; however, a higher power of the sample was achieved to support the results. Second, the clinical and biochemical examinations were conducted at the university (except for the PA, which was explained at the university and completed at home), selecting individuals with relatively better health conditions than those from the general population. Third, we did not investigate whether older adults practiced the activities outdoors or indoors. Fourth, cross-sectional analyses should be considered with caution because of the methodological limitations inherent in obtaining data. Finally, although we use a technique certified by the Vitamin D Standardization Certification Program for total 25-hydroxyvitamin D assays to measure the 25(OH)D, it is important to mention that it has differences from the gold standard [60].

Our study has the following strengths. First, the measures of adiposity were examined using DXA, which is accurate. An objective PA measurement was used, which is a precise method. Second, a DAG was created to represent the theoretical model and to elucidate the involvement of covariates in the association between PA, %fat, and 25(OH)D and the back-door criterion for the selection of the minimum set of adjusted covariates, which was essential to reduce confounding and selection bias. Third, this study followed a highly accurate method for the data quality as the trained and supervised interviewers, pilot study, face-to-face interviews, and interview quality control. Finally, to the best of our knowledge, this is the first study to use SEM analysis to investigate the direct and indirect effects of PA on 25(OH)D, mediated by adiposity.

5. Conclusion

Our findings show that MVPA had a direct positive effect on 25(OH)D and an immediate negative effect on %fat, and %fat had a direct negative effect on 25(OH)D in older adults living in southern Brazil. Given the high prevalence of hypovitaminosis D, these findings were relevant in this population. Therefore, strategies to increase the serum concentration of 25(OH)D are needed for the prevention of well-known conditions such as compromised bone health, and strategies to improve the practice of MVPA and reduce adiposity may be an option to increase 25(OH)D and prevent other health issues in this population. However, further studies with larger sample sizes and different populations are needed to corroborate these findings.

Acknowledgment

The authors have no acknowledgments to declare.

Sources of Support

This study was supported by partnerships established with the UFSC and assistance from students and teachers involved in this research. All the infrastructure and instruments needed to carry out the research were made available by the UFSC, except for the netbooks used for data collection that were provided by the Oswaldo Cruz Foundation, Rio de Janeiro. The process of collecting clinical and laboratory examinations was financed by the *Conselho Nacional de Desenvolvimento Científico e Tecnológico* (process number 475.904/2013-3) and developed within the scope of the Postgraduate Program in Collective Health at UFSC. This study was financed in part by the *Coordenação de Aperfeiçoamento de Pessoal de Nível Superior* (Finance Code 001).

Author contributions

All authors contributed to the study conception and design and take full responsibility for the integrity of the data and the accuracy of the data analysis. **Gilciane Ceolin**, conceptualization, methodology, formal analysis, writing – original draft, visualization, and validation; **Susana Cararo Confortin**, conceptualization, methodology, writing – review and editing, and validation; **Antônio Augusto Moura da Silva**, conceptualization, methodology, formal analysis, writing – review and editing, and validation; **Cassiano Ricardo Rech**, conceptualization, methodology, formal analysis, writing – review and editing, and validation; **Eleonora d'Orsi**, funding acquisition, project administration, conceptualization, methodology, investigation, writing – review and editing, and validation; **Débora Kurrle Rieger**, supervision, conceptualization, writing – review and editing, and validation; and **Júlia Dubois Moreira**, supervision, conceptualization, methodology, writing – review and editing, and validation. All authors read and approved the final manuscript.

Author Declarations

The authors declare no financial support or relationship that may represent a conflict of interest.

Availability of data and materials

The analyzed datasets from the study are available from the corresponding author upon reasonable request.

References

[1] Palacios C, Gonzalez L. Is vitamin D deficiency a major global public health problem? J Biochem Mol Biol 2014;144 Pt A:138–45. doi: 10.1016/j.jsbmb.2013.11.003.

[2] Roth DE, Abrams SA, Aloia J, Bergeron G, Bourassa MW, Brown KH, et al. Global prevalence and disease burden of vitamin D deficiency: a roadmap for action in low- and middle-income countries. Ann NY Acad Sci 2018;1430:44–79. doi: doi.org/10.1111/nyas.13968.

[3] Pereira-Santos M, Santos JYG dos, Carvalho GQ, Santos DB dos, Oliveira AM. Epidemiology of vitamin D insufficiency and deficiency in a population in a sunny country: Geospatial meta-analysis in Brazil. Crc Cr Rev Food Sci 2019;59:2102–9. doi: 10.1080/10408398.2018.1437711.

[4] Luo J, Quan Z, Lin S, Cui L. The association between blood concentration of 25-hydroxyvitamin D and sarcopenia: a meta-analysis. Asia Pac J Clin Nutr 2018;27:1258–70. doi: 10.6133/apjcn.201811_27(6).0013.

[5] Cesari M, Incalzi RA, Zamboni V, Pahor M. Vitamin D hormone: a multitude of actions potentially influencing the physical function decline in older persons. Geriatr Gerontol Int 2011;11:133–42. doi: 10.1111/j.1447-0594.2010.00668.x.

[6] Arabi A, El Rassi R, El-Hajj Fuleihan G. Hypovitaminosis D in developing countries—prevalence, risk factors and outcomes. Nat Rev Endocrinol 2010;6:550–61. doi: 10.1038/nrendo.2010.146.

[7] Holick MF. The vitamin D deficiency pandemic: Approaches for diagnosis, treatment and prevention. Rev Endocr Metab Dis 2017;18:153–65. doi: 10.1007/s11154-017-9424-1.

[8] Pereira-Santos M, Costa PRF, Assis AMO, Santos C a. ST, Santos DB. Obesity and vitamin D deficiency: a systematic review and meta-analysis. Obes Rev Off J Int Assoc Study Obes 2015;16:341–9. doi: 10.1111/obr.12239.

[9] Bouillon R, Marcocci C, Carmeliet G, Bikle D, White JH, Dawson-Hughes B, et al. Skeletal and Extraskeletal Actions of Vitamin D: Current Evidence and Outstanding Questions. Endocr Rev 2019;40:1109–51. doi: 10.1210/er.2018-00126.

[10] Hengist A, Perkin O, Gonzalez JT, Betts JA, Hewison M, Manolopoulos KN, et al. Mobilising vitamin D from adipose tissue: The potential impact of exercise. Nutr Bull 2019;44:25–35. doi: 10.1111/nbu.12369.

[11] Ding C, Gao D, Wilding J, Trayhurn P, Bing C. Vitamin D signalling in adipose tissue. Brit J Nutr 2012;108:1915–23. doi: 10.1017/S0007114512003285.

[12] Nimitphong H, Guo W, Holick MF, Fried SK, Lee M-J. Vitamin D Inhibits Adipokine Production and Inflammatory Signaling Through the Vitamin D Receptor in Human Adipocytes. Obesity 2021;29:562–8. doi: 10.1002/oby.23109.

[13] Nimitphong H, Holick MF, Fried SK, Lee M-J. 25-Hydroxyvitamin D3 and 1,25-Dihydroxyvitamin D3 Promote the Differentiation of Human Subcutaneous Preadipocytes. Plos One 2012;7:e52171. doi: 10.1371/journal.pone.0052171.

[14] Trayhurn P, O'Hara A, Bing C. Interrogation of microarray datasets indicates that macrophage-secreted factors stimulate the expression of genes associated with vitamin D metabolism (VDR and CYP27B1) in human adipocytes. Adipobiology 2011;3:31–6. doi: 10.14748/adipo.v3.269.

[15] Laird E, McNulty H, Ward M, Hoey L, McSorley E, Wallace JMW, et al. Vitamin D Deficiency Is Associated With Inflammation in Older Irish Adults. J Clin Endocr Metab 2014;99:1807–15. doi: 10.1210/jc.2013-3507.

[16] de Oliveira LF, de Azevedo LG, da Mota Santana J, de Sales LPC, Pereira-Santos M. Obesity and overweight decreases the effect of vitamin D supplementation in adults: systematic review and meta-analysis of randomized controlled trials. Rev Endocr Metab Dis 2020;21:67–76. doi: 10.1007/s11154-019-09527-7.

[17] Mallard SR, Howe AS, Houghton LA. Vitamin D status and weight loss: a systematic review and meta-analysis of randomized and nonrandomized controlled weight-loss trials. Am J Clin Nutr 2016;104:1151–9. doi: 10.3945/ajcn.116.136879.

[18] Lee HS, Lee J. Effects of Exercise Interventions on Weight, Body Mass Index, Lean Body Mass and Accumulated Visceral Fat in Overweight and Obese Individuals: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Int J Environ Res Pu 2021;18. doi: 10.3390/ijerph18052635.

[19] Wanner M, Richard A, Martin B, Linseisen J, Rohrmann S. Associations between objective and self-reported physical activity and vitamin D serum levels in the US population. Cancer Cause Control 2015;26:881–91. doi: 10.1007/s10552-015-0563-y.

[20] Klinedinst BS, Meier NF, Larsen B, Wang Y, Yu S, Mochel JP, et al. Walking in the Light: How History of Physical Activity, Sunlight, and Vitamin D Account for Body Fat—A UK Biobank Study. Obesity 2020;28:1428–37. doi: 10.1002/oby.22852.

[21] De Rui M, Toffanello ED, Veronese N, Zambon S, Bolzetta F, Sartori L, et al. Vitamin D deficiency and leisure time activities in the elderly: are all pastimes the same? Plos One 2014;9:e94805. doi: 10.1371/journal.pone.0094805.

[22] Scragg R, Camargo CA. Frequency of Leisure-Time Physical Activity and Serum 25-Hydroxyvitamin D Levels in the US Population: Results from the Third National Health and Nutrition Examination Survey. Am J Epidemiol 2008;168:577–86. doi: 10.1093/aje/kwn163.

[23] Og G, M C, Pv J, I T, A R. Associations of physical activity with vitamin D status depends on obesity status in old adults. Clin Nutr 2020;39:222–6. doi: 10.1016/j.clnesp.2020.06.009.

[24] Confortin SC, Schneider IJC, Danielewicz AL, Fassula AS, Souza BB de, Santos CES dos, et al. Estudo Longitudinal EpiFloripa Idoso – Rotinas de organização e protocolos referentes à coleta, análise e armazenamento de material biológico, exames de imagem e capacidade físico-funcional. Cad Saude Coletiva 2019;27:210–24. doi: 10.1590/1414-462x201900020169.

[25] Schneider IJC, Confortin SC, Bernardo C de O, Bolsoni CC, Antes DL, Pereira KG, et al. EpiFloripa Aging cohort study: methods, operational aspects, and follow-up strategies. Rev Saude Publica 2017;51. doi: 10.11606/s1518-8787.2017051006776.

[26] Faul F, Erdfelder E, Lang A-G, Buchner A. G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav Res Methods 2007;39:175–91. doi: 10.3758/bf03193146.

[27] Bianchi S, Maffei S, Prontera C, Battaglia D, Vassalle C. Preanalytical, analytical (DiaSorin LIAISON) and clinical variables potentially affecting the 25-OH Vitamin D estimation. Clin Biochem 2012;45:1652–7. doi: 10.1016/j.clinbiochem.2012.08.003.

[28] Ersfeld DL, Rao DS, Body J-J, Sackrison JL, Miller AB, Parikh N, et al. Analytical and clinical validation of the 25 OH vitamin D assay for the LIAISON® automated analyzer. Clin Biochem 2004;37:867–74. doi: 10.1016/j.clinbiochem.2004.06.006.

[29] Centers for Disease Control and Prevention. Laboratory Quality Assurance and Standardization Programs, https://www.cdc.gov/labstandards/hs_certified_participants.html; 2021 [accessed 8 March 2021].

[30] Genton L, Hans D, Kyle UG, Pichard C. Dual-Energy X-ray absorptiometry and body composition: differences between devices and comparison with reference methods. Nutrition 2002;18:66–70. doi: 10.1016/S0899-9007(01)00700-6.

[31] VanItallie TB, Yang MU, Heymsfield SB, Funk RC, Boileau RA. Height-normalized indices of the body's fat-free mass and fat mass: potentially useful indicators of nutritional status. Am J Clin Nutr 1990;52:953–9. doi: 10.1093/ajcn/52.6.953.

[32] Lohmann TG, Roche AF, Martorell R. Anthropometric Standardization Reference Manual. Human Kinetics Books. Champaign: 1988.

[33] Evenson KR, Buchner DM, Morland KB. Objective measurement of physical activity and sedentary behavior among US adults aged 60 years or older. Prev Chronic Dis 2012;9:E26.

[34] Keadle SK, Shiroma EJ, Freedson PS, Lee I-M. Impact of accelerometer data processing decisions on the sample size, wear time and physical activity level of a large cohort study. BMC Public Health 2014;14:1210. doi: 10.1186/1471-2458-14-1210.

[35] Sasaki JE, John D, Freedson PS. Validation and comparison of ActiGraph activity monitors. J Sci Med Sport 2011;14:411–6. doi: 10.1016/j.jsams.2011.04.003.

[36] Copeland JL, Esliger DW. Accelerometer Assessment of Physical Activity in Active, Healthy Older Adults. J Aging Phys Activ 2009;17:17–30. doi: 10.1123/japa.17.1.17.

[37] Textor J, van der Zander B, Gilthorpe MS, Liśkiewicz M, Ellison GTH. Robust causal inference using directed acyclic graphs: the R package 'dagitty.' Int J Epidemiol 2017:dyw341. doi: 10.1093/ije/dyw341.

[38] Shrier I, Platt RW. Reducing bias through directed acyclic graphs. BMC Med Res Methodol 2008;8:70. doi: 10.1186/1471-2288-8-70.

[39] Hernán MA, Robins JM. Causal Inference: What If. Chapman & Hall. Cambridge: 2020.

[40] Babor TF, Higgins-Biddle JC, Saunders JB, Monteiro MG. The alcohol use disorders identification test: guidelines for use in primary care. Geneva: 2001.

[41] Rosa TE da C, Benício MHD, Latorre M do RD de O, Ramos LR. Determinant factors of functional status among the elderly. Rev Saúde Pública 2003;37:40–8. doi: 10.1590/S0034-89102003000100008.

[42] Wang J, Wang X. Structural Equation Modeling: Applications Using Mplus. John Wiley & Sons; 2019.

[43] Kline RB. Principles and Practice of Structural Equation Modeling, 4th. ed. Guilford Publications: 2015.

[44] Marôco J. Análise de Equações Estruturais: Fundamentos teóricos, software & Aplicações. Brazil: 2010.

[45] Duarte C, Carvalheiro H, Rodrigues AM, Dias SS, Marques A, Santiago T, et al. Prevalence of vitamin D deficiency and its predictors in the Portuguese population: a nationwide population-based study. Arch Osteoporos 2020;15:36. doi: 10.1007/s11657-020-0695-x.

[46] Aspell N, Laird E, Healy M, Shannon T, Lawlor B, O'Sullivan M. The Prevalence and Determinants of Vitamin D Status in Community-Dwelling Older Adults: Results from the English Longitudinal Study of Ageing (ELSA). Nutrients 2019;11. doi: 10.3390/nu11061253.

[47] Brock K, Huang W-Y, Fraser DR, Ke L, Tseng M, Stolzenberg-Solomon R, et al. Low vitamin D status is associated with physical inactivity, obesity and low vitamin D intake in a large US sample of healthy middle-aged men and women. J Biochem Mol Biol 2010;121:462–6. doi: 10.1016/j.jsbmb.2010.03.091.

[48] World Health Organization. WHO guidelines on physical activity and sedentary behaviour, https://apps.who.int/iris/bitstream/handle/10665/336656/9789240015128-eng.pdf ; 2021 [accessed 22 March 2021].

[49] Chalcraft JR, Cardinal LM, Wechsler PJ, Hollis BW, Gerow KG, Alexander BM, et al. Vitamin D Synthesis Following a Single Bout of Sun Exposure in Older and Younger Men and Women. Nutrients 2020;12:2237. doi: 10.3390/nu12082237.

[50] Wacker M, Holick MF. Sunlight and Vitamin D: A global perspective for health. Dermatoendocrinol 2013;5:51–108. doi: 10.4161/derm.24494.

[51] Gil Á, Plaza-Diaz J, Mesa MD. Vitamin D: Classic and Novel Actions. Ann Nutr Metab 2018;72:87–95. doi: 10.1159/000486536.

[52] MacLaughlin J, Holick MF. Aging decreases the capacity of human skin to produce vitamin D3. J Clin Invest 1985;76:1536–8.

[53] Clemens TL, Adams JS, Henderson SL, Holick MF. Increased skin pigment reduces the capacity of skin to synthesise vitamin D3. Lancet 1982;1:74–6. doi: 10.1016/s0140-6736(82)90214-8.

[54] Gangloff A, Bergeron J, Lemieux I, Després J-P. Changes in circulating vitamin D levels with loss of adipose tissue. Curr Opin Clin Nutr 2016;19:464–70. doi: 10.1097/MCO.000000000000031

[55] Pannu PK, Zhao Y, Soares MJ. Reductions in body weight and percent fat mass increase the vitamin D status of obese subjects: a systematic review and metaregression analysis. Nutr Res 2016;36:201–13. doi: 10.1016/j.nutres.2015.11.013.

[56] Wortsman J, Matsuoka LY, Chen TC, Lu Z, Holick MF. Decreased bioavailability of vitamin D in obesity. Am J Clin Nutr 2000;72:690–3. doi: 10.1093/ajcn/72.3.690.

[57] Drincic AT, Armas LAG, Diest EE van, Heaney RP. Volumetric Dilution, Rather Than Sequestration Best Explains the Low Vitamin D Status of Obesity. Obesity 2012;20:1444–8. doi: 10.1038/oby.2011.404.

[58] Roizen JD, Long C, Casella A, O'Lear L, Caplan I, Lai M, et al. Obesity Decreases Hepatic 25-Hydroxylase Activity Causing Low Serum 25-Hydroxyvitamin D. J Bone Miner Res 2019;34:1068–73. doi: 10.1002/jbmr.3686.

[59] Wamberg L, Christiansen T, Paulsen SK, Fisker S, Rask P, Rejnmark L, et al. Expression of vitamin D-metabolizing enzymes in human adipose tissue—the effect of obesity and diet-induced weight loss. Int J Obesity 2013;37:651–7. doi: 10.1038/ijo.2012.112.

[60] Elsenberg EHAM, ten Boekel E, Huijgen H, Heijboer AC. Standardization of automated 25-hydroxyvitamin D assays: How successful is it? Clin Biochem 2017;50:1126–30. doi: 10.1016/j.clinbiochem.2017.06.011.

Supplementary Material

Supporting Information

Figure S1: Theoretical model of the minimum set of adjustment covariates indicated by the directed acyclic graph (DAG) of the association between physical activity and 25(OH)D.

Figure S2: Theoretical model of the direct effects of MVPA, %fat and 25(OH)D with covariates. EpiFloripa Aging cohort study. Florianopolis, Santa Catarina, Brazil, 2013-2015.

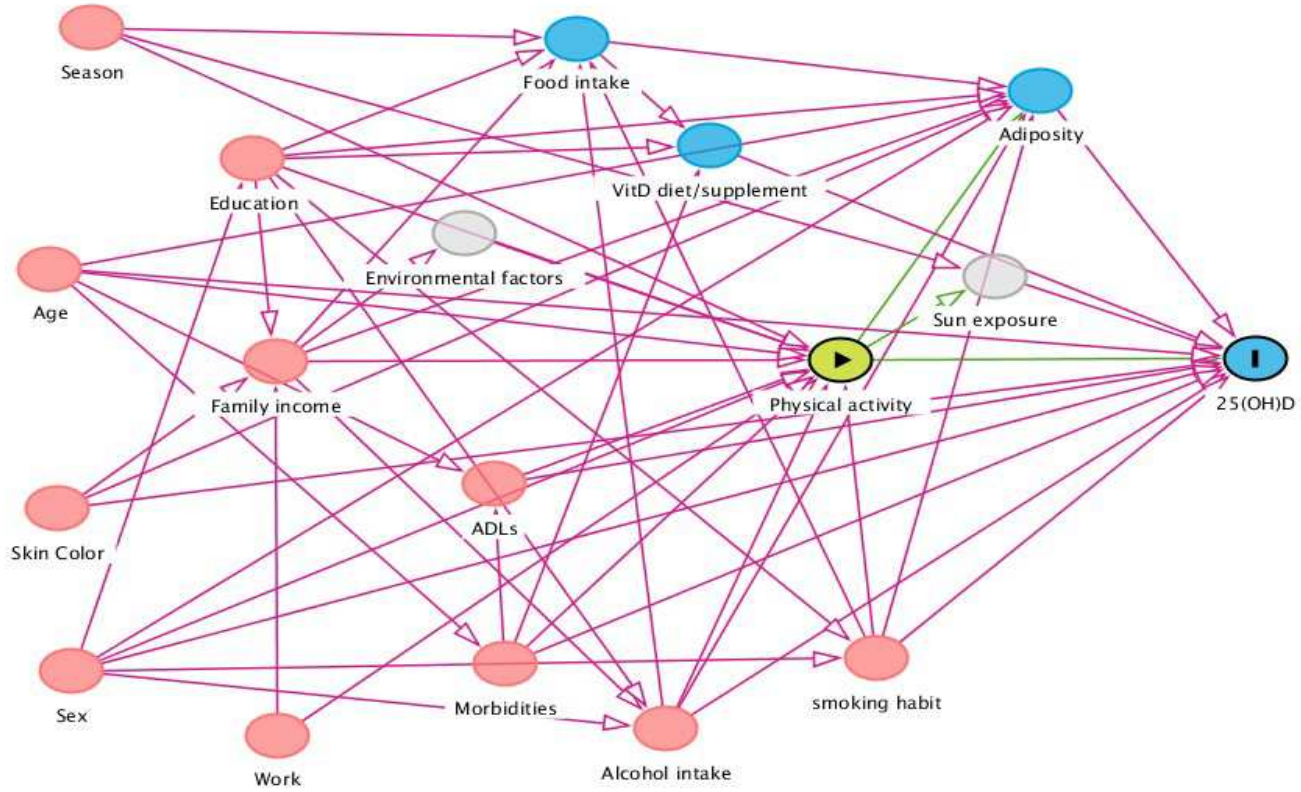
Table S1: The direct, indirect, and total effect of Physical Activity on Body Mass Index, Fat Mass Index, and 25(OH)D. EpiFloripa Aging cohort study. Florianopolis, Santa Catarina, Brazil, 2013-2015.

Table S2: The direct effect of covariates on the model of LPA, %fat and 25(OH)D. EpiFloripa Aging cohort study. Florianopolis, Santa Catarina, Brazil, 2013-2015.

Table S3: The direct effects of covariates on the model of MVPA on %fat and 25(OH)D. EpiFloripa Aging cohort study. Florianopolis, Santa Catarina, Brazil, 2013-2015.

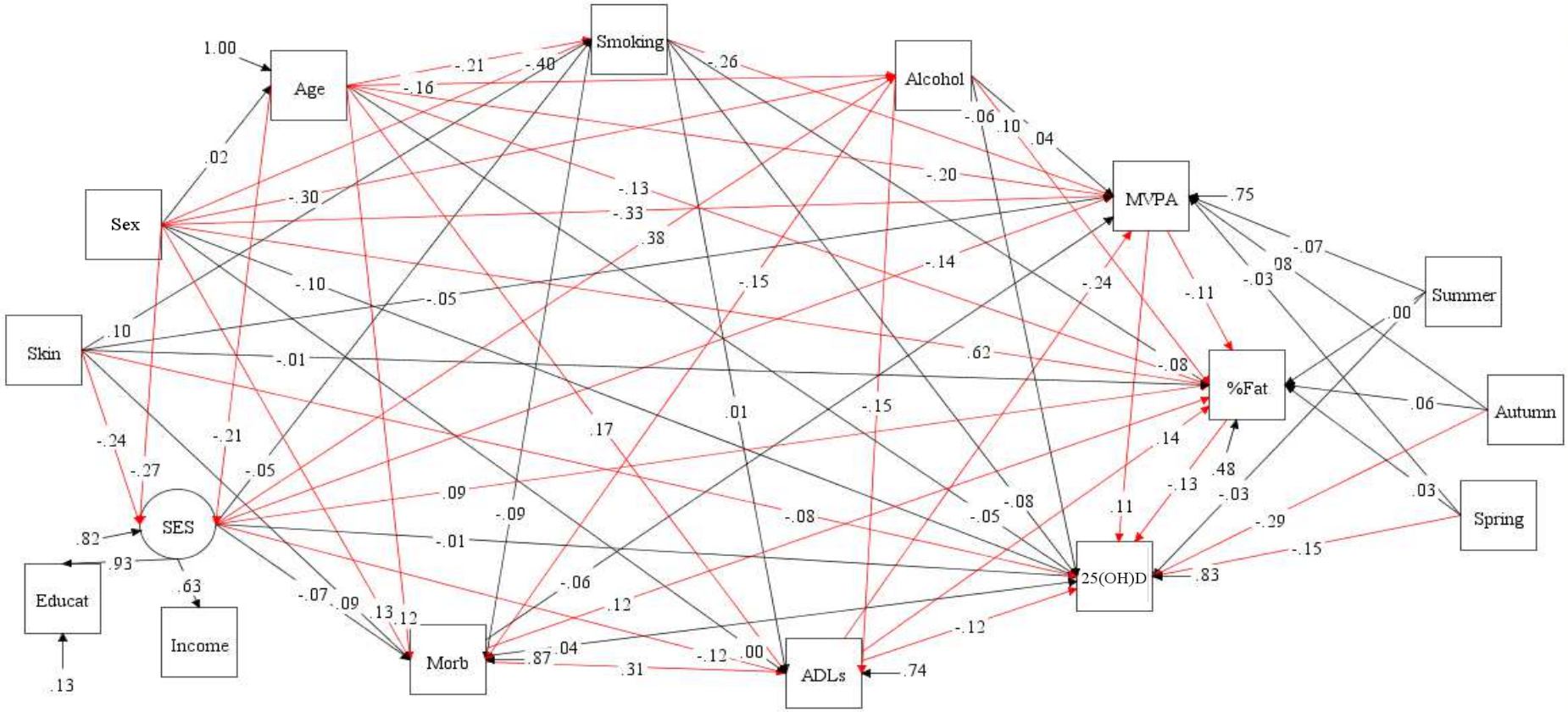
Table S4: The direct effects of covariates on the model of TPA on %fat and 25(OH)D. EpiFloripa Aging cohort study. Florianopolis, Santa Catarina, Brazil, 2013-2015.

Figure S1: Theoretical model of the minimum set of adjustment covariates indicated by the DAG of the association between physical activity and 25(OH)D.



The directed acyclic graph (DAG), used to determine to minimum set of adjustments covariates, was constructed based on literature associations between variables to test the directed effect of the exposure variable Physical Activity on the outcome variable concentration of 25-hydroxycholecalciferol [25(OH)D]. The mediators are adiposity and sun exposure. The variables identified by the bottom red are the ancestors of exposure and outcome; the bottom blue are the ancestors of outcome; and the bottom gray are the unobserved or latent (that was not collected in the research). The lines in pink are the biasing path, and in green are the causal path. ADLs, Activity of Daily Life.

Figure S2 - Theoretical model of the direct effects of MVPA, %fat and 25(OH)D with covariates. EpiFloripa Aging Cohort Study. Florianopolis, Santa Catarina, Brazil, 2013-2015.



The theoretical model (diagram) of the direct effect of variables was constructed by structural modeling equation analysis (SEM). The variables identified with a square are the observed variables and with a circle is the latent variable. Moderate and Vigorous Physical Activity (MVPA) is the exposure; 25-hydroxycholecalciferol [25(OH)D] is the outcome; and the mediator is body fat percentage (%fat). The other variables (covariates) were used as adjustments. Lines represent the direct effect and those in red are statistically significant ($p<0.05$). The numbers are the standard coefficient and should be interpreted as the example: -.21 = -0.21. Skin, Skin Color; Educat, Education; Income, Family Income; SES, Socioeconomic status; Morb, Morbidities; Smoking, Smoking Habit; Alcohol, Alcohol Consumption; ADLs, Activities of Daily Life; Adjustment parameters that validated the model: Chi-square (X^2) = 0.10; Root Mean Square Error of Approximation (RMSEA) = 0.02, 90%C.I. superior= 0.04, probability = 0.99; comparative fit index (CFI) = 0.99; Tucker–Lewis Index (TLI) = 0.98; standardized root mean square residual (SRMR) = 0.04.

Table S1: The direct, indirect, and total effect of PA on BMI, FMI, and 25(OH)D (n=559). EpiFloripa Aging cohort study. Florianopolis, Santa Catarina, Brazil, 2013-2015.

Pathways and estimates	Standardized coefficient	Standard error	p-value
Direct effects (With BMI)			
Model 1			
LPA → BMI	0.06	0.05	0.20
LPA → 25(OH)D	0.02	0.05	<0.05
BMI → 25(OH)D	- 0.12	0.04	<0.05
Model 2			
MVPA → BMI	- 0.04	0.06	0.51
MVPA → 25(OH)D	0.12	0.05	<0.05
BMI → 25(OH)D	- 0.11	0.04	<0.05
Model 3			
TPA → BMI	0.04	0.05	0.45
TPA → 25(OH)D	0.05	0.05	0.28
BMI → 25(OH)D	- 0.12	0.04	<0.05
Indirect effects			
LPA → BMI → 25(OH)D	- 0.01	0.01	0.24
MVPA → BMI → 25(OH)D	0.004	0.01	0.51
TPA → BMI → 25(OH)D	- 0.004	0.01	0.46
Total effects			
LPA (Model 1)	0.01	0.05	0.78
MVPA (Model 2)	0.12	0.05	<0.05
TPA (Model 3)	0.05	0.05	0.32
Direct effects (With FMI)			
Model 4			
LPA → FMI	- 0.03	0.04	0.46
LPA → 25(OH)D	0.01	0.05	0.85
FMI → 25(OH)D	- 0.16	0.05	<0.001
Model 5			
MVPA → FMI	- 0.08	0.05	0.13
MVPA → 25(OH)D	0.11	0.05	<0.05
FMI → 25(OH)D	- 0.15	0.05	<0.05
Model 6			
TPA → FMI	- 0.05	0.04	0.25
TPA → 25(OH)D	0.04	0.05	0.41
FMI → 25(OH)D	- 0.16	0.04	<0.001
Indirect effects			
LPA → FMI → 25(OH)D	0.01	0.01	0.47
MVPA → FMI → 25(OH)D	0.01	0.01	0.16
TPA → FMI → 25(OH)D	0.01	0.01	0.27

Total effects			
LPA (Model 4)	0.01	0.05	0.77
MVPA (Model 5)	0.12	0.05	<0.05
TPA (Model 6)	0.05	0.05	0.33

SEM analysis results of the direct, indirect, and total effect of Physical Activity (PA; LPA: Light Physical Activity; MVPA, Moderate and Vigorous Physical Activity; TPA, Total Physical Activity) on adiposity (BMI, Body Mass Index; FMI, Fat Mass Index), and on concentration of 25-hydroxycholecalciferol [25(OH)D]. The arrows represent the direct effect. Models are adjusted by Season, Socioeconomic status, Sex, Age, Skin Color, Smoking Habit, Alcohol Intake, Activities of Daily Life, Number of morbidities. Adjustment parameters that validated the **Model 1**: X^2= 0.10; RMSEA= 0.02, 90%C.I. superior= 0.04, probability= 0.99; CFI=0.99; TLI= 0.97; SRMR= 0.04. **Model 2**: X^2= 0.12; RMSEA= 0.02, 90%C.I. superior= 0.04, probability= 1.00; CFI=0.99; TLI= 0.97; SRMR= 0.04. **Model 3**: X^2= 0.12; RMSEA= 0.02, 90%C.I. superior= 0.04, probability= 1.00; CFI=0.99; TLI= 0.97; SRMR= 0.04. **Model 4**: X^2= 0.10; RMSEA= 0.02, 90%C.I. superior= 0.04, probability= 0.99; CFI=0.99; TLI= 0.97; SRMR= 0.04. **Model 5**: X^2= 0.12; RMSEA= 0.02; 90%C.I. superior= 0.04, probability= 1.00; CFI=0.99; TLI= 0.97; SRMR= 0.04. **Model 6**: X^2= 0.12; RMSEA= 0.02, 90%C.I. superior= 0.04, probability= 1.00; CFI=0.99; TLI= 0.97; SRMR= 0.04.

Table S2: The direct effect of covariates on the model of LPA, %fat and 25(OH)D. EpiFloripa Aging cohort study. Florianopolis, Santa Catarina, Brazil, 2013-2015.

Pathways and estimates	**Standardized coefficient**	**Standard error**	**p-value**
Latent variables			
SES			
Education	0.92	0.04	<0.001
Family income	0.64	0.04	<0.001
Direct effects			
LPA			
Season - Summer	- 0.06	0.05	0.24
Season - Spring	0.01	0.05	0.85
Season - Autumn	0.11	0.05	<0.05
SES	- 0.23	0.06	<0.001
Sex	0.01	0.06	0.84
Age	- 0.12	0.06	<0.05
Skin Color	- 0.04	0.05	0.46
Smoking Habit	- 0.15	0.07	<0.05
Alcohol Intake	0.06	0.08	0.44
ADLs	- 0.20	0.07	<0.05
Number of morbidities	- 0.06	0.06	0.26
%fat			
LPA	- 0.07	0.03	<0.05
Season - Summer	0.004	0.04	0.91

Season - Spring	0.03	0.03	0.31
Season - Autumn	0.06	0.03	0.09
SES	0.09	0.04	<0.05
Sex	0.66	0.03	<0.001
Age	- 0.12	0.03	<0.001
Skin Color	- 0.01	0.03	0.85
Smoking Habit	- 0.06	0.04	0.16
Alcohol Intake	0.10	0.04	<0.05
ADLs	0.15	0.03	<0.001
Number of morbidities	0.12	0.03	<0.001
25(OH)D			
LPA	0.002	0.05	0.97
%fat	- 0.15	0.05	<0.05
Season - Summer	- 0.04	0.04	0.36
Season - Spring	- 0.15	0.04	<0.001
Season - Autumn	- 0.28	0.04	<0.001
SES	- 0.02	0.06	0.69
Sex	- 0.12	0.06	0.03
Age	- 0.08	0.04	0.06
Skin Color	0.09	0.04	0.04
Smoking Habit	- 0.11	0.05	0.03
Alcohol Intake	- 0.05	0.06	0.38
ADLs	- 0.14	0.04	<0.05
Number of morbidities	0.03	0.05	0.48

Structural Equation Modeling (SEM) analysis results of the direct effect of each covariate on Light Physical Activity (LPA), body fat percentage (%fat), and concentration of 25-hydroxycholecalciferol [25(OH)D]. The latent variable, socioeconomic status (SES), was constructed by education (years of study) and family income. ADLs, Activities of Daily Life; Adjustment parameters that validated the model: X^2= 0.10; RMSEA= 0.02, 90%C.I. superior= 0.04, probability= 1.00; CFI=0.99; TLI= 0.98; SRMR= 0.04.

Table S3: The direct effects of covariates on the model of MVPA on %fat and 25(OH)D. EpiFloripa Aging cohort study. Florianopolis, Santa Catarina, Brazil, 2013-2015.

Pathways and estimates	**Standardized coefficient**	**Standard error**	**p-value**
Latent variables			
SES			
Education	0.93	0.04	<0.001
Family income	0.63	0.04	<0.001
Direct effects			
MVPA			

Season - Summer	- 0.07	0.05	0.18
Season - Spring	- 0.03	0.05	0.57
Season - Autumn	0.08	0.05	0.10
SES	- 0.14	0.06	<0.05
Sex	- 0.33	0.06	<0.001
Age	- 0.20	0.06	<0.001
Skin Color	- 0.05	0.06	0.35
Smoking Habit	- 0.26	0.06	<0.001
Alcohol Intake	0.04	0.07	0.57
ADLs	- 0.24	0.06	<0.001
Number of morbidities	- 0.06	0.05	
%fat			
MVPA	- 0.11	0.04	<0.05
Season - Summer	0.001	0.04	0.97
Season - Spring	0.03	0.03	0.37
Season - Autumn	0.06	0.03	0.09
SES	0.09	0.04	<0.05
Sex	0.63	0.04	<0.001
Age	- 0.13	0.03	<0.001
Skin Color	- 0.01	0.03	0.77
Smoking Habit	- 0.08	0.05	0.09
Alcohol Intake	0.10	0.05	<0.05
ADLs	0.14	0.03	<0.001
Number of morbidities	0.12	0.03	<0.001
25(OH)D			
MVPA	0.11	0.05	0.05
%fat	- 0.13	0.05	<0.05
Season - Summer	- 0.03	0.04	0.47
Season - Spring	- 0.15	0.04	<0.001
Season - Autumn	- 0.29	0.04	<0.001
SES	- 0.01	0.05	0.86
Sex	- 0.10	0.06	0.08
Age	- 0.05	0.04	0.22
Skin Color	- 0.08	0.04	<0.05
Smoking Habit	- 0.08	0.05	0.12
Alcohol Intake	- 0.06	0.06	0.32
ADLs	- 0.12	0.04	<0.05
Number of morbidities	0.04	0.04	0.43

Structural Equation Modeling (SEM)analysis results of the direct effect of each covariate on Moderate and Vigorous Physical Activity (MVPA), body fat percentage (%fat), and concentration of 25-hydroxycholecalciferol [25(OH)D]. The latent variable, socioeconomic status (SES), was constructed by education (years of study) and family income. ADLs, Activities of Daily Life. Adjustment parameters that

validated the model: X^2= 0.10; RMSEA= 0.02, 90%C.I. superior= 0.04, probability= 1.00; CFI=0.99; TLI= 0.98; SRMR= 0.04.

Table S4: The direct effects of covariates on the model of TPA, %fat, and 25(OH)D. EpiFloripa Aging cohort study. Florianopolis, Santa Catarina, Brazil, 2013-2015.

Pathways and estimates	Standardized coefficient	Standard error	p-value
Latent variables			
SES			
Education	0.92	0.04	<0.001
Family income	0.64	0.04	<0.001
Direct effects			
TPA			
Season - Summer	- 0.07	0.05	0.14
Season - Spring	- 0.003	0.05	0.96
Season - Autumn	0.12	0.06	<0.05
SES	- 0.23	0.06	<0.001
Sex	- 0.10	0.06	0.12
Age	- 0.17	0.06	<0.05
Skin Color	- 0.05	0.06	0.37
Smoking Habit	- 0.20	0.06	<0.05
Alcohol Intake	0.07	0.08	0.43
ADLs	- 0.25	0.07	<0.001
Number of morbidities	- 0.07	0.06	0.21
%fat			
TPA	- 0.10	0.04	<0.05
Season - Summer	0.002	0.04	0.96
Season - Spring	0.03	0.03	0.33
Season - Autumn	0.06	0.03	0.07
SES	0.09	0.04	<0.05
Sex	0.65	0.03	<0.001
Age	- 0.12	0.03	<0.001
Skin Color	- 0.01	0.03	0.80
Smoking Habit	- 0.07	0.04	0.11
Alcohol Intake	0.10	0.05	0.04
ADLs	0.14	0.03	<0.001
Number of morbidities	0.12	0.03	<0.05
25(OH)D			
TPA	0.04	0.05	0.48
%fat	- 0.14	0.05	<0.05
Season - Summer	- 0.03	0.04	0.40
Season - Spring	- 0.15	0.04	<0.001
Season - Autumn	- 0.28	0.04	<0.001
SES	- 0.02	0.06	0.79

Sex	- 0.12	0.06	<0.05
Age	- 0.07	0.04	0.09
Skin Color	- 0.09	0.04	<0.05
Smoking Habit	- 0.10	0.05	<0.05
Alcohol Intake	- 0.05	0.06	0.35
ADLs	- 0.13	0.04	<0.05
Number of morbidities	0.03	0.05	0.46

Structural Equation Modeling (SEM) analysis results of the direct effect of each covariate on Total Physical Activity (TPA), body fat percentage (%fat), and concentration of 25-hydroxycholecalciferol [25(OH)D]. The latent variable, socioeconomic status (SES), was constructed by education (years of study) and family income. ADLs, Activities of Daily Life. Adjustment parameters that validated the model: X^2= 0.10; RMSEA= 0.02, 90%C.I. superior= 0.04, probability= 1.00; CFI=0.99; TLI= 0.98; SRMR= 0.0

4.2 CAPÍTULO 2 - ESTUDOS DA RELAÇÃO ENTRE VITAMINA D E SINTOMAS DEPRESSIVOS

Neste capítulo são apresentados os artigos:

Artigo 3 - "V*itamin D and depression in older adults: lessons learned from observational and clinical studies"* (páginas 129 a 175).

Artigo publicado: CEOLIN, G. et al. VITAMIN D AND DEPRESSION IN OLDER ADULTS: LESSONS LEARNED FROM OBSERVATIONAL AND CLINICAL STUDIES. **Nutrition Research Reviews**, p. 1–63, 13 jan. 2022.

Artigo 4 - "*Vitamin D, depressive symptoms and COVID-19 pandemic: mind the gap*" (páginas 176 a 189).

Artigo publicado: CEOLIN, G. et al. Vitamin D, Depressive Symptoms, and Covid-19 Pandemic. **Frontiers in Neuroscience**, v. 15, 2021.

Artigo 5 - "*Lower serum 25-hydroxycholecalciferol is associated with depressive symptoms in older adults in Southern Brazil*" (páginas 190 a 216).

Artigo publicado: CEOLIN, G. et al. Lower serum 25-hydroxycholecalciferol is associated with depressive symptoms in older adults in Southern Brazil. **Nutrition Journal**, v. 19, n. 1, p. 123, 14 nov. 2020.

4.2.1 Artigo 3

VITAMIN D AND DEPRESSION IN OLDER ADULTS: LESSONS LEARNED FROM OBSERVATIONAL AND CLINICAL STUDIES

Vitamin D and Depression in Older Adults

Gilciane Ceolin[a,d], Luciana da Conceição Antunes[b,d], Morgana Moretti[c], Débora Kurrle Rieger[b,d], Júlia Dubois Moreira[b,d,].

[a] Postgraduate Program in Nutrition. Universidade Federal de Santa Catarina.

[b] Department of Nutrition. Universidade Federal de Santa Catarina.

[c] Postgraduate Program in Biochemistry. Universidade Federal de Santa Catarina.

[d] Translational Nutritional Neuroscience working group. Universidade Federal de Santa Catarina.

ABSTRACT

Depression is a mental disorder triggered by the interaction of social, psychological, and biological factors that have an important impact on an individual's life. Despite being a well-studied disease with several established forms of treatment, its prevalence is increasing, especially among older adults. New forms of treatment and prevention are encouraged, and some researchers have been discussing the effects of vitamin D (VitD) on depression; however, the exact mechanism by which VitD exerts its effects is not yet conclusive. In this study, we aimed to discuss the possible mechanisms underlying the association between VitD and depression in older adults. Therefore, we conducted a systematic search of databases for indexed articles published until April 30, 2021. The primary focus was on both observational studies documenting the association between VitD and depression/depressive symptoms, and clinical trials documenting the effects of VitD supplementation on depression/depressive symptoms, especially in older adults. Based on pre-clinical, clinical, and observational studies, it is suggested that the maintenance of adequate VitD concentrations is an important issue, especially in older adults, which are a risk population for both VitD deficiency and depression. Nevertheless, it is necessary to carry out more studies using longitudinal approaches in low- and middle-income countries to develop a strong source of evidence to formulate guidelines and interventions.

Keywords: Depression. 25-hydroxycholecalciferol. Vitamin D. Review. Observational Studies. Clinical Trials. Older Adults. Aging.

INTRODUCTION

Depression is a mental disorder that causes clinically significant suffering and/or impairment in the social, professional, economic, and other important areas of an individual's life, and is the main cause of suicide in more severe cases [1–4]. The prevalence of depression in 2015 was estimated to be 4.4% globally, with a higher prevalence among those between 55 and 77 years of age. Women appear to be more affected (7.5%) than men (5.5%) [5]. Among those over 60 years old, depression occurs in 7.0% of the general older population [6]. According to the Global Burden of Disease, Injuries, and Risk Factors – GBD survey, depression is among the top three causes of disability [7]. There has been a significant increase in the global burden of disease in years lived with disabilities (YLDs) in the past 20 years due to depressive disorders. In 1990, depression occupied the fourth position, moving to the third in 2007 with an increase of 33.4%, and remained in the third position between 2007 and 2017; however, it has increased by 14.3% [8]. Moreover, people with depressive symptoms are undiagnosed, otherwise, their prevalence could be higher [4].

Mental disorders are among the main problems in public health, and mood disorders are diseases with higher costs to health systems worldwide [2,3,9,10]. According to the Mental Health Atlas of the World Health Organization (WHO), low- and middle-income countries spend less than $ 1 per year *per capita* in the treatment and prevention of mental disorders, compared to an average of > $ 80 in high-income countries due to socioeconomic issues [11]. Therefore, there is an urgent need to identify the modifiable risk factors associated with the etiology of depression, helping with the treatment and prevention of this disorder, especially in low- and middle-income countries [12,13].

Depression is a complex disease triggered by the interaction between social, psychological, and biological factors [4,14]. In older adults, depression can be triggered by a series of factors such as limitations in daily activities, cognition, mobility, and social changes such as retirement, social isolation, and relocation to long-term institutions [15]. Among the biological factors, genetic predisposition, neurotransmitter and neuroendocrine system imbalance, functional and structural brain anatomy, and cognition are the most studied mechanisms [16,17]. Recently, nutritional factors have shown an important relationship with the evolution, prevention, and treatment of mental disorders

[18]. The association between VitD and depression has emerged in scientific scenarios, and this nutrient seems to be relevant in the prevention of depressive symptom development. However, the mechanism by which VitD exerts its effects remains unclear [19,20].

Many clinical trials have been conducted to investigate the potential therapeutic effect of vitD on patients with depression, but the results remain inconclusive due to methodological issues [21]. VitD is a fat-soluble vitamin that is present in two forms: VitD2 (ergosterol) and VitD3 (cholecalciferol). It is obtained from diet, supplementation, and sun exposure [22,23]. VitD has a well-established role in mineral bone metabolism, but its effects are not restricted to bone health and are also important in maintaining many biological processes, such as the regulation of gene expression, cell proliferation and differentiation, and immune system regulation [24–26]. In the central nervous system (CNS), the presence of nuclear (Vitamin D Receptor, VDR) and membrane (Protein disulfide isomerase family A member 3, PDIA3) receptors for VitD and some enzymes (cytochrome P450 family enzymes CYP27a1, CYP27b1, and CYP24a1) responsible for converting its active form has raised the hypothesis that VitD may be involved in the pathophysiology of depression [27–31].

Low serum VitD concentrations [25-hydroxycholecalciferol, 25(OH)D] have been considered a public health problem worldwide, especially in the elderly [32]. For older adults, the prevalence of 25(OH)D deficiency (<50 nmol/L or <20 ng/mL) was 36% in the United States [33], 19% in Canada [34], 36% in China [35], and 4–89% in European countries [32]. In low- and middle-income countries, the prevalence was approximately 41% for older adults in Brazil [36], 91% in India [37], and 46% in Guatemala [38]. However, different cutoff points have been suggested, and a single value to define VitD deficiency or insufficiency has been debated [39]. Moreover, the establishment of desirable serum VitD concentrations is based on bone health to maintain mineral and skeletal homeostasis [39,40].

It is important to mention that VitD levels via skin synthesis and intestinal absorption are influenced by various factors such as skin pigmentation, latitude, season, age, obesity, and inflammatory bowel diseases, among others [41–43]. Due to reduced sun exposure, decreased skin synthesis and dietary intake, and intestinal malabsorption, the elderly are among the top risk groups for VitD deficiency [41,44]. They also present significant complications related to low VitD concentrations (<20 ng/mL), such as the risk of fractures due to fragility and bone loss, which contribute to age-related muscle

weakness and sarcopenia [28,43,45,46]. In addition, VitD concentrations <20 ng/mL have been associated with an increased risk of all-cause mortality [47].

In this review, we aimed to update the role of VitD in depression, discussing the metabolism of VitD, its mechanism of action in the brain, and the main evidence of pre-clinical, clinical, and observational studies, especially those involving older adults, a population risk for both conditions, in an attempt to highlight the potential preventive and therapeutic effects of this nutrient. Also, we aimed to suggest future directions for new studies. To this end, we conducted a systematic search for articles published until April 30, 2021. The databases used were PubMed, Scopus, Embase, Science Direct, and Web of Science (details are presented in the supplementary material).

VITAMIN D: SYNTHESIS AND METABOLISM

The synthesis of VitD (Figure 1) by epidermal epithelial cells begins when the exposure to ultraviolet B radiation (UVB, 290–315 nm) promotes the non-enzymatic transformation of 7-dehydrocholesterol (7-DHC or pro-VitD) in pre-VitD3 [48,49]. A photolytic break forms a secosteroid molecule, which then undergoes an isomerization reaction induced by heat to transform it into VitD3 (or cholecalciferol), a process that takes about 8 h [48–50]. Keratinocytes are the main cells of the epidermis that have the enzymatic machinery to metabolize VitD in its active form and express the vitamin D receptor (VDR) [22,51]. In contrast, the synthesis of the active form of VitD from either food or supplementation begins with incorporation into micelles and absorption through the enterocyte membrane by apical membrane transporters or by passive diffusion [52]. A fraction of VitD is incorporated into the chylomicrons, which are transported to the lymphatic system and then to the venous system by vitamin D binding protein (DBP) [50]. The other fraction is incorporated into adipose tissue and skeletal muscles [53].

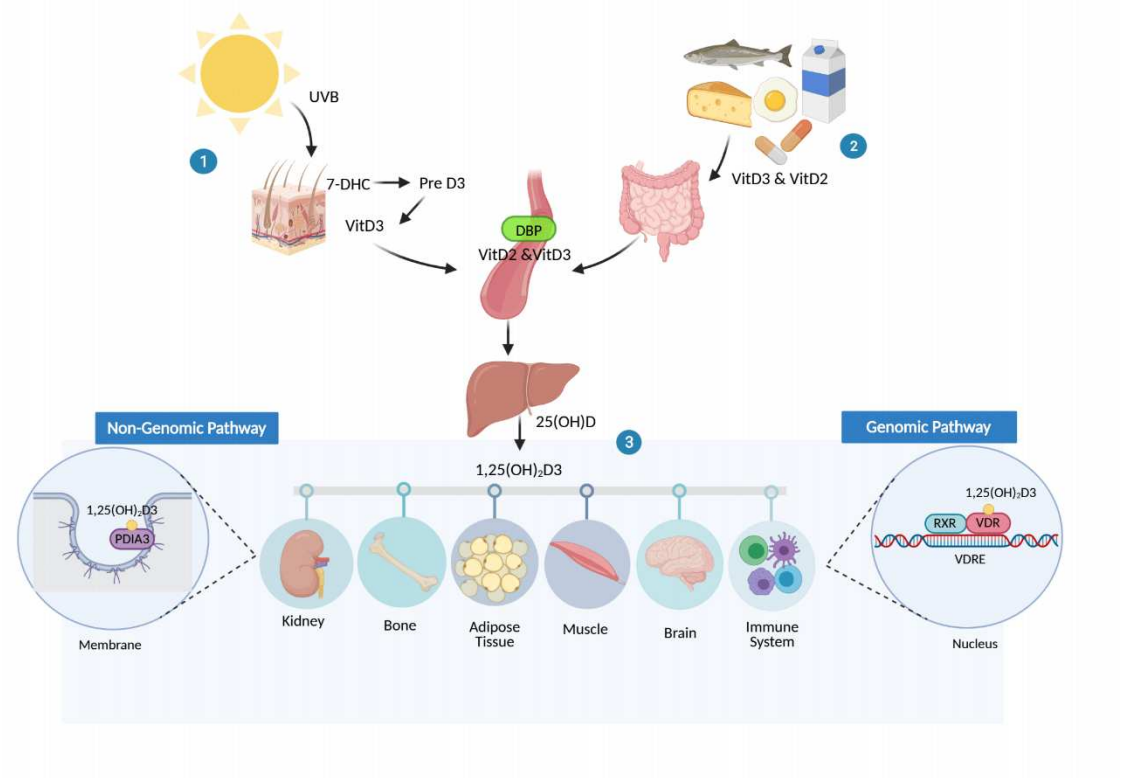


Figure 1. Vitamin D synthesis, metabolism, and target tissue actions

1. The synthesis of VitD from sunlight initiates in the skin when 7-DHC is converted in pre-vitD3 and then vitD3 [25(OH)D3 or cholecalciferol] and is carried by DBP through blood circulation. **2.** The VitD from dietary intake (VitD2/ergocalciferol and D3/cholecalciferol) is absorbed in the small intestine and packed into chylomicrons to reach the systemic circulation. Both VitD3 and VitD2 are also transported through blood circulation by DBP to the liver, when are converted to 25-hydroxyvitamin D [calcidiol or 25(OH)D], by the action of 25-hydroxylases. **3.** 25(OH)D coupled to DBP is transported to the target organs such as kidney, bones, adipose tissue, muscle, and brain, and cells such as in the immune system containing the enzyme 1-α-hydroxylase, which convert 25(OH)D to 1,25-dihydroxyvitamin D [calcitriol or $1,25(OH)_2D$], the active form of VitD. VitD act through both genomic and non-genomic pathways. In the genomic pathway, VitD active form enters the nucleus linked to the VDR where it binds to the RXR and then binds to the VDRE, resulting in modulation of target gene expression. In the non-genomic pathway, the VitD active form binds to the PDIA3 and starts signaling cascades including the activation of phospholipase A2 activating protein (PLAA), phospholipase A2 (PLA2), phospholipase C (PLC), and opening Ca^{2+} channels that results in the activation of secondary messengers. This figure was made using Bio Render (License: YN235V4QZA)

Both VitD2 and VitD3 are transported in the blood by DBP and must undergo activation through two consecutive enzymatic hydroxylation reactions in the liver and kidneys. In the liver, VitD2 and VitD3 are converted into 25-hydroxyvitamin D (calcidiol or 25(OH)D) by the action of 25-hydroxylases (cytochrome P450 enzymes group, CYP2R1, or CYP27A1) [54–56]. The 25(OH)D coupled with DBP is transported to various

tissues with cells containing the enzyme 1-α-hydroxylase (CYP27B1), as in the kidney, where it converts 25(OH)D to 1,25-dihydroxyvitamin D (calcitriol or 1,25$(OH)_2$D), the active form of VitD [54–56].

The conversion of 1,25$(OH)_2$D in the kidney is regulated by several factors, including circulating concentrations of parathyroid hormone (PTH) in the parathyroid glands, serum phosphorus, calcium, fibroblast growth factor 23 (FGF-23) in the bone, and its self-regulation. 1,25$(OH)_2$D decreases its own synthesis by negative feedback; it decreases the secretion of parathyroid hormone and increases the expression of 24-hydroxylase [57]. This self-regulation by the expression of 24-hydroxylase is found in most tissues and is essential for the catabolism of 25(OH)D and 1,25$(OH)_2$D [58].

The biological effects of 1,25$(OH)_2$D are largely mediated by VDR, which is expressed in almost all human cells [59,60]. The VDR belongs to a subfamily of nuclear receptors, which contains two sites for ligand binding, called the genomic pocket (VDR-GP) that binds in a bowl-like configuration for gene transcription and the alternative pocket (VDR-AP), which connects in a planar-like configuration for quick responses [60]. When VDR-GP binds to 1,25$(OH)_2$D, it enters the cell nucleus and binds to the retinoid X receptor (RXR). This complex then binds to the vitamin D responsive element (VDRE) in the promoter regions of the target genes by recruiting co-activator or co-repressor complexes that regulate either positively or negatively the transcription of genes[53,60]. The other suggested VitD receptor is the PDIA3, also known as endoplasmic reticulum protein (ERp60, ERp57, and Grp58), or VitD membrane-associated rapid-response steroid-binding protein (1,25-MARRS)[61]. PDIA3 is present in caveolae (lipid rafts) and is linked to the rapid responses of 1,25$(OH)_2$D by activating signaling cascades, where it physically interacts with downstream mediators [61,62] including the activation of phospholipase A2 activating protein (PLAA), phospholipase A2 (PLA2), phospholipase C (PLC), and opening Ca^{2+} channels that result in the activation of secondary messengers [63]. PDIA3 is involved in the function of immune and musculoskeletal systems as well as mammary gland growth and development, and participates in the intestinal uptake of calcium and phosphate[63]. PDIA3 also mediates the effect of 1,25$(OH)_2$D on the regulation of osteoblasts and chondrocytes [64].

VITAMIN D: MECHANISM OF ACTION IN THE BRAIN

The first evidence of the role of VitD in brain function began with autoradiographic findings of the presence of VDR in the brain tissue of laboratory animals [65]. VDR is found in neurons and glial cells in most regions of the brain, including the cortex (temporal, frontal, parietal, and cingulate); deep gray matter (thalamus, basal ganglia, hypothalamus, hippocampus, and amygdala); cerebellum, nuclei of the brain stem, substantia nigra (an area abundant in dopaminergic neurons); spinal cord; and ventricular system [66]. In addition, an alternative mechanism was observed in post-mortem human brain tissue samples. It was demonstrated that $1,25(OH)_2D$ can be activated locally through the expression of the enzyme 1α-hydroxylase, which is classically expressed in the kidney and is responsible for catalyzing the conversion of 25(OH)D into $1,25(OH)_2D$, showing that both forms (VitD and 25(OH)D) can pass through the blood-brain barrier [67,68].

It has been proposed that within the neurovascular unit, the machinery for conversion of both VitD forms involves the cytochrome P450 family enzymes CYP27a1, CYP27b1, and CYP24a1, which are expressed in neurons, and CYP27a1, which are expressed in all neural cell types and are highly expressed in endothelial cells [31]. The active form of VitD triggers genomic actions associated with VDR or non-genomic actions related to PDIA3, which is expressed in small amounts in extra-cerebral tissues such as the liver and kidney. On the other hand, PDIA3 is highly expressed in the brain and appears to be the main brain receptor for VitD in neural tissue (Figure 2).

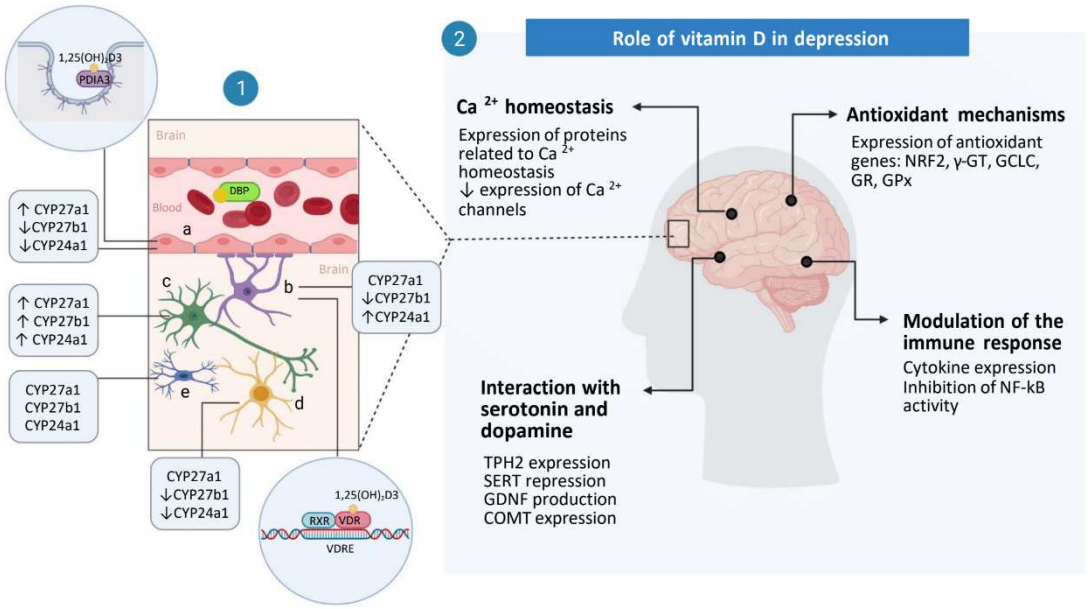


Figure 2. The role of Vitamin D in depression

1. In the brain, both active and inactive VitD is carried through blood circulation binding to DBP and can permeate the blood-brain barrier. All brain cells [endothelial cells (a), astrocytes (b), neurons (c), oligodendrocytes (d), and microglia (e)] have the machinery to transform VitD. VitD is turned into 25(OH)D by CYP27a1 in endothelial cells and neurons, and it is metabolized to $1,25(OH)_2D$ by CYP27b1 in neurons or microglia. All brain cells can express VDR, but it is highly expressed by astrocytes. When it enters the cell, $1,25(OH)_2D$ can bind to VDR, and then to the RXR in the nucleus. The complex VDR-RXR binds to the VDRE and initiate gene transcription or can be inactivated when in excess by CYP24a1. All brain cells can express PDIA3 but is highly expressed in endothelial cells when $1,25(OH)_2D$ can bind and PDIA3 physically interacts with downstream mediators to initiate rapid responses and induce signaling cascades. **2.** VitD regulates the expression of many processes related to depression. It maintains Ca^{2+} homeostasis, activates the expression of many antioxidant genes, regulates the formation of serotonin and dopamine, and reduces inflammation by reducing the expression of inflammatory cytokines. TPH2: tryptophan hydroxylase 2. SERT: serotonin reuptake transporter. GDNF: Glial cell-derived neurotrophic factor. COMT: catechol-o-methyltransferase. NRF2: nuclear factor-erythroid-2-related factor 2. γ-GT: γ-glutamyl transpeptidase. GCLC: glutamate-cysteine ligase. GR: glutathione reductase. GPx: glutathione peroxidase. NF-κB: Nuclear factor-kappa B. This figure was made using Bio Render (License: FB235V4MBD)

VitD is known as a *neurosteroid* because of its important role in the CNS in processes related to cell differentiation, production and release of neurotrophic factors, synthesis of neurotransmitters, intracellular calcium homeostasis, influence on the redox

state, function, and metabolism of neuronal cells and cognition (Figure 2) [29,69]. The active form of VitD stimulates the synthesis of nerve growth factor (NGF), which acts on cholinergic neurons, and positively regulates the synthesis of neurotrophic factors derived from the glial cell line (GDNF), which acts on dopaminergic neurons, and neurotrophin 3 (NT-3), which are key to neuronal promotion, survival, differentiation, and plasticity[66]. Due to its involvement in several brain functions, in humans, observational studies have linked low serum VitD concentrations with some brain disorders, such as schizophrenia, failure in synaptic plasticity related to learning and memory, cognitive decline, and mood disorders [27,29,70].

VITAMIN D AND DEPRESSIVE SYMPTOMS: EVIDENCE FROM PRE-CLINICAL AND CLINICAL STUDIES

Pre-clinical Studies

Depression is a multifactorial disease, which makes it challenging to identify the precise biological mechanisms that link VitD to depression. However, some hypotheses have been proposed based on the experimental research data. Calcium homeostasis, glutamatergic/GABAergic and monoaminergic system modulation, influence on circadian rhythm, anti-inflammatory properties, and redox balance modulation are among the most investigated mechanisms.

The homeostasis of intracellular and extracellular calcium (Ca^{2+}) is an important factor responsible for driving the onset of depression, which links VitD with the development of depressive symptoms because of its interaction with excitatory synapses [27]. The imbalance in intracellular Ca^{2+} is caused by an elevation in glutamate and by activation of the phosphoinositide signaling pathway that generates inositol triphosphate (IP3), which releases Ca^{2+} from internal stores [27,71,72]. The elevation of Ca^{2+} can affect both ionotropic (NMDA) and metabotropic (mGluR) receptors [73]. This change in neural activity drives excitatory neurons and is responsible for the decline in the activity and the number of GABAergic inhibitory neurons and modulation of the activity of other neurotransmitter systems, including the inhibition of the serotonergic system and the release of norepinephrine and dopamine [74]. However, $1,25(OH)_2D$ can act in this pathway by inducing the expression of proteins related to the maintenance of Ca^{2+} homeostases, such as calbindin, parvalbumin, Na^+/Ca^{2+} exchanger (NCX1), and pump

Ca^{2+} -ATPase (PMCA). It also regulates Ca^{2+} concentrations by reducing the expression of the CaV1.2 calcium channel [27,75].

Concerning other neurotransmitter systems, it has been proposed that depression could result from a deficiency of serotonin (5-HT) in the synaptic cleft [76–78]. 5-HT is derived from the essential amino acid tryptophan. To produce 5-HT in the brain, tryptophan must first be transported across the blood-brain barrier and then metabolized by the enzyme tryptophan hydroxylase 2 (TPH2). VDR activation by $1,25(OH)_2D$ can induce the expression of the TPH2 gene in serotonergic neurons [79,80]. In addition, $1,25(OH)_2D$ could act in the repression of the serotonin reuptake transporter (SERT or 5-HTT), and the mitochondrial enzyme responsible for 5-HT catabolism, monoamine oxidase-A (MAO-A), resulting in potentiated serotonergic transmission [81].

In the dopaminergic system, VitD is involved in the maturation of dopaminergic neurons. VDR is present in the nucleus of positive neurons for tyrosine hydroxylase (TH) and can stimulate glial cell line-derived neurotrophic factor (GDNF) in dopaminergic neurons [82]. VDR also modulates metabolism through the genomic regulation of catechol-o-methyl transferase (COMT) expression, a key enzyme involved in dopamine turnover [82,83]. In addition, in a rat model of depression, VitD appears to produce therapeutic effects comparable to antidepressant drugs such as fluoxetine, improving anhedonia-like symptoms, probably by regulating the effect of dopamine-related actions on the nucleus accumbens [84].

From a chronobiological perspective, a growing body of evidence suggests that VitD participates in the mechanisms orchestrating the circadian rhythm, suggesting that hypovitaminosis D might play a role in sleep disorders [85]. VitD has been associated with the regulation and maintenance of optimal sleep [86]. The mediating role of VitD in the circadian rhythm is supported by studies demonstrating the association between lower concentrations of VitD and sleep [87,88]. In addition, a circadian oscillation pattern can be equally observed in plasma $1,25(OH)_2D$ concentration and DBP, which corroborates the association between VitD and the circadian system [87].

Because sunlight partially regulates the synthesis of VitD and is the main zeitgeber in the regulation of the circadian rhythm, it is conceivable that VitD might contribute to the transduction of signs regulating it [89,90]. The suprachiasmatic nucleus (SCN) is a hypothalamic structure found directly above the optic chiasm, and its strategic anatomical position allows prompt central response to sunlight stimuli through the retina. SCN is the main oscillator, which accounts for the control of circadian rhythms by regulating several

body functions during a 24-h cycle, sending peripheral signals through neurohumoral mechanisms [91]. For this reason, the authors postulated that VitD is likely involved in the regulation of the sleep/wake rhythm [90].

Melatonin is a neurohormone involved in the regulation of mammalian circadian rhythms and sleep. It is released in response to darkness and is synthesized by the pineal gland [92]. Its synthesis occurs from the metabolism of serotonin [93], which, in turn, is also regulated by VitD. Along with VDR, $1,25(OH)_2D$ triggers the central expression of *TPH2*, the gene responsible for encoding the enzyme catalyzing the conversion of tryptophan into 5-hydroxytryptophan, which is then metabolized into serotonin and subsequently as melatonin [67,79]. Therefore, it is thought that the combination of deficits in serum VitD levels and circadian rhythm impairments could induce a robust increase in depressive symptoms and/or act as an interplay variable in the pathophysiology of major depressive disorder.

Regarding anti-inflammatory pathways, it is also relevant to point out that both melatonin and VitD mediate the mitochondrial function in homeostasis, such as downregulating mechanistic target of rapamycin (mTOR), inducible nitric oxide synthase (iNOS), and nuclear factor kappa B (NF-κB) pathways, and upregulating Sirtuin-1 (SIRT-1) and adenosine monophosphate-activated protein kinase (AMPK) pathways, which are critical mechanisms to avoid anomalous inflammatory responses related to oxidative stress and apoptosis [94].

Pro-inflammatory cytokines, interleukins, and other inflammatory markers such as prostaglandins and acute-phase C-reactive protein (CRP) have been implicated to play role in the pathophysiology of depression [95–97]. Inflammation leads to increased blood-brain barrier permeability, allowing easier entry of inflammatory molecules into the CNS [98]. At a cellular level, it has been observed that TNF-α can induce glutamate release by activated microglia *in vitro*, leading to excitotoxic damage to neurons [99]. Some cytokines can directly increase enzymatic activity for converting tryptophan to kynurenine and decreasing the production of serotonin [100–102]. Considering that macrophages, dendritic cells, and activated B and T lymphocytes express 1α-hydroxylase and VDR, VitD could act by modulating the immune response and regulating cytokine expression [97,103]. Moreover, it was demonstrated that the activity of NF-κB, a transcription factor involved in the synthesis of pro-inflammatory cytokines, was inhibited by $1,25(OH)_2D$, which helps to maintain the balance of T helper cells (T helper, Th), inhibiting the production of Th1 and Th17 cytokines and increasing Th2 cytokine synthesis [75].

Interestingly, Boontanrart et al. (2016) reported that activated microglia were associated with an increased expression of VitD receptor and Cyp27b1, which encodes the 1α-hydroxylase enzyme for converting 25(OH)D into its active form, thereby enhancing their responsiveness to 25(OH)D. Moreover, activated microglia exposed to 25(OH)D had reduced expression of pro-inflammatory cytokines, IL-6, IL-12, and TNFα, and increased expression of IL-10. The decrease in pro-inflammatory cytokines was dependent on IL-10 induction of suppressor of cytokine signaling-3 (SOCS3). Therefore, 25(OH)D increases the expression of IL-10, creating a feedback loop via SOCS3, which reduces the pro-inflammatory immune response by activated microglia and probably protects the CNS from damage [(104)]. In agreement with these findings, Lee et al. (2020) showed that VitD signaling in neurons elicits an anti-inflammatory state in microglia. Moreover, the partial deletion of VDR in neurons during early life exacerbates CNS autoimmunity in adult mice. Therefore, by changing the immune response of microglia, VitD may be an interesting mechanism for avoiding a prolonged inflammatory state in the CNS [(105)].

In addition, VDR activation stimulates the expression of many antioxidant genes, such as the nuclear factor erythroid-2 (NRF2), γ-glutamyl transpeptidase (γ-GT), glutamate-cysteine ligase (GCLC), glutathione reductase (GR), and glutathione peroxidase (GPx) [(27)]. VitD negatively regulates the expression of iNOS in monocyte-derived cells and increases the activity of γ-GT, an important enzyme in the glutathione pathway [(106,107)]. Reinforcing the modulation of oxidative stress as a mechanism associated with the antidepressant-like effect of VitD, repeated administration of this compound (2.5, 7.5, and 25 μg/kg, for 7 days) prevented depressive-like behavior and brain oxidative stress induced by chronic administration of corticosterone (21 days) in male and female mice[(108,109)]. It has been demonstrated that ROS triggers a variety of molecular cascades that increase the permeability of the blood-brain barrier, allowing inflammatory cytokines to enter the CNS [(110)]. Moreover, it has been well established that inflammation and oxidative stress, which mutually amplify each other, play an important role in the pathophysiology of depression and can be a target for therapeutic strategies [(111)].

Clinical Studies

Nineteen randomized clinical trials using VitD supplementation for depressive symptoms in adults were published until 2020 (Table 1). Nine studies were double-blinded, and 12/19 included individuals aged >65 years. Most of the studies were

conducted in high-income countries (13/19). Seven studies were conducted with community-dwelling, healthy volunteers or individuals with no specification, three studies only with VitD-deficient individuals [112–114]. Six included only individuals with the diagnosis of depression, and two with individuals with VitD deficiency and diagnosed depression [115,116]. Considering only the studies that included individuals with a diagnosis of depression (with or without VitD deficiency), the majority (4/8) presented improvement in depressive symptoms after VitD supplementation.
[Table 1].

Eight (7/19) studies reported an improvement in depressive symptoms after VitD supplementation, 11/19 reported no improvement, and one study lacked the power to assess due to sampling size [123]. Considering the studies that observed depressive symptom improvement, 5/7 were conducted with individuals with depression, and one of these (1/7) reported individuals with concomitant depression and VitD deficiency. VitD doses ranged from 600–300,000 IU, and the majority (6/7) used VitD doses above the DRI ul(> 4,000 UI/day). VitD doses of 600–4,000 UI were used on a daily basis; 20,000–50,000 UI were used weekly; and the effect of a single doses of 150,000–300,000 UI was evaluated.

Compared to the seven studies with positive results, the 11 studies that did not report improvements tended to use lower VitD doses (<4,000 UI) and longer periods (from 6 months to 5 years of supplementation). Of the 11 negative studies, only 4/11 used higher doses: Sanders et al. (2011) used a single dose of 500,000 IU in the winter for 3–5 years; Dean et al. (2011) used 5,000 UI/day for 6 weeks; Kjægaard et al. (2012) used 20,000 UI/week for 6 months; and Gugger et al. (2019) used 24,000 UI or 60,000 UI for 12 months [113,120,128,129]. The age range was higher in the studies that did not observe any improvement in depressive symptoms (individuals > 70 years).

Two meta-analyses have shown controversial results in clinical trials with vitamin D supplementation. Spedding et al. (2014) showed that VitD supplementation (a daily doses of ≥800 IU) could have an effect comparable to that of antidepressants in depressive symptoms [21]. Due to the methodological variability of the studies, the other meta-analysis conducted by Gowda et al. (2015) showed results that did not support this hypothesis [131]. In addition, a 5-year follow-up study found no potential effect of VitD on the incidence of depression [117]. Comparing the findings of the published meta-analysis with the studies searched in the present review, we observed that studies that did not observe improvements in depressive symptoms were conducted with older people

with no diagnosis of depression, with lower VitD doses, and for longer periods of follow-up. On the contrary, studies with positive results were conducted with younger populations with a diagnosis of depression and higher VitD doses for short periods of follow-up.

Key-points of pre-clinical and clinical studies

Preclinical studies have pointed to the potential and possible effect of vitD on depression. However, despite a considerable number of clinical studies, it has not yet been possible to prove whether VitD can prevent or be used as an adjuvant treatment in depression. The data remain controversial. In addition, it is not possible yet to define which doses/amount of vitamin D would be most appropriate for depression.

VITAMIN D AND DEPRESSIVE SYMPTOMS: EVIDENCE FROM OBSERVATIONAL STUDIES

Table 2 summarizes the information from 44 observational studies that investigated the relationship between VitD and depression/depressive symptoms in both adults and older adults since 2006.

Over 15 years of research published we observed that most studies included a mixed population with adults and older adults (27/44), were composed of people from cohort studies (27/44), and high-income economies countries (38/44), and used screening scales of depressive symptoms (37/44). The majority of studies performed a cross-sectional (27/44), followed by both a cross-sectional and longitudinal (10/44), and finally, a longitudinal analysis (7/44). Considering the studies that included only older adults (≥60 years, 17/44), most were composed of people from a cohort (14/17) and performed a cross-sectional (10/17), followed by both a cross-sectional and longitudinal (4/17), and finally, a longitudinal analysis (3/17). Moreover, only three studies were performed in low- or middle-income countries. This is an important issue because, according to the Mental Health Action Plan 2013–2030, there is an imbalance between research in high-and-low/middle-income countries that needs to be corrected to ensure that they have appropriate cultural and economic strategies to respond to mental health needs and priorities[13]. One of their main goals is to strengthen information systems, evidence, and research on mental health, and it suggests the development of more studies from low/middle-income countries.

It is difficult to compare the main differences between the studies because each study used a different method to analyze data, the cutoff point for the classification of serum VitD concentrations, and the screening for depressive symptoms or diagnosis for depression. However, an increasing number of studies have found an association between VitD and both depressive symptoms (32/44) and depression (7/44), specifically in those with cross-sectional analyses (24/44 and 7/44 respectively). Considering the studies in which researchers stratified the analysis by sex (7/44), the association was divergent because some authors [147,169] found an association in both sexes, while other studies found an association for women [163,175] or men [139,154,161]. In studies that included both adults and older adults, only five (5/27) reported no association[136,138,157,171,172].

Among the studies that exclusively analyzed data of older adults, those that performed a cross-sectional analysis (10/17) found an association between VitD and either depression[161,173] or depressive symptoms [135,146,154–156,165,170,174], but two studies that stratified the analysis by sex and found an association only for men [154,161]. In studies that performed either longitudinal or cross-sectional and longitudinal analyses combined, the results are controversial. In the longitudinal analysis, one [153] did not find any effect of VitD on the course of depression or remission, while another found a decrease in the score of depression with an increase in VitD [134], and another [169] found an increase in score of depression in a low level of VitD in 3- and 6-years follow-up in women and 3 years follow-up for men. In the cross-sectional and longitudinal combined analysis, some found a cross-sectional but not longitudinal association[159,167]; another study[160] did not find an association at baseline and 1-year follow-up, just found in a 4-years follow-up, and another found a cross-sectional association only for women and not in the follow-up[163]. Nevertheless, most of these studies found a higher risk for depression when considering VitD concentrations below 20 ng/mL or 50 nmol/L [135,146,154,159,160,163,169,174]. Other studies found higher risk when concentrations were below 10 ng/mL or 30 nmol/L[156,161,165,170], and two studies found a lower risk to depression in concentrations > 36.7 nmol/L [176] and 92 nmol/L[167]. Moreover, a meta-analysis with a mixed population showed that an increase of 10 ng/ml in individuals with low serum concentrations of 25(OH)D had a protective effect against depression, with a decrease of 4% in the risk of depression in cross-sectional studies, and a decrease of 8% in the incidence of depression in cohort studies [177]. In studies involving only the elderly population, the same 10 ng/mL increase in serum 25(OH)D level was associated with a 12% reduction in the risk of depression [178].

Key-points of observational studies

Despite the controversial results from observational studies, the major part has pointed to a higher risk of depression in low levels of VitD (20 ng/mL or 50 nmol/L). However, the variability between the study's methodology is important to place. At this moment is not possible to suggest a possible VitD cutoff point specifically to depression. Few studies were carried out with only older adults and those in low- and middle-income countries. Few longitudinal studies were carried out to point the causality of depression due to low levels.

FUTURE PERSPECTIVE

Older adults are considered a risk group for both depression and vitamin D deficiency, which justifies further studies to focus on this population. The aging process is associated with a reduced ability to sustain homeostasis, which could make elderly people more susceptible to pathological alterations, including neuropsychiatric disorders[179,180]. Also, women in menopausal transition are at risk of depression due to a lot of changes (i.e. hormone-related context, stressful events in life)[181]. Moreover, older adults with depression present a higher risk of mortality[182], especially in low- and middle-income countries, and have difficulties accessing treatment [4,183]. Another important factor is related to the adverse effects caused by antidepressant medications and the polypharmacy common in the elderly due to the concomitance of several pathologies, which can facilitate the discontinuation of treatment [184–186].

Facing the urgency to identify the modifiable risk factors associated with the etiology of depression, helping with the treatment and prevention of this disorder, it is important to carry out more studies following a proper methodology since we have an important background related to preclinical studies. As highlighted by WHO, these studies need to be developed especially in low- and middle-income countries, since these places have more prevalence of depression [12,13]. Further, observational studies have pointed to the preventive effect of adequate serum vitamin D concentrations on the development of depressive symptoms. More longitudinal studies have been suggested [178,187] to better elucidate the preventive effects of VitD on depression/depressive symptoms.

Besides, the variability in the diagnosis of depression, differences in VitD cut-off reference values, and methods for serum VitD analysis could influence these findings that

are still controversial [21,188,189]. Recently, the use of the standardized measurement of VitD proposed by the VitD Standardization Program (VDSP) has been recommended to improve clinical and public health practice and it is important to future studies apply in their methodology [190,191]. Considering the RCT that included the elderly population (>65 years), most of them did not present any improvements in depressive symptoms after VitD supplementation. This could be due to the lower VitD doses used in those studies and because they were not performed in older individuals diagnosed with depression. This is an important aspect to be addressed in future RCTs.

CONCLUSION

Overall, this updated review suggests that the monitoring and maintenance of adequate VitD concentrations are crucial, especially in older adults, a risk population for both VitD deficiency and depression. Several preclinical, clinical, and observational studies have suggested that VitD could have a beneficial effect on depression/depressive symptoms due to its genomic and non-genomic actions in many pathways involved in the pathophysiology of depression.

Although studies presented controversial results, clinical studies have shown that older adults with depression/depressive symptoms could benefit from higher doses of VitD supplementation for short periods. However, more RCTs are needed to confirm which doses and for how long the treatment is needed to achieve the greatest benefit. From the observational studies, the results are still controversial, but the major part has reported an association between low serum concentrations of VitD and high risk for depression/depressive symptoms in older adults, pointing to a possible preventive effect of VitD. Additional studies with prospective designs, especially in low- and middle-income countries, possibly will help to elucidate better the impact of deficient VitD status for mental health in adulthood and, consequently, for the elderly.

Financial Support

This work was supported by the *Coordenação de Aperfeiçoamento de Pessoal de Nível Superior – CAPES/Brasil* (Finance Code 001).

Conflict of Interest

None.

Authorship

All authors contribute to conception of this study. Material preparation and the first draft of the manuscript was written by [GC] and [JDM], and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

REFERENCES

1. AMERICAN PSYCHIATRIC ASSOCIATION. Manual diagnóstico e estatístico de transtornos mentais: DSM-5. 5th ed. Porto Alegre: Artmed; 2014.
2. Chisholm D, Sweeny K, Sheehan P, et al. Scaling-up treatment of depression and anxiety: a global return on investment analysis. The Lancet Psychiatry. 2016 May 1;3(5):415–24.
3. Olesen J, Gustavsson A, Svensson M, et al. The economic cost of brain disorders in Europe. Eur J Neurol. 2012 Jan;19(1):155–62.
4. World Health Organization. Depression [Internet]. 2020 [cited 2020 Feb 13]. Available from: https://www.who.int/news-room/fact-sheets/detail/depression
5. World Health Organization. Depression and Other Common Mental Disorders: Global Health Estimates [Internet]. Geneva: World Health Organization; 2017 p. 27. Available from: http://www.who.int/mental_health/management/depression/prevalence_global_health_estimates/en/
6. World Health Organization. Mental health of older adults [Internet]. 2017 [cited 2021 Apr 22]. Available from: https://www.who.int/news-room/fact-sheets/detail/mental-health-of-older-adults
7. Global Health Metrics. Depressive disorders — Level 3 cause [Internet]. Institute for Health Metrics and Evaluation. 2019 [cited 2021 Jan 6]. Available from: http://www.healthdata.org/results/gbd_summaries/2019/depressive-disorders-level-3-cause
8. James SL, Abate D, Abate KH, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. The Lancet. 2018 Nov 10;392(10159):1789–858.
9. DiLuca M, Olesen J. The Cost of Brain Diseases: A Burden or a Challenge? Neuron. 2014 Jun 18;82(6):1205–8.
10. Knapp M, Wong G. Economics and mental health: the current scenario. 2020 Jan 10;19:3–14.
11. World Health Organization, editor. Mental health atlas 2017 [Internet]. Geneva, Switzerland: World Health Organization; 2018. Available from: https://apps.who.int/iris/bitstream/handle/10665/272735/9789241514019-eng.pdf
12. Whiteford HA, Ferrari AJ, Degenhardt L, et al. The global burden of mental, neurological and substance use disorders: an analysis from the Global Burden of Disease Study 2010. PloS one. 2015 Feb 6;10(2):e0116820–e0116820.
13. World Health Organization. WHO | Mental health action plan 2013 - 2020 [Internet]. WHO. 2013 [cited 2020 Feb 13]. Available from: http://www.who.int/entity/mental_health/publications/action_plan/en/index.html

14. Li M, D'Arcy C, Meng X. Maltreatment in childhood substantially increases the risk of adult depression and anxiety in prospective cohort studies: systematic review, meta-analysis, and proportional attributable fractions. Psychol Med. 2016 Mar;46(4):717–30.
15. Andrade FCD, Wu F, Lebrão ML, et al. Life expectancy without depression increases among Brazilian older adults. Rev. Saúde Pública. 2016 Apr 15;50:12.
16. Kaltenboeck A, Harmer C. The neuroscience of depressive disorders: A brief review of the past and some considerations about the future. Brain and Neuroscience Advances. SAGE Publications Ltd STM; 2018 Jan 1;2:2398212818799269.
17. Otte C, Gold SM, Penninx BW, et al. Major depressive disorder. Nature Reviews Disease Primers. 2016 Sep 15;2(1):1–20.
18. Lai JS, Hiles S, Bisquera A, et al. A systematic review and meta-analysis of dietary patterns and depression in community-dwelling adults. Am J Clin Nutr. 2014 Jan 1;99(1):181–97.
19. Camargo A, Dalmagro AP, Rikel L, et al. Cholecalciferol counteracts depressive-like behavior and oxidative stress induced by repeated corticosterone treatment in mice. European Journal of Pharmacology. 2018 Aug 15;833:451–61.
20. Fedotova J, Dudnichenko T, Kruzliak P, et al. Different effects of vitamin D hormone treatment on depression-like behavior in the adult ovariectomized female rats. Biomedicine & Pharmacotherapy. 2016 Dec 1;84:1865–72.
21. Spedding S. Vitamin D and Depression: A Systematic Review and Meta-Analysis Comparing Studies with and without Biological Flaws. Nutrients. 2014 Apr;6(4):1501–18.
22. Bikle DD. Vitamin D and the skin: Physiology and pathophysiology. Rev Endocr Metab Disord. 2012 Mar;13(1):3–19.
23. Jäpelt RB, Jakobsen J. Vitamin D in plants: a review of occurrence, analysis, and biosynthesis. Frontiers in Plant Science [Internet]. Frontiers Media SA; 2013 [cited 2020 Apr 2];4. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3651966/
24. Johnson EJ, Mohn ES. Fat-Soluble Vitamins. Nutrition for the Primary Care Provider. 2015;111:38–44.
25. Norman AW. The History of the Discovery of Vitamin D and Its Daughter Steroid Hormone. ANM. 2012;61(3):199–206.
26. Umar M, Sastry KS, Chouchane AI. Role of Vitamin D Beyond the Skeletal Function: A Review of the Molecular and Clinical Studies. Int J Mol Sci [Internet]. 2018 May 30 [cited 2020 Sep 17];19(6). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6032242/
27. Berridge MJ. Vitamin D and Depression: Cellular and Regulatory Mechanisms. Pharmacol Rev. 2017 Apr 1;69(2):80–92.
28. Kesby JP, Eyles DW, Burne THJ, et al. The effects of vitamin D on brain development and adult brain function. Molecular and Cellular Endocrinology. 2011 Dec 5;347(1):121–7.
29. Mayne PE, Burne THJ. Vitamin D in Synaptic Plasticity, Cognitive Function, and Neuropsychiatric Illness. Trends in Neurosciences. 2019 Apr 1;42(4):293–306.
30. Smaga I, Niedzielska E, Gawlik M, et al. Oxidative stress as an etiological factor and a potential treatment target of psychiatric disorders. Part 2. Depression, anxiety, schizophrenia and autism. Pharmacol Rep. 2015 Jun;67(3):569–80.

31. Landel V, Stephan D, Cui X, et al. Differential expression of vitamin D-associated enzymes and receptors in brain cell subtypes. The Journal of Steroid Biochemistry and Molecular Biology. 2018 Mar 1;177:129–34.
32. Palacios C, Gonzalez L. Is vitamin D deficiency a major global public health problem? The Journal of steroid biochemistry and molecular biology. 2014 Oct;144 Pt A:138–45.
33. Ganji V, Zhang X, Tangpricha V. Serum 25-hydroxyvitamin D concentrations and prevalence estimates of hypovitaminosis D in the U.S. population based on assay-adjusted data. J Nutr. 2012 Mar;142(3):498–507.
34. Whiting SJ, Langlois KA, Vatanparast H, et al. The vitamin D status of Canadians relative to the 2011 Dietary Reference Intakes: an examination in children and adults with and without supplement use. The American Journal of Clinical Nutrition. 2011 Jul 1;94(1):128–35.
35. Lu H-K, Zhang Z, Ke Y-H, et al. High prevalence of vitamin D insufficiency in China: relationship with the levels of parathyroid hormone and markers of bone turnover. PLoS One. 2012;7(11):e47264.
36. Pereira-Santos M, Santos JYG dos, Carvalho GQ, et al. Epidemiology of vitamin D insufficiency and deficiency in a population in a sunny country: Geospatial meta-analysis in Brazil. Critical Reviews in Food Science and Nutrition. 2019 Jul 20;59(13):2102–9.
37. Marwaha RK, Tandon N, Garg MK, et al. Vitamin D status in healthy Indians aged 50 years and above. J Assoc Physicians India. 2011 Nov;59:706–9.
38. Sud SR, Montenegro-Bethancourt G, Bermúdez OI, et al. Older Mayan residents of the western highlands of Guatemala lack sufficient levels of vitamin D. Nutr Res. 2010 Nov;30(11):739–46.
39. Bouillon R. Comparative analysis of nutritional guidelines for vitamin D. Nature Reviews Endocrinology. Nature Publishing Group; 2017 Aug;13(8):466–79.
40. Sempos CT, Heijboer AC, Bikle DD, et al. Vitamin D assays and the definition of hypovitaminosis D: results from the First International Conference on Controversies in Vitamin D. Br J Clin Pharmacol. 2018 Oct;84(10):2194–207.
41. Arabi A, El Rassi R, El-Hajj Fuleihan G. Hypovitaminosis D in developing countries—prevalence, risk factors and outcomes. Nature Reviews Endocrinology. 2010 Oct;6(10):550–61.
42. Feizabad E, Hossein-Nezhad A, Maghbooli Z, et al. Impact of air pollution on vitamin D deficiency and bone health in adolescents. Arch Osteoporos. 2017 Dec;12(1):34.
43. Amrein K, Scherkl M, Hoffmann M, et al. Vitamin D deficiency 2.0: an update on the current status worldwide. European Journal of Clinical Nutrition. Nature Publishing Group; 2020 Jan 20;1–16.
44. Cesari M, Incalzi RA, Zamboni V, et al. Vitamin D hormone: a multitude of actions potentially influencing the physical function decline in older persons. Geriatrics & gerontology international. 2011 Apr;11(2):133–42.
45. Holick MF. High Prevalence of Vitamin D Inadequacy and Implications for Health. Mayo Clinic Proceedings. 2006 Mar 1;81(3):353–73.
46. Luo J, Quan Z, Lin S, et al. The association between blood concentration of 25-hydroxyvitamin D and sarcopenia: a meta-analysis. Asia Pac J Clin Nutr. 2018;27(6):1258–70.
47. Dudenkov DV, Mara KC, Petterson TM, et al. Serum 25-Hydroxyvitamin D Values and Risk of All-Cause and Cause-Specific Mortality: A Population-Based Cohort Study. Mayo Clin Proc. 2018 Jun;93(6):721–30.

48. Tian XQ, Holick MF. Catalyzed thermal isomerization between previtamin D3 and vitamin D3 via beta-cyclodextrin complexation. J. Biol. Chem. 1995 Apr 14;270(15):8706–11.
49. Bikle D, Christakos S. New aspects of vitamin D metabolism and action — addressing the skin as source and target. Nature Reviews Endocrinology. Nature Publishing Group; 2020 Apr;16(4):234–52.
50. Wacker M, Holick MF. Sunlight and Vitamin D: A global perspective for health. Dermato-Endocrinology. 2013 Jan 1;5(1):51–108.
51. Bouillon R, Marcocci C, Carmeliet G, et al. Skeletal and Extraskeletal Actions of Vitamin D: Current Evidence and Outstanding Questions. Endocr Rev. Oxford Academic; 2019 Aug 1;40(4):1109–51.
52. Reboul E. Intestinal absorption of vitamin D: from the meal to the enterocyte. Food Funct. The Royal Society of Chemistry; 2015 Feb 12;6(2):356–62.
53. Gil Á, Plaza-Diaz J, Mesa MD. Vitamin D: Classic and Novel Actions. ANM. Karger Publishers; 2018;72(2):87–95.
54. Holick MF. Sunlight and vitamin D for bone health and prevention of autoimmune diseases, cancers, and cardiovascular disease. Am J Clin Nutr. Oxford Academic; 2004 Dec 1;80(6):1678S-1688S.
55. Prabhu AV, Luu W, Li D, et al. DHCR7: A vital enzyme switch between cholesterol and vitamin D production. Prog. Lipid Res. 2016;64:138–51.
56. Wacker M, Holick MF. Vitamin D—Effects on Skeletal and Extraskeletal Health and the Need for Supplementation. Nutrients. 2013 Jan 10;5(1):111–48.
57. Holick MF. Vitamin D Deficiency. N Engl J Med. 2007 Jul 19;357(3):266–81.
58. Bikle DD, Patzek S, Wang Y. Physiologic and pathophysiologic roles of extra renal CYP27b1: Case report and review. Bone Rep. 2018 Jun;8:255–67.
59. Bouillon R, Carmeliet G, Verlinden L, et al. Vitamin D and Human Health: Lessons from Vitamin D Receptor Null Mice. Endocr Rev. 2008 Oct;29(6):726–76.
60. Haussler MR, Jurutka PW, Mizwicki M, et al. Vitamin D receptor (VDR)-mediated actions of 1α,25(OH)2vitamin D3: Genomic and non-genomic mechanisms. Best Practice & Research Clinical Endocrinology & Metabolism. 2011 Aug 1;25(4):543–59.
61. Chen J, Olivares-Navarrete R, Wang Y, et al. Protein-disulfide Isomerase-associated 3 (Pdia3) Mediates the Membrane Response to 1,25-Dihydroxyvitamin D3 in Osteoblasts. J. Biol. Chem. American Society for Biochemistry and Molecular Biology; 2010 Nov 19;285(47):37041–50.
62. Boyan BD, Chen J, Schwartz Z. Mechanism of Pdia3-dependent 1α,25-dihydroxy vitamin D3 signaling in musculoskeletal cells. Steroids. 2012 Aug 1;77(10):892–6.
63. Zmijewski MA, Carlberg C. Vitamin D receptor(s): In the nucleus but also at membranes? Experimental Dermatology. 2020;29(9):876–84.
64. Doroudi M, Plaisance MC, Boyan BD, et al. Membrane actions of 1α,25(OH)2D3 are mediated by Ca2+/calmodulin-dependent protein kinase II in bone and cartilage cells. The Journal of Steroid Biochemistry and Molecular Biology. 2015 Jan 1;145:65–74.
65. Stumpf WE, Sar M, Clark SA, et al. Brain target sites for 1,25-dihydroxyvitamin D3. Science. American Association for the Advancement of Science; 1982 Mar 12;215(4538):1403–5.

66. DeLuca GC, Kimball SM, Kolasinski J, et al. Review: The role of vitamin D in nervous system health and disease. Neuropathology and Applied Neurobiology. John Wiley & Sons, Ltd; 2013 Aug 1;39(5):458–84.
67. Eyles DW, Smith S, Kinobe R, et al. Distribution of the Vitamin D receptor and 1α-hydroxylase in human brain. Journal of Chemical Neuroanatomy. 2005 Jan 1;29(1):21–30.
68. Pardridge WM, Sakiyama R, Coty WA. Restricted Transport of Vitamin D and A Derivatives Through the Rat Blood-Brain Barrier. Journal of Neurochemistry. 1985;44(4):1138–41.
69. Eyles DW, Feron F, Cui X, et al. Developmental vitamin D deficiency causes abnormal brain development. Psychoneuroendocrinology. 2009 Dec 1;34:S247–57.
70. Cui X, Gooch H, Petty A, et al. Vitamin D and the brain: Genomic and non-genomic actions. Molecular and Cellular Endocrinology. 2017 Sep 15;453:131–43.
71. Warsh JJ, Andreopoulos S, Li PP. Role of intracellular calcium signaling in the pathophysiology and pharmacotherapy of bipolar disorder: current status. Clinical Neuroscience Research. 2004 Dec 1;4(3):201–13.
72. Yuan JP, Kiselyov K, Shin DM, et al. Homer binds TRPC family channels and is required for gating of TRPC1 by IP3 receptors. Cell. 2003 Sep 19;114(6):777–89.
73. Kandel ER, Schwartz JH, JesselI TM, et al. Princípios de neurociências. 5th ed. Porto Alegre: AMGH; 2014.
74. Croarkin PE, Levinson AJ, Daskalakis ZJ. Evidence for GABAergic inhibitory deficits in major depressive disorder. Neuroscience & Biobehavioral Reviews. 2011 Jan 1;35(3):818–25.
75. Bivona G, Agnello L, Bellia C, et al. Non-Skeletal Activities of Vitamin D: From Physiology to Brain Pathology. Medicina (Kaunas) [Internet]. 2019 Jul 5 [cited 2020 Oct 18];55(7). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6680897/
76. Domínguez-López S, Howell R, Gobbi G. Characterization of serotonin neurotransmission in knockout mice: implications for major depression. Reviews in the Neurosciences. De Gruyter; 2012 Aug 1;23(4):429–43.
77. Fakhoury M. Revisiting the Serotonin Hypothesis: Implications for Major Depressive Disorders. Mol Neurobiol. 2016 Jul 1;53(5):2778–86.
78. Ogawa S, Fujii T, Koga N, et al. Plasma L-tryptophan concentration in major depressive disorder: new data and meta-analysis. J Clin Psychiatry. 2014 Sep;75(9):e906-915.
79. Kaneko I, Sabir MS, Dussik CM, et al. 1,25-Dihydroxyvitamin D regulates expression of the tryptophan hydroxylase 2 and leptin genes: implication for behavioral influences of vitamin D. The FASEB Journal. 2015;29(9):4023–35.
80. Patrick RP, Ames BN. Vitamin D and the omega-3 fatty acids control serotonin synthesis and action, part 2: relevance for ADHD, bipolar disorder, schizophrenia, and impulsive behavior. The FASEB Journal. Federation of American Societies for Experimental Biology; 2015 Feb 24;29(6):2207–22.
81. Sabir MS, Haussler MR, Mallick S, et al. Optimal vitamin D spurs serotonin: 1,25-dihydroxyvitamin D represses serotonin reuptake transport (SERT) and degradation (MAO-A) gene expression in cultured rat serotonergic neuronal cell lines. Genes Nutr [Internet]. 2018 Jul 11 [cited 2020 Oct 1];13. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6042449/

82. Cui X, Pelekanos M, Liu P-Y, et al. The vitamin D receptor in dopamine neurons; its presence in human substantia nigra and its ontogenesis in rat midbrain. Neuroscience. 2013 Apr 16;236:77–87.
83. Cui X, Pertile R, Liu P, et al. Vitamin D regulates tyrosine hydroxylase expression: N-cadherin a possible mediator. Neuroscience. 2015 Sep 24;304:90–100.
84. Sedaghat K, Yousefian Z, Vafaei AA, et al. Mesolimbic dopamine system and its modulation by vitamin D in a chronic mild stress model of depression in the rat. Behavioural Brain Research. 2019 Jan 1;356:156–69.
85. McCarty DE, Reddy A, Keigley Q, et al. Vitamin D, Race, and Excessive Daytime Sleepiness. J Clin Sleep Med. 2012 Dec 15;8(6):693–7.
86. Mosavat M, Smyth A, Arabiat D, et al. Vitamin D and sleep duration: Is there a bidirectional relationship? Horm Mol Biol Clin Investig. 2020 Nov 13;41(4).
87. Jones KS, Redmond J, Fulford AJ, et al. Diurnal rhythms of vitamin D binding protein and total and free vitamin D metabolites. J Steroid Biochem Mol Biol. 2017 Sep;172:130–5.
88. Muscogiuri G, Barrea L, Scannapieco M, et al. The lullaby of the sun: the role of vitamin D in sleep disturbance. Sleep Med. 2019;54:262–5.
89. Lucock M, Jones P, Martin C, et al. Vitamin D: Beyond Metabolism. J Evid Based Complementary Altern Med. SAGE Publications Inc STM; 2015 Oct 1;20(4):310–22.
90. Romano F, Muscogiuri G, Di Benedetto E, et al. Vitamin D and Sleep Regulation: Is there a Role for Vitamin D? Curr. Pharm. Des. 2020;26(21):2492–6.
91. Dibner C, Schibler U, Albrecht U. The mammalian circadian timing system: organization and coordination of central and peripheral clocks. Annu Rev Physiol. 2010;72:517–49.
92. Stehle JH, von Gall C, Korf H-W. Melatonin: a clock-output, a clock-input. J Neuroendocrinol. 2003 Apr;15(4):383–9.
93. Zhao D, Yu Y, Shen Y, et al. Melatonin Synthesis and Function: Evolutionary History in Animals and Plants. Front. Endocrinol. [Internet]. Frontiers; 2019 [cited 2021 May 4];10. Available from: https://www.frontiersin.org/articles/10.3389/fendo.2019.00249/full
94. Mocayar Marón FJ, Ferder L, Reiter RJ, et al. Daily and seasonal mitochondrial protection: Unraveling common possible mechanisms involving vitamin D and melatonin. J. Steroid Biochem. Mol. Biol. 2020;199:105595.
95. Berk M, Williams LJ, Jacka FN, et al. So depression is an inflammatory disease, but where does the inflammation come from? BMC Med. 2013 Sep 12;11:200.
96. Swardfager W, Rosenblat JD, Benlamri M, et al. Mapping inflammation onto mood: Inflammatory mediators of anhedonia. Neuroscience & Biobehavioral Reviews. 2016 May 1;64:148–66.
97. Ticinesi A, Meschi T, Lauretani F, et al. Nutrition and Inflammation in Older Individuals: Focus on Vitamin D, n-3 Polyunsaturated Fatty Acids and Whey Proteins. Nutrients [Internet]. 2016 Mar 29 [cited 2020 Apr 14];8(4). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4848655/
98. Lee C-H, Giuliani F. The Role of Inflammation in Depression and Fatigue. Front Immunol [Internet]. 2019 Jul 19 [cited 2020 Oct 9];10. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6658985/
99. Takeuchi H, Jin S, Wang J, et al. Tumor Necrosis Factor-α Induces Neurotoxicity via Glutamate Release from Hemichannels of Activated Microglia in an

Autocrine Manner. J. Biol. Chem. American Society for Biochemistry and Molecular Biology; 2006 Jul 28;281(30):21362–8.
100. Capuron L, Ravaud A, Gualde N, et al. Association between immune activation and early depressive symptoms in cancer patients treated with interleukin-2-based therapy. Psychoneuroendocrinology. 2001 Nov 1;26(8):797–808.
101. Capuron L, Neurauter G, Musselman DL, et al. Interferon-alpha–induced changes in tryptophan metabolism: relationship to depression and paroxetine treatment. Biological Psychiatry. 2003 Nov 1;54(9):906–14.
102. Zhang J, Terreni L, De Simoni MG, et al. Peripheral interleukin-6 administration increases extracellular concentrations of serotonin and the evoked release of serotonin in the rat striatum. Neurochemistry International. 2001 Apr 1;38(4):303–8.
103. Calton EK, Keane KN, Newsholme P, et al. The Impact of Vitamin D Levels on Inflammatory Status: A Systematic Review of Immune Cell Studies. PLoS One [Internet]. 2015 Nov 3 [cited 2020 Apr 17];10(11). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4631349/
104. Boontanrart M, Hall SD, Spanier JA, et al. Vitamin D3 alters microglia immune activation by an IL-10 dependent SOCS3 mechanism. J Neuroimmunol. 2016 Mar 15;292:126–36.
105. Lee PW, Selhorst A, Lampe SG, et al. Neuron-Specific Vitamin D Signaling Attenuates Microglia Activation and CNS Autoimmunity. Front Neurol. 2020;11:19.
106. Garcion E, Sindji L, Leblondel G, et al. 1,25-dihydroxyvitamin D3 regulates the synthesis of gamma-glutamyl transpeptidase and glutathione levels in rat primary astrocytes. J Neurochem. 1999 Aug;73(2):859–66.
107. Garcion E, Sindji L, Montero-Menei C, et al. Expression of inducible nitric oxide synthase during rat brain inflammation: regulation by 1,25-dihydroxyvitamin D3. Glia. 1998 Mar;22(3):282–94.
108. Camargo A, Dalmagro AP, Platt N, et al. Cholecalciferol abolishes depressive-like behavior and hippocampal glucocorticoid receptor impairment induced by chronic corticosterone administration in mice. Pharmacology Biochemistry and Behavior. 2020 Sep 1;196:172971.
109. da Silva Souza SV, da Rosa PB, Neis VB, et al. Effects of cholecalciferol on behavior and production of reactive oxygen species in female mice subjected to corticosterone-induced model of depression. Naunyn-Schmiedeberg's Arch Pharmacol. 2020 Jan 1;393(1):111–20.
110. Neurauter G, Schrocksnadel K, Scholl-Burgi S, et al. Chronic Immune Stimulation Correlates with Reduced Phenylalanine Turnover. Current Drug Metabolism. 2008 Sep 1;9(7):622–7.
111. Lindqvist D, Dhabhar FS, James SJ, et al. Oxidative Stress, Inflammation and Treatment Response in Major Depression. Psychoneuroendocrinology. 2017 Feb;76:197–205.
112. Zhu C, Zhang Y, Wang T, et al. Vitamin D supplementation improves anxiety but not depression symptoms in patients with vitamin D deficiency. Brain and Behavior. 2020;10(11):e01760.
113. Kjærgaard M, Waterloo K, Wang CEA, et al. Effect of vitamin D supplement on depression scores in people with low levels of serum 25-hydroxyvitamin D: nested case—control study and randomised clinical trial. The British Journal of Psychiatry. Cambridge University Press; 2012 Nov;201(5):360–8.

114. Vieth R, Kimball S, Hu A, et al. Randomized comparison of the effects of the vitamin D3 adequate intake versus 100 mcg (4000 IU) per day on biochemical responses and the wellbeing of patients. Nutr J. 2004 Jul 19;3:8.
115. Vellekkatt F, Menon V, Rajappa M, et al. Effect of adjunctive single dose parenteral Vitamin D supplementation in major depressive disorder with concurrent vitamin D deficiency: A double-blind randomized placebo-controlled trial. Journal of Psychiatric Research. 2020 Oct 1;129:250–6.
116. de Koning EJ, Lips P, Penninx BWJH, et al. Vitamin D supplementation for the prevention of depression and poor physical function in older persons: the D-Vitaal study, a randomized clinical trial. Am. J. Clin. Nutr. 2019 01;110(5):1119–30.
117. Okereke OI, Reynolds CF, Mischoulon D, et al. Effect of Long-term Vitamin D3 Supplementation vs Placebo on Risk of Depression or Clinically Relevant Depressive Symptoms and on Change in Mood Scores: A Randomized Clinical Trial. JAMA. 2020 04;324(5):471–80.
118. Alghamdi S, Alsulami N, Khoja S, et al. Vitamin D Supplementation Ameliorates Severity of Major Depressive Disorder. J Mol Neurosci. 2020 Feb 1;70(2):230–5.
119. Zajac IT, Barnes M, Cavuoto P, et al. The Effects of Vitamin D-Enriched Mushrooms and Vitamin D3 on Cognitive Performance and Mood in Healthy Elderly Adults: A Randomised, Double-Blinded, Placebo-Controlled Trial. Nutrients. 2020 Dec 16;12(12).
120. Gugger A, Marzel A, Orav EJ, et al. Effect of Monthly High-Dose Vitamin D on Mental Health in Older Adults: Secondary Analysis of a RCT. Journal of the American Geriatrics Society. 2019;67(6):1211–7.
121. Alavi NM, Khademalhoseini S, Vakili Z, et al. Effect of vitamin D supplementation on depression in elderly patients: A randomized clinical trial. Clinical Nutrition. Elsevier; 2019 Oct 1;38(5):2065–70.
122. Hansen JP, Pareek M, Hvolby A, et al. Vitamin D3 supplementation and treatment outcomes in patients with depression (D3-vit-dep). BMC Res Notes. 2019 Apr 3;12(1):203.
123. Aucoin M, Cooley K, Anand L, et al. Adjunctive Vitamin D in the treatment of non-remitted depression: Lessons from a failed clinical trial. Complementary Therapies in Medicine. 2018 Feb 1;36:38–45.
124. Yalamanchili V, Gallagher JC. Dose ranging effects of Vitamin D3 on the Geriatric Depression Score: A Clinical Trial. J Steroid Biochem Mol Biol. 2018 Apr;178:60–4.
125. Mozaffari-Khosravi H, Nabizade L, Yassini-Ardakani SM, et al. The effect of 2 different single injections of high dose of vitamin D on improving the depression in depressed patients with vitamin D deficiency: a randomized clinical trial. J Clin Psychopharmacol. 2013 Jun;33(3):378–85.
126. Khoraminya N, Tehrani-Doost M, Jazayeri S, et al. Efeitos terapêuticos da vitamina D como terapia adjuvante à fluoxetina em pacientes com transtorno depressivo maior. Aust N Z J Psychiatry. 2013 Mar 1;47(3):271–5.
127. Bertone-Johnson ER, Powers SI, Spangler L, et al. Vitamin D Supplementation and Depression in the Women's Health Initiative Calcium and Vitamin D Trial. Am J Epidemiol. 2012 Jul 1;176(1):1–13.
128. Dean AJ, Bellgrove MA, Hall T, et al. Effects of Vitamin D Supplementation on Cognitive and Emotional Functioning in Young Adults – A Randomised Controlled Trial. PLOS ONE. Public Library of Science; 2011 Nov 4;6(11):e25966.

129. Sanders KM, Stuart AL, Williamson EJ, et al. Annual high-dose vitamin D3 and mental well-being: randomised controlled trial. The British Journal of Psychiatry. Cambridge University Press; 2011 May;198(5):357–64.
130. Jorde R, Sneve M, Figenschau Y, et al. Effects of vitamin D supplementation on symptoms of depression in overweight and obese subjects: randomized double blind trial. J Intern Med. 2008 Dec;264(6):599–609.
131. Gowda U, Mutowo MP, Smith BJ, et al. Vitamin D supplementation to reduce depression in adults: Meta-analysis of randomized controlled trials. Nutrition. 2015 Mar 1;31(3):421–9.
132. Di Gessa G, Biddulph JP, Zaninotto P, et al. Changes in vitamin D levels and depressive symptoms in later life in England. Sci Rep. 2021 Apr 8;11(1):7724.
133. Mulugeta A, Lumsden A, Hyppönen E. Relationship between Serum 25(OH)D and Depression: Causal Evidence from a Bi-Directional Mendelian Randomization Study. Nutrients. Multidisciplinary Digital Publishing Institute; 2021 Jan;13(1):109.
134. van den Berg KS, Hegeman JM, van den Brink RHS, et al. A prospective study into change of vitamin D levels, depression and frailty among depressed older persons. Int J Geriatr Psychiatry. 2021 Feb 8;
135. Ceolin G, Matsuo LH, Confortin SC, et al. Lower serum 25-hydroxycholecalciferol is associated with depressive symptoms in older adults in Southern Brazil. Nutrition Journal. 2020 Nov 14;19(1):123.
136. Sahasrabudhe N, Lee JS, Scott TM, et al. Serum Vitamin D and Depressive Symptomatology among Boston-Area Puerto Ricans. The Journal of Nutrition. 2020 Dec 10;150(12):3231–40.
137. Köhnke C, Herrmann M, Berger K. Associations of major depressive disorder and related clinical characteristics with 25-hydroxyvitamin D levels in middle-aged adults. Nutritional Neuroscience. Taylor & Francis; 2020 Dec 9;0(0):1–10.
138. Granlund LE, Ramnemark AK, Andersson C, et al. Vitamin D status was not associated with anxiety, depression, or health-related quality of life in Middle Eastern and African-born immigrants in Sweden. Nutrition Research. 2020 Mar 1;75:109–18.
139. Rhee SJ, Lee H, Ahn YM. Serum Vitamin D Concentrations Are Associated With Depressive Symptoms in Men: The Sixth Korea National Health and Nutrition Examination Survey 2014. Front. Psychiatry [Internet]. Frontiers; 2020 [cited 2021 Mar 25];11. Available from: https://www.frontiersin.org/articles/10.3389/fpsyt.2020.00756/full
140. Bigman G. Vitamin D metabolites, D3 and D2, and their independent associations with depression symptoms among adults in the United States. null. Taylor & Francis; 2020 Jul 20;1–9.
141. Ronaldson A, Arias de la Torre J, Gaughran F, et al. Prospective associations between vitamin D and depression in middle-aged adults: findings from the UK Biobank cohort. Psychol Med. 2020 Oct 21;1–9.
142. Briggs R, McCarroll K, O'Halloran A, et al. Vitamin D Deficiency Is Associated With an Increased Likelihood of Incident Depression in Community-Dwelling Older Adults. Journal of the American Medical Directors Association. 2019 May 1;20(5):517–23.
143. Elstgeest LEM, de Koning EJ, Brouwer IA, et al. Change in serum 25-hydroxyvitamin D and parallel change in depressive symptoms in Dutch older adults. Eur. J. Endocrinol. 2018 01;179(4):239–49.

144. Sherchand O, Sapkota N, Chaudhari RK, et al. Association between vitamin D deficiency and depression in Nepalese population. Psychiatry Res. 2018;267:266–71.
145. Vidgren M, Virtanen JK, Tolmunen T, et al. Serum Concentrations of 25-Hydroxyvitamin D and Depression in a General Middle-Aged to Elderly Population in Finland. J Nutr Health Aging. 2018 Jan 1;22(1):159–64.
146. Yao Y, Fu S, Zhang H, et al. The prevalence of depressive symptoms in Chinese longevous persons and its correlation with vitamin D status. BMC Geriatrics. 2018 Aug 29;18(1):198.
147. de Oliveira C, Hirani V, Biddulph JP. Associations Between Vitamin D Levels and Depressive Symptoms in Later Life: Evidence From the English Longitudinal Study of Ageing (ELSA). J Gerontol A Biol Sci Med Sci. 2018 Sep 11;73(10):1377–82.
148. Jovanova O, Aarts N, Noordam R, et al. Vitamin D serum levels are cross-sectionally but not prospectively associated with late-life depression. Acta Psychiatrica Scandinavica. 2017;135(3):185–94.
149. Collin C, Assmann KE, Deschasaux M, et al. Plasma vitamin D status and recurrent depressive symptoms in the French SU.VI.MAX cohort. Eur J Nutr. 2017 Oct;56(7):2289–98.
150. Lee S-H, Suh E, Park K-C, et al. Association of serum 25-hydroxyvitamin D and serum total cholesterol with depressive symptoms in Korean adults: the Fifth Korean National Health and Nutrition Examination Survey (KNHANES V, 2010-2012). Public Health Nutr. 2017 Jul;20(10):1836–43.
151. Shin Y-C, Jung C-H, Kim H-J, et al. The associations among vitamin D deficiency, C-reactive protein, and depressive symptoms. J Psychosom Res. 2016 Nov;90:98–104.
152. Rabenberg M, Harisch C, Rieckmann N, et al. Association between vitamin D and depressive symptoms varies by season: Results from the German Health Interview and Examination Survey for Adults (DEGS1). J Affect Disord. 2016 Nov 1;204:92–8.
153. van den Berg KS, Marijnissen RM, van den Brink RHS, et al. Vitamin D deficiency, depression course and mortality: Longitudinal results from the Netherlands Study on Depression in Older persons (NESDO). J Psychosom Res. 2016 Apr;83:50–6.
154. Song BM, Kim HC, Rhee Y, et al. Association between serum 25-hydroxyvitamin D concentrations and depressive symptoms in an older Korean population: A cross-sectional study. J Affect Disord. 2016 Jan 1;189:357–64.
155. Brouwer-Brolsma EM, Dhonukshe-Rutten RAM, van Wijngaarden JP, et al. Low vitamin D status is associated with more depressive symptoms in Dutch older adults. Eur J Nutr. 2016;55:1525–34.
156. Rocha-Lima MT, Custódio O, Moreira PFP, et al. DEPRESSIVE SYMPTOMS AND LEVEL OF 25-HYDROXYVITAMIN D IN FREE-LIVING OLDEST OLD. The Journal of Aging Research and Clinical Practice (JARCP); 2016 [cited 2020 Dec 10]; Available from: http://www.jarcp.com/all-issues.html?article=373
157. Husemoen LLN, Ebstrup JF, Mortensen EL, et al. Serum 25-hydroxyvitamin D and self-reported mental health status in adult Danes. European Journal of Clinical Nutrition. Nature Publishing Group; 2016 Jan;70(1):78–84.
158. Jääskeläinen T, Knekt P, Suvisaari J, et al. Higher serum 25-hydroxyvitamin D concentrations are related to a reduced risk of depression. Br. j. nutr. Cambridge University Press; 2015;113(9):1418–26.

159. Almeida OP, Hankey GJ, Yeap BB, et al. Vitamin D concentration and its association with past, current and future depression in older men: The Health In Men Study. Maturitas. 2015 May;81(1):36–41.
160. Williams JA, Sink KM, Tooze JA, et al. Low 25-Hydroxyvitamin D Concentrations Predict Incident Depression in Well-Functioning Older Adults: The Health, Aging, and Body Composition Study. J Gerontol A Biol Sci Med Sci. 2015 Jun;70(6):757–63.
161. Imai CM, Halldorsson TI, Eiriksdottir G, et al. Depression and serum 25-hydroxyvitamin D in older adults living at northern latitudes – AGES-Reykjavik Study. J Nutr Sci [Internet]. 2015 Nov 20 [cited 2020 Feb 24];4. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4678766/
162. Józefowicz O, Rabe-Jabłońska J, Woźniacka A, et al. Analysis of vitamin D status in major depression. J Psychiatr Pract. 2014 Sep;20(5):329–37.
163. Toffanello ED, Sergi G, Veronese N, et al. Serum 25-hydroxyvitamin d and the onset of late-life depressive mood in older men and women: the Pro.V.A. study. J. Gerontol. A Biol. Sci. Med. Sci. 2014 Dec;69(12):1554–61.
164. Milaneschi Y, Hoogendijk W, Lips P, et al. The association between low vitamin D and depressive disorders. Molecular Psychiatry. 2014 Apr;19(4):444–51.
165. Lapid MI, Cha SS, Takahashi PY. Vitamin D and depression in geriatric primary care patients. Clin Interv Aging. 2013;8:509–14.
166. Jaddou HY, Batieha AM, Khader YS, et al. Depression is associated with low levels of 25-hydroxyvitamin D among Jordanian adults: results from a national population survey. Eur Arch Psychiatry Clin Neurosci. 2012 Jun 1;262(4):321–7.
167. Chan R, Chan D, Woo J, et al. Association between serum 25-hydroxyvitamin D and psychological health in older Chinese men in a cohort study. Journal of Affective Disorders. 2011 Apr 1;130(1):251–9.
168. Lee DM, Tajar A, O'Neill TW, et al. Lower vitamin D levels are associated with depression among community-dwelling European men. J Psychopharmacol. 2011 Oct 1;25(10):1320–8.
169. Milaneschi Y, Shardell M, Corsi AM, et al. Serum 25-hydroxyvitamin D and depressive symptoms in older women and men. J Clin Endocrinol Metab. 2010 Jul;95(7):3225–33.
170. Stewart R, Hirani V. Relationship Between Vitamin D Levels and Depressive Symptoms in Older Residents From a National Survey Population. Psychosomatic Medicine. 2010 Sep;72(7):608.
171. Nanri A, Mizoue T, Matsushita Y, et al. Association between serum 25-hydroxyvitamin D and depressive symptoms in Japanese: analysis by survey season. European Journal of Clinical Nutrition. 2009 Dec;63(12):1444–7.
172. Pan A, Lu L, Franco OH, et al. Association between depressive symptoms and 25-hydroxyvitamin D in middle-aged and elderly Chinese. Journal of Affective Disorders. 2009 Nov 1;118(1):240–3.
173. Hoogendijk WJG, Lips P, Dik MG, et al. Depression Is Associated With Decreased 25-Hydroxyvitamin D and Increased Parathyroid Hormone Levels in Older Adults. Arch Gen Psychiatry. 2008 May 1;65(5):508–12.
174. Wilkins CH, Sheline YI, Roe CM, et al. Vitamin D deficiency is associated with low mood and worse cognitive performance in older adults. Am J Geriatr Psychiatry. 2006 Dec;14(12):1032–40.
175. de Koning EJ, Elstgeest LEM, Comijs HC, et al. Vitamin D Status and Depressive Symptoms in Older Adults: A Role for Physical Functioning? The American Journal of Geriatric Psychiatry. 2018 Nov 1;26(11):1131–43.

176. Brouwer-Brolsma EM, Vaes AMM, van der Zwaluw NL, et al. Relative importance of summer sun exposure, vitamin D intake, and genes to vitamin D status in Dutch older adults: The B-PROOF study. The Journal of Steroid Biochemistry and Molecular Biology. 2016 Nov;164:168–76.
177. Ju S-Y, Lee Y-J, Jeong S-N. Serum 25-hydroxyvitamin D levels and the risk of depression: A systematic review and meta-analysis. J Nutr Health Aging. 2013 May 1;17(5):447–55.
178. Li H, Sun D, Wang A, et al. Serum 25-Hydroxyvitamin D Levels and Depression in Older Adults: A Dose–Response Meta-Analysis of Prospective Cohort Studies. The American Journal of Geriatric Psychiatry. 2019 Nov 1;27(11):1192–202.
179. Sibille E. Molecular aging of the brain, neuroplasticity, and vulnerability to depression and other brain-related disorders. Dialogues Clin Neurosci. 2013 Mar;15(1):53–65.
180. Pomatto LCD, Davies KJA. The role of declining adaptive homeostasis in ageing. The Journal of Physiology. 2017;595(24):7275–309.
181. Soares CN, Shea AK. The Midlife Transition, Depression, and Its Clinical Management. Obstetrics and Gynecology Clinics of North America. 2021 Mar 1;48(1):215–29.
182. Brandão DJ, Fontenelle LF, da Silva SA, et al. Depression and excess mortality in the elderly living in low- and middle-income countries: Systematic review and meta-analysis. International Journal of Geriatric Psychiatry. John Wiley & Sons, Ltd; 2019 Jan 1;34(1):22–30.
183. Lopes CS, Hellwig N, e Silva G de A, et al. Inequities in access to depression treatment: results of the Brazilian National Health Survey – PNS. Int J Equity Health. 2016 Dec;15(1):154.
184. Falci DM, Mambrini JV de M, Castro-Costa É, et al. Uso de psicofármacos prediz incapacidade funcional entre idosos. Rev. Saúde Pública. 2019 Jan 31;53:21.
185. Kim J, Parish AL. Polypharmacy and Medication Management in Older Adults. Nursing Clinics of North America. 2017 Sep 1;52(3):457–68.
186. Read J, Gee A, Diggle J, et al. The interpersonal adverse effects reported by 1008 users of antidepressants; and the incremental impact of polypharmacy. Psychiatry Research. 2017 Oct 1;256:423–7.
187. Parker GB, Brotchie H, Graham RK. Vitamin D and depression. Journal of Affective Disorders. 2017 Jan 15;208:56–61.
188. Wong SK, Ima-Nirwana* K-YC and S. Vitamin D and Depression: The Evidence from an Indirect Clue to Treatment Strategy [Internet]. Current Drug Targets. 2018 [cited 2020 Aug 6]. p. 888–97. Available from: https://www.eurekaselect.com/155568/article
189. Jorde R, Kubiak J. No improvement in depressive symptoms by vitamin D supplementation: results from a randomised controlled trial. J Nutr Sci. 2018;7:e30.
190. Sempos CT, Binkley N. 25-Hydroxyvitamin D assay standardisation and vitamin D guidelines paralysis. Public Health Nutrition. Cambridge University Press; 2020 May;23(7):1153–64.
191. Giustina A, Adler RA, Binkley N, et al. Consensus statement from 2nd International Conference on Controversies in Vitamin D. Rev Endocr Metab Disord. 2020 Mar 1;21(1):89–116.

Table 1 - Vitamin D supplementation and depression/depressive symptoms: clinical trials with older adults

Authors (Country)	Classification	Age range	Vitamin D supplementation	Depressive symptoms assessment	25(OH)D assessment	Main results
Okereke et al., 2020 [117] (USA)	RCT N= 9,181 vitD; n= 9,172 placebo.	≥50	2000 IU/d of cholecalciferol for 5.3 years (interquartile range, 5.0-5.7 years)	PHQ-8	NA	No improvement.
Zhu et al., 2020 [112] (China)	RCT N= 62 vitD; n= 44 placebo	18–60 years [individuals with serum 25(OH) D levels ≤75 nmol/L]	1,600 mg VD daily supplementation for 6 months	MINI HAMD-17 RSAS RPAS HAMA-14	Radioimmunoassay	**No improvement.**
Vellekkatt et al., 2020 [115] (India)	Double-blind RCT N= 23 vitD; n=23 placebo.	18–65 years(diagnose with depression and individuals with serum 25(OH) D levels <20 mg/mL)	One single 300,000 I.U. of cholecalciferol (Arachitol) injection (intervention) intramuscularly. Follow-up in 12 weeks.	DSM-5 MINI HDRS-17	Automated chemiluminescent immunoassay	Improvement in supplemented group. Depression score at baseline 3,0 (2,0–4,0); 12 weeks 5,0 (3,2–8,0); p=0.001 for vit D group. No effects on placebo group.
Alghamdi et al., 2020 [118] (Saudi Arabia)	RCT N=49 SOC+vitD; N= 13 SOC.	18–65 years (diagnose with MDD)	50,000 IU of vitamin D (Calciferol) for 3 months.	DSM-5 BDI	Automated chemiluminescent immunoassay	Mildly depressed Men → no significant changes in BDI scores after VitD supplementation. Moderate, severe, and extreme depression showed significant

						decreases in BDI scores after vitamin D supplementation ($p < 0.05$). Women → moderate, severe, and extreme depression had lower BDI scores after VitD supplementation ($p < 0.05$). Moderate depression changed from 28 ± 1.2 to 23 ± 1.4 ($p < 0.05$); Severe depression improved from 36 ± 0.9 to 27 ± 3.6 ($p < 0.05$); Extreme depression improved from 44 ± 1.5 to 34 ± 2.5 ($p < 0.05$)
Zajac et al., 2020 [119] (Australia)	Double-blinded, 4-armed parallel-group RCT N= 91 vitD; N=94 standard mushroom; N=147 vitD2-enriched mushroom; N= 92 placebo.	60–90 years	Daily 600 IU of either D2 or D3 for 24 weeks	PANAS DASS−21 General Happiness Scale	High throughput liquid chromatography tandem mass spectroscopy (LC-MSMS)	No improvement.
De Koning et al., 2019 [116] (The Netherlands)	RCT N=77 vitD; N=78 placebo.	60–80 years [clinically relevant depressive symptoms, ≥1 functional limitation, and serum 25(OH)D concentrations of	1200 IU/d vitamin D3 for 12 months	CES-D	Liquid chromatography followed by tandem mass spectrometry method.	No improvement.

		15–50/70 nmol/L (depending on the season)]				
Gugger et al., 2019 [120] (Switzerland)	RCT N= 67 24,000 IU vit D3; n= 67 60,000 IU vitD3; n= 66 24,000 IU vitD3plus 300µg calcifediol	≥70 (commu-nity-dwelling adult with a prior fall event)	Monthly 24,000 IU vitamin D as the conventional treatment; monthly 60,000 IU vitamin D3 as the high doses; monthly 24,000 IU vitamin D3plus 300 µg calcifediol during 12 months.	GDS-15	N.A.	No improvement.
Alavi et al., 2019 [121] (Iran)	RCT N= 39 vit D, n=39 placebo.	>60 years (outpatients with depression)	50,000 UI of vitD3 weekly for 8 week	GDS-15	Chemiluminescent immunoassay	The depression score decreased from 9.25 (DP 2.4) to 7.48 (DP 1.66) in vitamin D group (p=0.0001), while there was a non-significant increase in the depression score in the placebo group. Vitamin D could explain the 81.8% of the depression score after intervention.
Hansen et al., 2019 [122] (Denmark)	RCT N=26 vitD; n=19 placebo.	18–65 years (individuals diagnosed with mild to severe depression)	2800 IU/d vitD3 for 12 weeks	HAMD-17 MDI	High performance liquid chromatography followed by tandem mass spectrometry	No improvement.
Aucoin et al., 2018 [123] (Canada)	Double-blinded RCT. N=125	18–75 years (patients with non-remitted depression)	weekly (bolus) doses of 28,000 IU of Vitamin D3 or placebo for 8 weeks	BDI-II FCPS	N.A.	The sample size of enrolled participants (7/125, 5.6%) lacks power to conduct a full assessment of findings.

Yalamanchili & Gallagher, 2018 [124] (USA)	Double-blind, multi-doses RCT N= 273 (VIDOS study)	57–90 (older Caucasian and African American women)	Low (400-800 IU), medium (1600-3200 IU) and high (4000-4800 IU) doses of vitD3 for one year.	GDS-LF30	Radioimmunoassay	No improvement.
Mozaffari-Khosravi et al., 2013 [125] (Iran)	RCT. N= 39 G300, N=36 G150, N=34 no injection	20–60 years (depression symptoms for at least 2 weeks)	A single doses of 300,000 or 150,000 IU of vitamin D intramuscularly, and the NTG (non-test group) received no injection for 3 months.	BDI-II	ELISA	Significant difference in mean of Beck Depression Inventory II test score between G300 and NTG after treatment (17.4±9.8 vs 24.3±6.2 BDI score, respectively; P = 0.001).
Khoraminya et al., 2013 [126] (Iran)	Double-blind, placebo-controlled RCT. N=20 fluoxetine, N=20 fluoxetine+vit3	18–65 years (outpatients' diagnosis of major depressive disorder)	1500 IU of vitD3 + one capsule (20 mg) fluoxetine or vitD3 placebo plus 20 mg fluoxetine for 8 weeks.	HDRS-24 BDI-21	ELISA	Analysis of covariance for depression severity adjusted for baseline values at weeks 2, 4, 6 and 8 showed that the vitamin D–fluoxetine combination was significantly better than fluoxetine alone from the fourth week of treatment.
Kjægaard et al., 2012 [113] (Norway)	RCT. N=120 vitD3. N=110 placebo (Tromsø study)	30–75 years [participants with low serum 25(OH)D]	20 000 IU vitD3 per week or placebo for 6 months.	BDI-II HADS-14 The Seasonal Pattern Assessment Scale MADRS	Liquid chromatography followed by tandem mass spectrometry method.	No improvement.
Bertone-Johnson et al., 2012 [127] (USA)	Double-blinded, placebo-controlled RCT. N= 18,176 vitD3+Ca; N=18,106 placebo	50–79 years (postmenopausal women)	400 IU daily supplementation with of vitD3 + 1,000 mg of elemental calcium for 01 and 03 years.	Burnam scale	Not described.	No improvement.

	(Women's Health Initiative study)					
Dean et al., 2011 [128] (Australia)	Parallel-arm, double-blind, placebo-controlled RCT. N= 63 vitD3; N=65 placebo.	≥18 years (healthy volunteers)	5,000 IU/day vitD3 or placebo for 6 weeks.	BDI	High performance liquid chromatography followed by tandem mass spectrometry	No improvement.
Sanders et al., 2011 [129] (Australia)	Double-blind, placebo-controlled RCT. N=1001 vitD3, N=1011 placebo.	≥70 years (community-dwelling women)	500.000 IU vitD3 orally or placebo every autumn/winter for 3–5 consecutive years.	General Health Questionnaire, the 12-item Short Form Health Survey, the Patient Global Impression–Improvement scale and the WHO Well-Being Index500	Radioimmunoassay	No improvement.
Jorde et al., 2008 [130] (Norway)	Double-blinded, placebo-controlled RCT. N=116 40.000 UI (DD); N=106 20.000 UI (DP); N=112 placebo (PP).	21–70 years (BMI 28.0–47.0 kg/ m²)	20.000 (DP) or 40.000 IU (DD) vitD3 per week versus placebo (PP) for 1 year.	BDI	Immunometry (electrochemiluminescence)	There was a significant reduction (improvement) in the total BDI and the BDI subscale scores in the DD group, a significant reduction in the BDI 14–21 subscale score in the DP group, but no significant change in the PP group.
Vieth et al., 2004 [114] (Canada)	Single-blinded RT Study I. N=64. Study II. N=66	Study I: 39–67 years (if summer 2001 25(OH)D <61nmol/L). Study II: 39–67 y (if summer 2001	Study I: 4000 IU/day or 600 IU/day December 2001 and February 2002. Study II: 4000 IU/day or 600 IU/day December 2002 and February 2003	Brief questionnaire, based on conventional depression-screening tools, and incorporating	Radioimmunoassay	Study I: Wellbeing score improved more for the 100-mcg/day group than for the lower-dosed group (1-tail Mann-Whitney $p = 0.036$). Study II: Wellbeing scores improved with both doses of vitamin D (two-tail $p < 0.001$)

		25(OH)D was <51nmol/L)		questions relating to energy and mood		

NA: Not assessed. RCT: Randomized Controlled Trial. VitD: Vitamin D. PHQ-8: Patient Health Questionnaire depression scale. MINI: Mini-International Neuropsychiatric Interview. HAMD-17: Hamilton Depression Rating Scale-17. RSAS: Revised Social Anhedonia Scale. RPAS: Revised Physical Anhedonia scale. HAMA-14: Hamilton Anxiety Rating Scale-14. HDRS-17: Hamilton Depression Rating scale-17. BDI: Beck depression inventory. PANAS: Positive and Negative Affect Schedule. DASS-21: 21-item Depression. CES-D: Center for Epidemiological Studies Depression. GDS-15: 15-item Geriatric Depression Scale. MDI: Major Depression Inventory. BDI-II: Beck Depression Inventory-II. FCPS: Fawcett-Clark Pleasure Capacity Scale. GDS-LF30: Long Form 30-item GDS. HDRS-24: Hamilton Depression rating scale-24. BDI-21: Beck Depression Inventory-21. HADS-14: Hospital Anxiety and Depression Scale. MADRS: Montgomery–Åsberg Depression Rating Scale.

Table 2 - Vitamin D supplementation and depression/depressive symptoms: observational studies with older adults

Authors (Country)	Age range (years)	Classification	Depression assessment	25(OH)D Classification	Main results
Di Gessa et al, 2021 [132] (England)	≥50	Cohort Population-based Longitudinal analysis (n=3,365)	CES-D-8	Sufficient ≥50 nmol/L Insufficient <50 nmol/L	Those with insufficient levels were more likely to report elevated depressive symptoms at follow-up (OR=1.39; 95%CI: 1.00–1.93)
Mulugeta et al, 2021 [133] (United Kingdom)	37–73	Cohort (Biobank) Cross-sectional analysis (n= 307,618)	Hospital diagnosed depression and self-reported depression	Quartiles: >75 nmol/L ≥50 and <75 nmol/L ≥25 and <50 nmol/L <25 nmol/L	In observational analysis, the odds of depression decreased with higher 25(OH)D concentrations (adjusted OR per 50% increase 0.95, 95%CI 0.94–0.96)
Van Den Berg et al, 2021 [134] (Netherlands)	≥60	Cohort of depressed people Longitudinal analysis (n=232)	DSM-IV CIDI IDS-SR	Mean nmol/L	An increase in vitamin D of 0.22 nmol/L was associated with a decrease with each point of the IDS score (SE= 0.11; p = 0.049; ES= 0.12).
Ceolin et al, 2020 [135] (Brazil)	≥60	Cohort Population-based Cross-sectional analysis (n=557)	GDS-15	Sufficiency ≥30 ng/mL Insufficiency 21–29 ng/mL Deficiency ≤20 ng/mL	Found a significant association between 25(OH)D and depressive symptoms with OR=2.27; 95%CI: 1.05–4.94 for deficient compared with sufficient.
Sahasrabudhe et al 2020 [136] (United States)	45–75	Cohort of Puerto Rican people Cross-sectional and longitudinal analysis (n=1,434)	CES-D	Sufficient ≥20 ng/mL Insufficient 12 to >20 ng/mL Deficient <12 ng/mL	No association between serum 25(OH)D and depressive symptomatology
Köhnke et al, 2020 [137] (Germany)	35–65	Cohort Cross-sectional analysis (n=1,169)	IDS DSM-IV HAM-D-17	Adequate ≥20 ng/mL Insufficient 12 to <20 ng/mL Deficient <12 ng/mL	Compared to non-depressed, patients with MDD had OR=1.91 (95%CI:1.39–2.62) to insufficiency and OR=2.10 (95%CI:1.46–3.02) to deficiency in 25(OH)D
Granlund et al, 2020 [138]	25–64	Population-based Cross-sectional analysis	HAD	< 25 nmol/L (<10 ng/mL)	No association between depression and 25(OH)D

(Sweden)		(n=195)		<50 nmol/L (<20 ng/mL) ≥ 50 nmol/L (≥20 ng/mL)	
Rhee et al, 2020 (139) (South Korea)	19–76	Nationally representative population Cross-sectional analysis (n=1,736)	PHQ-9	Mean ng/mL	The association between serum 25(OH)D concentrations and total PHQ-9 scores was statistically significant (IRR= 0.74; 95%CI = 0.59–0.93) only in men.
Bigman, 2020 (140) (United States)	20–80	Nationally representative population Cross-sectional analysis (n= 11,471)	PHQ-9	25(OH)D3**:** Sufficiency <30 ng/mL Inadequacy 20–30 ng/mL Deficiency <20 ng/mL 25(OH)D2: Presence >0.6 ng/mL Nearly no presence ≤0.6 ng/mL	Participants with deficiency in 25(OH)D3 presented OR=1,19 (95% CI: 1.03–1.37) to report symptoms of depression compared with sufficient. Participants with presence of 25(OH)D2 presented OR= 1.35 (95% CI: 1.18–1.55) to report symptoms of depression compared with nearly no presence.
Ronaldson et al, 2020 (141) (United Kingdom)	40–69	Cohort (Biobank) Cross-sectional and longitudinal analysis (n= 139,128)	PHQ-2 PHQ-9	Sufficient >50 nmol/L Insufficient 20–50 nmol/L Deficient <20 nmol/L	Participants with no depression at baseline with insufficiency (OR= 1.14, 95%CI:1.07–1.22) and with deficiency (OR= 1.24, 95% CI: 1.13–1.36) were more likely to develop new-onset depression at follow-up. Similar prospective associations were reported for those with depression at baseline with insufficiency (OR= 1.11, 95% CI 1.00–1.23) and deficiency (OR= 1.30, 95% CI 1.13–1.50).
Briggs et al., 2019 (142) (Ireland)	≥50	Cohort Population-based Longitudinal analysis (n= 3,965)	CES-D-20 CES-D-8	Sufficiency >50 nmol/L Insufficiency 30–50 nmol/L Deficiency <30 nmol/L	Only participants with vitamin D deficiency had a significantly higher likelihood of incident depression (OR=1.56, 95%CI:1.07–2.26).
Elstgeest et al., 2018 (143) (Netherlands)	Two cohorts: 55–65 65–88	Cohort Population-based Longitudinal analysis (n=173; n=450)	CES-D-20	Mean nmol/L Tertiles	The older cohort → change in 25(OH)D was not associated with the change in CES-D score (follow-up, 13 years) The younger cohort → increase in 25(OH)D was associated with a decrease in CES-D score [adjusted B

					per 10 nmol/L 25(OH)D increase: −0.62 (95% CI: −1.17, −0.07) (follow-up, 6 years)].
De koning et al., 2018 [143] (Netherlands)	Two cohorts: 55–65 >65	Cohort Population-based Cross-sectional and longitudinal analysis (n=1,282; n=737)	CES-D-20	Sufficiency 50-75 nmol/L and >75 nmol/L Insufficiency 30–50 nmol/L Deficiency <30 nmol/L	In the cross-sectional analysis, no associations were significant. In the longitudinal analysis, women in the older cohort with baseline 25(OH)D concentrations up to 75 nmol/L presented 17–24% more depressive symptoms (follow-up 6 years) compared to those with >75 nmol/L. In men and in the younger-old cohort, no significant associations were observed.
Sherchand et al., 2018 [144] (Nepal)	≥18	Cross-sectional analysis (n=300)	BDI	Sufficient 30–100 ng/mL Insufficient 20–29 ng/mL Deficient <20 ng/mL	The association presented OR=3.5 (95% CI: 1.1–11.9) for clinically significant depression in the vitamin D deficient category when compared to sufficient.
Vidgren et al., 2018) [145] (Finland)	53–73	Cohort Population-based Cross-sectional analysis (n=1,602)	DSM-III	Tertiles: T1 8.5–34.4 nmol/L T2 34.4–50.7 nmol/L T3 50.8–112.8 nmol/L	Lower serum 25(OH)D concentrations (<34.4 nmol/L) were associated with depression (OR=1.64; 95%CI: 1.03, 2.59) compared to those with higher serum 25(OH)D concentrations.
Yao et al., 2018 [146] (China)	≥100	Cohort of centenarian people Cross-sectional analysis (n=940)	GDS-15	Deficiency < 20 ng/mL or 50 nmol/L	Vitamin D deficiency was an independent risk factor for depression (OR= 1.47, 95%CI:1.08–2.00). The multivariate analysis showed OR=1.73 (95%CI: 1.10–2.72) of depressive symptoms for the lowest versus highest quartiles of vitamin D levels and the adjusted OR= 1.10 (95%CI: 1.01–1.19) for 5 ng/mL decrement of serum 25(OH)D levels.
De Oliveira; Hirani; Biddulph, 2018 [147] (England)	≥50	Cohort Population-based Cross-sectional analysis (n=5,607)	CES-D	Mean nmol/L Quartiles (≤30; 30.01–46.00; 46.01–64.00; >64.01 nmol/L) >50 nmol/L	Low 25OHD presented an association with elevated depressive symptoms (OR= 1.58; 95%CI:1.20–2.07) for the lowest quartile; for <30 nmol/L (OR=1.45; 95%CI:1.15–1.83); and for ≤50 nmol/L (OR=1.34; 95%CI:1.10–1.62). Women→ the lowest (OR=1.67;95%CI:1.20–2.34) and second lowest (OR=1.68; 95%CI:1.20–2.35)

				30–50 nmol/L <30 nmol/L ≤50 nmol/L >50 nmol/L	quartiles as well as those with levels <30 nmol/L (OR=1.40; 95%CI:1.06–1.86) and ≤50 nmol/L (OR=1.35; 95%CI:1.07–1.72) were more likely to report elevated depressive symptoms. Men → the association only remained significant for those with <30 nmol/L (OR=1.60; 95%CI:1.06–2.42).
Jovanova et al., 2017 [148] (Netherlands)	≥55	Cohort Population-based Cross-sectional and longitudinal analysis (n=3,251)	CES-D DSM-IV	Mean nmol/L Cutoff: <37.5 vs. >37.5; <50 vs. >50; <75 vs. >75 nmol/l Quartiles <28.57; 28.58–43.81; 43.82–63.21; >63.21 nmol/L sufficiency (>50 nmol/l) deficiency (<50 nmol/l)	Cross-sectionally → Low 25(OH)D were associated with more depressive symptoms (B=−0.27; 95%C:−0.51;−0.04). A serum ≤37.5 nmol/L was associated with depressive symptoms (B= 0.48, 95%CI =0.01; 0.95) compared with >37.5 nmol/L. Longitudinally → Low 25(OH)D were not associated with change of depressive symptoms or incident MDD.
Collin et al., 2017 [149] (France)	≥40	Cohort Case–control study from a randomized double-blind, placebo-controlled (Vitamin D was not part of the supplementation) Longitudinal analysis (n=1,196)	CES-D	Cutoff: <30 vs. ≥ 30; <20 vs. ≥20; <10 vs. ≥10 ng/mL Based on: Suboptimal status 20–29 ng/mL Insufficiency 10–19 ng/mL Deficiency <10 ng/mL	25(OH)D above 10 ng/mL was related to a lower probability of recurrent depressive symptoms (PR= 0.48; 95%CI:0.33–0.69). When comparing individuals with concentrations < versus ≥20 or < versus ≥30 ng/mL, no significant results were obtained.
Lee et al., 2017 [150] (South Korea)	20–88	Population-based Cross-sectional analysis (n=7,198)	Self-reporting	No deficiency ≥20 ng/mL Deficiency <20 ng/mL	Positive association between vitamin D deficiency and depressive symptoms (OR=1.54; 95%CI:1.20–1.98) was found.
Shin et al., 2016 [151] (Japan)	20–70	Cross-sectional analysis Medical record data (n=52,228)	CES-D	Sufficiency ≥ 20 ng/mL Insufficiency 10–19.99 ng/mL	The presence of depressive symptoms was significantly increased in participants with vitamin D deficiency

				Deficiency < 10 ng/mL	after adjusting for potentially confounding factors (OR=1.158; 95%CI:1.003–1.336)
Rabenberg et al., 2016 [152] (Germany)	18–79	Nationwide representative Population-based Cross-sectional analysis (n=6,331)	PHQ-9	Quartiles: 9–27; 28–42; 43–59; and 60–347nmol/L	A significant association with severity of depressive symptoms remained in summer, with 0.73 (95%CI:−1.31;−0.14; P=0.02) point lower in PHQ-9 scores in the highest versus lowest quartile. In the logistic regression the association no remained significant in fully adjusted models.
Van Den Berg et al., 2016 [153] (Netherlands)	≥60	Cohort of depressed people Longitudinal analysis (n=367)	CIDI IDS-SR	Sufficient ≥ 75 nmol/L Hypovitaminosis D 50–75 nmol/L Insufficient 25–50 nmol/L Deficient 10–25 nmol/L Severely deficient < 10 nmol/L	Vitamin D had no effect on the course of depression or remission.
Song et al., 2016 [154] (South Korea)	≥65	Cohort Cross-sectional analysis (n= 2,853)	GDS-15	≥30.0 ng/mL 20.0-29.9 ng/mL 10.0-19.9 ng/mL <10.0 ng/mL	Men → Compared with those with ≥30.0 ng/mL People with 10.0–19.9ng/mL presented OR=2.50 (95%CI: 1.20–5.18) and those with <10.0 ng/mL presented OR=2.81 (95%CI:1.15–6.83) to depressive symptoms. Women → the associations between 25(OH)D and depressive symptoms were not significant.
Brouwer-Brolsma et al., 2016 [155] (Netherlands)	≥65	Cohort Randomized, double-blind, placebo-controlled Cross-sectional analysis (baseline) (n=2,839)	GDS-15	Quartiles: <36.7; 36.7-53.4; 53.4-71.7; >71.7 nmol/L	Fully adjusted models indicated a 22 % (RR=0.78, 95%CI: 0.68–0.89), 21 % (RR=0.79, 95%CI: 0.68–0.90), and 18 % (RR=0.82, 95%CI: 0.71–0.95) lower score of depressive symptoms in people in the second (36.7–53.4 nmol/L), third (53.4–71.7 nmol/L), and fourth (>71.7 nmol/L) quartiles, when compared to people in the first quartile (<36.7nmo/L).
Rocha-Lima et al, 2016 [156]	≥80	Cohort of free-living independent elderly	GDS-15	Sufficiency >30ng/mL Insufficiency 10-30ng/mL	Found a difference between GDS score comparing the groups: deficiency (U=144,50; z=−3,126; p=0,002) and

(Brazil)		Cross-sectional analysis (n=182)		Deficiency <10ng/mL	insufficiency groups (U=975,50; z=−2,793; p=0.005) are different than sufficiency group
Husemoen, et al, 2016 [157] (Denmark)	18–64	Nationwide representative Cross-sectional and longitudinal analysis (n=5,308)	SCL	Mean nmol/L	Low serum 25(OH)D is not associated with self-reported symptoms/diagnosis of depression
Jääskeläinen, et al, 2015 [158] (Finland)	30–79	Nationwide representative Population-based Cross-sectional analysis (n=5,371)	BDI Munich-Composite International Diagnostic Interview	Deficiency <50 nmol/L Quartiles:7–33; 34–43; 44–55; and 56–134 nmol/L	Inverse association between serum 25(OH)D concentration and depressive disorder comparing the highest and lowest quartiles (OR=0.65; 95%CI: 046–0.93)
Almeida et al., 2015 [159] (Australia)	71–88	Cohort of men Cross-sectional and longitudinal analysis (n=3,105)	GDS-15 PHQ-9	Sufficient ≥50 nmol/L Mild deficiency 30–49 nmol/L Moderate to severe deficiency <30 nmol/L	Vitamin D concentration <50 nmol/L was associated with current depression (OR=1.65, 95%CI:1.13–2.42) but not past or future depression.
Williams et al., 2015 [160] (United States)	70–79	Cohort Cross-sectional and longitudinal analysis (n=2,598)	CES-D-10	Sufficiency ≥30 ng/mL Insufficiency 20–<30 ng/mL Deficiency <20 ng/mL	Serum 25(OH)D was not associated with CES-D scores at baseline and 1-year follow-up. Participants with <20ng/mL were at greater risk of developing depression (HR= 1.65; 95%CI:1.23–2.22) over 4 years of follow-up compared with those with ≥30ng/mL.
Imai et al., 2015 [161] (Iceland)	66–96	Cohort Population-based Cross-sectional analysis (n=5,006)	GDS-15 DSM-IV	Adequate ≥50 nmol/L Inadequate 30–49·9 nmol/L Deficient <30 nmol/L	Men → deficient status were more likely to have current major depressive disorder (OR= 2.51; 95%CI: 1.03–6.13) compared with adequate Women → Associations were not significant.

Józefowicz et al., 2014 [162] (Poland)	18–65	Cross-sectional analysis (n=180)	HDRS	Recommended 30–80 ng/mL Insufficiency 21–29 ng/mL Deficiency <20 ng/mL	HDRS scores were negatively correlated with levels of vitamin D ($p < 0.02$), however, did not differ significantly between the groups of classification.
Toffanello et al., 2014 [163] (Italy)	≥65	Cohort Population-based Cross-sectional and longitudinal analysis (n=1,675)	GDS	Sufficiency ≥75 nmol/L Insufficiency ≥50 to <75 nmol/L Deficiency <50 nmol/L	Women → deficiency had higher GDS scores than those with sufficiency in mean [SE] GDS scores: 9.57 [0.37] vs. 8.31 [0.31], respectively, p =.02. Men → no significance. 25OHD deficiency and insufficiency were not associated with a higher probability of developing depressed mood during the follow-up.
Milaneschi et al., 2014 [164] (Netherlands)	18–65	Cohort Cross-sectional and longitudinal analysis (n=2,386)	DSM-IV CIDI IDS	Mean nmol/L	Lower 25(OH)D levels were found in participants with current depression (P=0.001, Cohen's d=0.21), particularly in those with the most severe symptoms (P=0.001, Cohen's d=0.44). In currently depressed persons, 25(OH)D was inversely associated with symptom severity (β=−0.19, s.e.=0.07, P=0.003) suggesting a dose-response and risk (RR=0.90, 95%CI:0.82–0.99) of having a depressive disorder at 2-year follow-up.
Lapid et al, 2013 [165] (United States)	≥60	Cross-sectional analysis (n=1,618)	HICDA	Optimal range ≥25 ng/mL Mild to moderate deficiency 10–24 ng/mL Severe deficiency <10 ng/mL	25(OH)D was correlated with depression (OR= 0.990; 95%CI:0.983–0.998). Those with severe vitamin D deficiency were twice as likely to have depression (OR= 2.093; 95%CI: 1.092–4.011).
Jaddou et al, 2012 [166] (Jordan)	≥25	Nationwide representative Population-based Cross-sectional analysis (n=4,002)	DASS21	Cutoff: <30 and ≥30 ng/mL Quartiles: >63.22; 42.31–63.22; 27.61–42.30; ≤27.60 ng/mL	Depression was significantly higher in the level <30 ng/ml compared to those with ≥30 ng/ml (OR= 1.38, P=0.00). In the quartiles, the lowest (OR=1.48, P=0.00) and the second lowest (OR=1.24, P=0.03) showed higher depression compared to the highest quartile.

Chan et al., 2011 [167] (Hong Kong/China)	≥65	Cohort of men Cross-sectional and longitudinal analysis (n=939)	GDS-15	Mean nmol/L Quartiles: ≤63; 64–76; 77–91; ≥92 nmol/L	An inverse association was observed, with the highest (≥92 nmol/L) compared with lowest (≤ 63 nmol/L) quartile of serum 25OHD had an OR=0.46 (95% CI: 0.22–0.98) for depression. No association was observed between serum 25OHD and incident depression at 4 years.
Lee et al., 2011 [168] (Italy, Belgium, Poland, Sweden, United Kingdom, Spain, Hungary, Estonia)	40–79	Cohort of men Cross-sectional analysis (n=3,369)	BDI-II	Mean nmol/L Quartiles: >78.4; 57.0–78.4; 39.0–56.9; <39.0 Sufficient ≥75 nmol/L Sub-optimum 50–74.9 nmol/L Insufficient 25–49.9 nmol/L Deficient <25 nmol/L	A 10 nmol/L decrease in 25(OH)D was associated with an average increase of 3.2% (95%CI:1.1–5.5; p = 0.05) in the BDI-II score. In the quartiles, the association between depression and 25(OH)D quartiles only just remained significant for the lowest vs. highest quartile (OR = 1.74; 95%CI = 1.00; 3.00). In the categories, the deficiency (OR = 1.73; 95%CI = 1.03; 2.93) and insufficiency remained significant (OR = 1.80; 95%CI = 1.09; 2.98).
Milaneschi et al., 2010 [169] (Italy)	≥65	Cohort Population-based Longitudinal analysis (n=954)	CES-D	Optimal levels ≥50 nmol/L Insufficiency <50 nmol/L	Women → the 3- and 6-year average increases in CES-D scores were, respectively 2.1 (se = 0.9; P = 0.02) and 2.2 (se = 1.1; P = 0.04) points higher in <50 nmol/L compared to ≥50 nmol/L. Low vitamin D had significantly higher risk of developing depressive mood over the follow-up (HR= 2.0; 95% CI: 1.2–3.2). Men → only in the 3-yr average increases 1.9 (se = 0.8; P = 0.01) points higher in <50 nmol/L compared to ≥50 nmol/L. The risk of developing a depressed mood was not significant by HR.
Stewart; Hirani, 2010 [170] (England)	≥65	Population-based Cross-sectional analysis (n=2,070)	GDS-10	Mean ng/mL Severe deficiency <10 ng/mL	Only the most severe deficiency (<10 ng/mL) remained associated with depression (OR=1.46; 95%CI:1.02-2.04)

				Deficiency <20 ng/mL Optimal ≥30 ng/mL	Dose-response association between 25(OH)D and depressive symptoms was shown strongly significance (B=−1.94; 95%CI: −2.67, −1.20).
Nanri et al., 2009 [171] (Japan)	21-67	Cross-sectional analysis (n=527)	CES-D	Mean ng/mL Quartiles (median)	Depressive symptoms were not associated with serum 25-hydroxyvitamin D concentrations.
Pan et al., 2009 [172] (China)	50-70	Population-based Cross-sectional analysis (n=3,262)	CES-D	Tertiles (mean/sd)	Depressive symptoms were not associated with serum 25-hydroxyvitamin D concentrations after adjustments.
Hoogendijk et al., 2008 [173] (Netherlands)	≥65	Cohort Cross-sectional analysis (n=1,282)	CES-D Diagnostic Interview Schedule	Mean ng/mL Quartiles: ≤14.7; 14.7–20.4; 20.4–27.4;>27.4 ng/mL	Depression severity was significantly associated with decreased serum 25(OH)D levels (B=8.0; 95%CI: 15.2–0.8; P = 0.03).
Wilkins et al, 2006 [174] (United States)	≥60	Cross-sectional analysis (n=80)	Depressive Symptoms Inventory	Sufficient ≥20 ng/mL Insufficient 10–19.9 ng/mL Deficient <10 ng/mL	Vitamin D deficiency (OR= 11.69; 95%CI:2.04 – 66.86) and insufficient (OR: 2.54; 95% CI: 0.63–10.51) were more likely to have a mood disorder compared with those with sufficient vitamin D.

95%CI: 95% confidence interval, OR: Odds ratio, SE: standard error, ES: effect size, IRR: incidence rate ratio, B: unstandardized beta, RR: relative risk, 25(OH)D: 25-hydroxycholecalciferol; 25-hydroxyvitamin D; 25(OH)D2: 25-hydroxyvitamin D2. 25(OH)D2: 25-hydroxyvitamin D3. DSM-IV: Diagnostic and Statistical Manual of Mental Disorders. CIDI: Composite International Diagnostic Interview; IDS-SR: self-report version of the Inventory of Depressive Symptoms. GDS-15: Geriatric Depression Scale with 15 items. CES-D: Center for Epidemiologic Studies Depression Scale. HAM-D-17: Hamilton Depression Rating Scale-17items HAD: Hospital Anxiety and Depression Scale PHQ-9: Patient Health Questionnaire-9. BDI: Beck Depression Inventory CIDI: Composite International Diagnostic Interview. IDS-SR: Inventory of Depressive Symptoms — Self-Report SCL: Symptom checklist. HDRS: Hamilton Depression Rating Scale. HICDA: Hospital International Classification of Disease Adaptation. DASS21: Depression Anxiety Stress Scale

Supporting Information

Box S1. Search strategy and results in observational studies
Box S2. Search strategy and results in clinical trials
Box S3. PICOS criteria for inclusion of studies

Box S1. Database search strategy and results of observational studies

Database	Search strategy	Items found	Items selected
PubMed : http://www.ncbi.nlm.nih.gov/pubmed	(((depression) OR (depressive symptoms) OR (Major Depressive Disorder)) AND ((vitamin D) OR (25-hydroxyvitamin D) OR (25-hydroxycholecalciferol) OR ((25(OH)D)) AND ((aged) OR (aging) OR (“older adults”) OR (“older people”) OR (elderly)))	610	22
Web of science- http://apps-webofknowledge.ez10.periodicos.capes.gov.br/WOS_GeneralSearch_input.do?product=WOS&search_mode=GeneralSearch&SID=3DPjTQtaLeODIEzPIty&preferencesSaved=	("vitamin d" OR 25-hydroxycholecalciferol OR 25(OH)D OR 25-hydroxyvitamin D) AND (depression OR "depressive symptoms" OR "Major Depressive Disorder") AND (aged OR aging OR “older adults” OR “older people” OR elderly)	651	7
Science Direct: http://www.sciencedirect.com/	(depression OR "depressive symptoms") AND ("25-hydroxyvitamin D" OR "vitamin D" OR "25-hydroxycholecalciferol") AND (“older adults” OR “older people” OR elderly)	6,173	0
Scopus: http://www.scopus.com/	(TITLE-ABS-KEY ("depressive symptoms" OR depression) AND TITLE-ABS-KEY ("vitamin D" OR "25-Hydroxyvitamin D" OR 25-hydroxycholecalciferol) AND	1,074	5

	TITLE-ABS-KEY (elderly OR aged OR "older adults" OR "older people")		
Embase - https://www.embase.com/#search	('major depression':ti,ab,kw OR depression:ti,ab,kw) AND ('vitamin d':ti,ab,kw OR calcifediol:ti,ab,kw OR '25 hydroxyvitamin d':ti,ab,kw OR 'vitamin d deficiency':ti,ab,kw) AND ('older adults':ti,ab,kw OR aged:ti,ab,kw OR 'older people':ti,ab,kw)	301	0
From article references	-	-	9

Box S2. Database search strategy and results of clinical trial studies

Database	Search strategy	Items found	Items selected
PubMed : http://www.ncbi.nlm.nih.gov/pubmed	((depression OR "depressive symptoms" OR "major depressive disorder") AND ("vitamin D" OR Cholecalciferol OR Ergocalciferol OR "vitamin D3" OR "vitamin D2")) AND ("older adults" OR elderly OR "older people")	569	13
Web of science- http://apps-webofknowledge.ez10.periodicos.capes.gov.br/WOS_GeneralSearch_input.do?product=WOS&search_mode=GeneralSearch&SID=3DPjTQtaLeODIEzPIty&preferencesSaved=	depress*) AND TÓPICO: ("vitamin D" OR Cholecalciferol OR Ergocalciferol OR "vitamin D3" OR "vitamin D2") AND TÓPICO: ("older adults" OR elderly OR "older people")	253	2

Scopus: http://www.scopus.com/	(TITLE-ABS-KEY ("depressive symptoms" OR depression OR "major AND depressive AND disorder") AND TITLE-ABS-KEY ("vitamin D" OR cholecalciferol OR ergocalciferol OR "vitamin D3" OR "vitamin D2") AND TITLE-ABS-KEY (elderly OR aged OR "older adults" OR "older people"))	159	4
Science Direct: http://www.sciencedirect.com/	(depression OR "depressive symptoms") AND (Cholecalciferol OR "vitamin D3" OR "vitamin D2") AND ("older adults" OR "older people" OR elderly)	1132	0
Embase https://www.embase.com/#search	(depression:ti,ab,kw OR 'major depression':ti,ab,kw) AND ('vitamin d':ti,ab,kw OR colecalciferol:ti,ab,kw OR ergocalciferol:ti,ab,kw) AND ('older adults':ti,ab,kw OR aged:ti,ab,kw OR 'older people':ti,ab,kw)	281	3
From article reference	-	-	1

Box S2. PICOS criteria for inclusion of studies

Parameter	**Inclusion criteria**
Population	Older adults
Intervention	Vitamin D (for clinical studies)
Comparator	No comparators were identified for this study
Outcome	Depression, depressive symptoms
Study design	Observational studies (cohort, cross-sectional and case-control studies) and Clinical trials published before April 30, 2021

4.2.2 Artigo 4

Vitamin D, depressive symptoms and covid-19 pandemic.

Gilciane Ceolin[1,3], Giulia Pipolo Rodrigues Mano[2,3], Natália Schmitt Hames[2,3], Luciana da Conceição Antunes[3,4], Elisa Brietzke[5,6,7], Débora Kurrle Rieger[1,3], Júlia Dubois Moreira[1,3.]

[1] Postgraduate Program in Nutrition, Federal University of Santa Catarina, Florianopolis, Santa Catarina, Brazil

[2] Nutrition Graduation Course, Federal University of Santa Catarina, Florianopolis, Santa Catarina, Brazil

[3] Translational Nutritional Neuroscience working group, Federal University of Santa Catarina, Florianopolis, Santa Catarina, Brazil

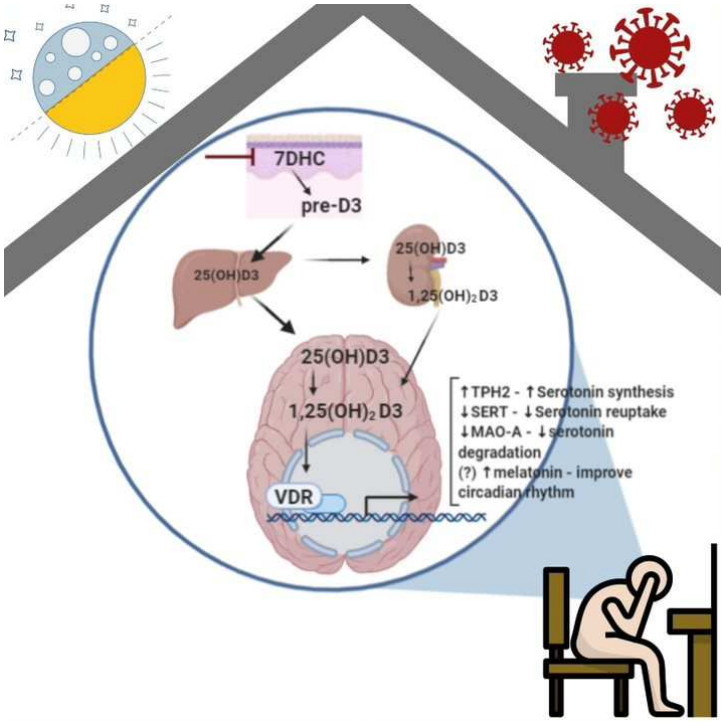
[4] Department of Nutrition, Federal University of Santa Catarina, Florianopolis, Santa Catarina, Brazil

[5] Department of Psychiatry, Queens University, Kingston, ON, Canada

[6] Inpatient Psychiatric Unit, Kingston General Hospital, Kingston Health Sciences Centre, Kingston, ON, Canada

[7] Centre for Neuroscience Studies (CNS), Kingston, ON, Canada

Graphical Abstract



Role of vitamin D in the development of depressive symptoms. The synthesis of vitamin D from sunlight is impaired by lockdown and social distance measures imposed by the governments around the world during COVID-10 pandemic. Endogenous vitamin D synthesis initiates in the skin when 7-DHC is converted in pre-vitamin D3 and then vitamin D3 [25(OH)D_3]. It is transported through blood circulation by the vitamin D binding protein (VDBP) to the liver, the kidney, and the brain, where can be converted in its the active form [1,25$(OH)_2$D]. In the brain, the biological effects of 1,25$(OH)_2$D are largely mediated by vitamin D receptor (VDR) through genomic mechanisms, which influence several aspects of serotonin metabolism, such as increasing serotonin synthesis by induction of the tryptophan hydroxylase 2 (TPH2) gene expression; influencing the expression of serotonin reuptake transporter (SERT) and the levels of monoamine oxidase-A (MAO-A), responsible to serotonin catabolism; and indirectly may regulate the synthesis of melatonin that improve the circadian rhythm. This mechanism can be impaired during social isolation and consequent reduction of vitamin D due to low sun exposure during the pandemic, which could contribute to the development of depressive symptoms.

Abstract

Since the COVID-19 outbreak, studies across diverse countries have strongly pointed towards the emergence of a mental health crisis, with a dramatic increase in the prevalence of depressive psychopathology and suicidal tendencies. Vitamin D deficiency has been associated with an increased risk of mental health problems as well as individual responses to stress. Studies have discussed the relationship between low serum vitamin D concentrations and depressive symptoms, suggesting that maintaining adequate concentrations of serum vitamin D seems to have a protective effect against it. Vitamin D was found to contribute to improved serotonergic neurotransmission in the experimental model of depression by regulating serotonin metabolism. The signaling of 1,25-dihydroxyvitamin D3, the active form of vitamin D, through vitamin D receptor (VDR) induces the expression of the gene of tryptophan hydroxylase 2 (TPH2), influences the expression of serotonin reuptake transporter (SERT) as well as the levels of monoamine oxidase-A (MAO-A), the enzyme responsible for serotonin catabolism. Vitamin D also presents a relevant link with chronobiological interplay, which could influence the development of depressive symptoms when unbalance between light-dark cycles occurs. In this Perspective, we discussed the significant role of vitamin D in the

elevation of stress-related depressive symptoms during the COVID-19 pandemic. It is suggested that vitamin D monitoring and, when deficiency is detected, supplementation could be considered as an important healthcare measure while lockdown and social isolation procedures last during the COVID19 pandemic.

Keywords: Vitamin D, Cholecalciferol, Depressive Symptoms, Social Isolation, Pandemics, COVID-19.

Depression and Covid-19 pandemic

The current pandemic of coronavirus (COVID-19) has imposed social isolation measures, forcing many people to stay confined at home, canceling routine outdoor activities (working routine, sidewalks, exercises in fitness centers, and park visits), and limiting social interaction among friends, coworkers, and family. A study concentrated on a general population from China within the first two weeks of the COVID-19 outbreak indicated that the lifestyle changes prompted individuals to stay indoors for over 20-24 h per day (Wang et al., 2020).

Since the COVID-19 outbreak, studies across diverse countries have strongly pointed towards the emergence of a mental health crisis, with a dramatic increase in the prevalence of depressive psychopathology and suicidal tendencies. A systematic review of the instances of mental health conditions during the period of the COVID-19 pandemic showed that the prevalence of depressive symptoms ranged from 14.6% to 48.3% across all populations (China, Spain, Italy, Iran, the US, Turkey, Nepal, and Denmark) (Xiong et al., 2020). In the USA, the prevalence of symptoms associated with depression increased more than threefold during the COVID-19 pandemic compared to the times before the viral outbreak (8.5% before to 27.8% during COVID-19) (Ettman et al., 2020) In London, after lockdown the prevalence of feeling worse on the depression was 12,8% and to anxiety was 12.3% in people with 50 years or over(Robb et al., 2020). Restriction of public circulation and social isolation, despite those being essential measures to contain the pandemic, has been postulated to be responsible for increased stress, loneliness, and unhealthy lifestyle habits (Luo et al., 2020; Smith and Lim, 2020).

Recently, a longitudinal study involving older adults (Santini et al., 2020) demonstrated that social disconnectedness could contribute to a greater risk of depression and anxiety, which has also been reported in adolescent and adult

populations (Smith and Lim, 2020). In a survey conducted by UNICEF, Australia on 1000 young people (aged 13–17 years), almost half of the respondents asserted that COVID-19 had negatively affected their levels of stress and anxiety. An elevated level of stress, fear, irritability, frustration, and boredom was reported by individuals who were in social isolation and had experienced a major deflection from their usual routine and interaction with other people (Smith and Lim, 2020). In addition to the increase in the risk of mental health problems, the pandemic has also exacerbated preexisting psychiatric conditions. Vulnerability to psychological stress might depend on social support, isolation time, COVID-19 infection-related factors, the amount of mass media exposure, physical activity, and eating patterns (Kontoangelos et al., 2020).

Vitamin D and sunlight exposure: breakdown by social isolation measures during COVID19 pandemic

Vitamin D deficiency has been associated with an increased risk of mental health problems as well as individual responses to stress (Amrein et al., 2020). There are several risk factors related to vitamin D deficiency such as obesity, dark skin, living in countries with low sunlight incidence, gastrointestinal malabsorption, renal insufficiency, liver disease, and the use of covered clothing and sunscreen (Kennel et al., 2010; Holick et al., 2011). Furthermore, reduced exposure to sunlight, thereby reducing the biosynthesis of vitamin D in the skin, is a strong factor in the pathophysiology of vitamin D deficiency and studies have been demonstrated that sun exposure can enhance vitamin D synthesis (Jorde et al., 2010; Chel et al., 2011; Macdonald et al., 2011; Chalcraft et al., 2020).

After adequate exposure to sunlight, the conversion of 7-dehydrocholesterol (7-DHC) to 25-hydroxycholecalciferol [25(OH)D] takes approximately 8 h and an additional time to enter the dermal capillary bed. The daily exposure of 20% of the body surface is sufficient to increase 25(OH)D, which points towards the importance of sunlight in the maintenance of vitamin D levels at the appropriate concentration (Wacker and Holick, 2013). The half-life of 25(OH)D was estimated to 15 to 25 days, approximately (Lips, 2007; Jones et al., 2014). The half-life of serum 25(OH)D was estimated to be ~82 days when calculated after one single loading dose of 100 000 IU of cholecalciferol was administered at the beginning of the study, followed by a daily dose of 4800 IU from days 7 to 20, and none from day 21 (Oliveri et al., 2015). In Nordic countries, which experience low amounts of sunlight, vitamin D concentrations were found to be reduced by 20% to

40% during the winter (Jorde et al., 2010). These data suggest that vitamin D supplementation is crucial in individuals who experience long periods of indoor activities and/or low sunshine exposure.

Social isolation and lockdown measures caused a reduction in the time spent outdoors and possibly less exposure to sunlight necessary to maintain vitamin D concentrations. When associated with a change in eating habits, with a predominance of meals ordered through food delivery joints, which have a reduced nutritional and vitamin D content, it could also reduce the daily amount of vitamin D for organism maintenance. One study conducted in Verona (Italy) during the COVID19 pandemic, which intends to investigate whether social isolation could impact the vitamin D status of the general population, conclude that this was not an issue in Verona (the region in which data was collected) (Lippi et al., 2021). Despite scarce publications address this issue, research groups, and professionals already start to concern about vitamin D deficiency during the COVID19 pandemic. Some postulate that home reclusion could lead to a surge of vitamin D deficiency around the world, which has been associated with developing type 2 diabetes, cognitive decline, malignant neoplasms, autoimmune diseases, cardiovascular diseases, osteoporosis, risk of fall in the elderly, and overall mortality (Alpalhão and Filipe, 2020). In fact, the diminished vitamin D intake and sun exposure might result in severe manifestations since the worldwide prevalence of vitamin D deficiency had been documented as a health concern even before the pandemic (Luo et al., 2018; Zhou et al., 2019; Amrein et al., 2020).

Vitamin D and depressive symptoms

Vitamin D low levels have been previously associated with the risk of depressive symptoms and depression worldwide (Song et al., 2016; Vidgren et al., 2018; Yao et al., 2018; Ceolin et al., 2020; Köhnke et al., 2020). However, few publications have been discussing this relationship during the covid-19 pandemic (Di Nicola et al., 2020; Mehta et al., 2021). Mehta et al. (2021) discussed that vitamin D can be hypothesized to trigger as well as sustain the psychiatric symptoms and can also be expected to alleviate the psychiatric manifestations in COVID-19. An observational study in Rome showed that low 25-hydroxyvitamin D serum levels were significantly associated with higher psychological distress in patients with mood disorders during the COVID-19 outbreak (Di Nicola et al., 2020).

The mechanisms associated with vitamin D antidepressant effects at the cellular level are under investigation in experimental studies, and some hypotheses have been presented in different reports in the literature. The VDR and some cytochrome P450 enzymes, which are responsible for the transformation of vitamin D into its active form, were found in cerebral cells and in brain areas that have been implicated in the pathophysiology of depression (He et al., 2020). The optimal vitamin D status was found to contribute to improved serotonergic neurotransmission deficits in an experimental model of depression by regulating serotonin synthesis (Sabir et al., 2018). To increase serotonin concentrations, tryptophan must first be transported across the blood-brain barrier and metabolized by TPH2. The signaling of 1,25-dihydroxycholecalciferol [1,25$(OH)_2$D], the active form of vitamin D, through VDR induces the expression of the gene TPH2 (Kaneko et al., 2015; Patrick and Ames, 2015). Moreover, 1,25$(OH)_2$D influences the expression of SERT as well as the levels of MAO-A, the enzyme responsible for serotonin catabolism (Sabir et al., 2018).

Another important aspect related to vitamin D and brain function is its link with chronobiological interplay. Indeed, the interface between vitamin D and the circadian system has been revealed as both plasma concentrations of 1,25$(OH)_2$D and vitamin D binding protein (DBP) display circadian oscillation patterns (Jones et al., 2017). However, available evidence suggests a mediatory role of vitamin D in the sleep-wake cycle, since the lower concentrations of vitamin D were correlated with impaired sleep quality and abbreviated sleep duration (Jones et al., 2017; Muscogiuri et al., 2019). Melatonin, a hormone involved in the regulation of circadian rhythm, is synthesized from the metabolism of serotonin. The widespread presence of VDR has been documented in postmortem human brain samples, in areas involved in sleep regulation, which are also brain regions that showed the strongest expression of the enzyme 1-alpha-hydroxylase, enzymes responsible for the formation of 1,25$(OH)_2$D (Eyles et al., 2005). In this way, it is possible to hypothesize that the chronic combined deficits of vitamin D and sleep-wake cycle impairment due to social isolation measures and lockdown might play an essential role as a modulator of amplified depressive symptomatology and/or the pathophysiology of major depressive disorder (MDD).

Depression has also been associated with mitochondrial dysfunctions and an increase in the formation of reactive oxygen species (ROS) inducing redox to unbalance and reduction in the energy production (adenosine triphosphate-ATP) (Caruso et al.,

2019). Oxidative stress activates several transcription factors, such as nuclear factor kappa B (NF-kB) leading to the production of pro-inflammatory cytokines and other inflammatory molecules acting as potent inducers of inducible nitric oxide synthase (iNOS) (Morris and Berk, 2015). Inflammation may induce depression through many mechanisms such as an alteration in the formation of key transmitters such as serotonin and an increase in Ca2+ signaling (Leonard and Maes, 2012; Berridge, 2017). Also, dysfunction in mTOR signaling can lead to ROS production and the mTOR inhibition enhance sirtuin signaling contributing to mitochondrial integrity (Mocayar Marón et al., 2020). Vitamin D and melatonin share common signaling pathways that mediate homeostatic mitochondrial function, which includes the downregulation of mTOR, iNOS, and NF-κB pathways that are involved in increasing oxidative stress and cell damage. Also, Vitamin D and melatonin decrease oxidative stress by upregulation of sirtuin 1 (SIRT-1) and adenosine monophosphate-activated protein kinase (AMPK) pathways and activating antioxidant defense pathways by expression of antioxidant proteins. These pathways are crucial to avoid abnormal inflammatory responses related to oxidative stress and apoptosis (Mocayar Marón et al., 2020).

The studies aiming to investigate the antidepressant effect of vitamin D supplementation when depression was already diagnosed observed conflicting results (Alavi et al., 2019; Alghamdi et al., 2020; Okereke et al., 2020; Vellekkatt et al., 2020; Zhu et al., 2020). To mention some of them, in randomized clinical trials (RCT), Vellekkatt et al. (2020), Alghamdi et al. (2020), and Alavi et al. (2019) observed a reduction of depressive symptoms after vitamin D supplementation in patients with different stages of depression. Nevertheless, Okereke et al. (2020) and Zhu et al. (2020) did not observe improvements in depressive symptoms after vitamin D supplementation. Data from a previous meta-analysis with RCT showed that supplementation with vitamin D (≥800 I.U. daily dose) had a positive effect when compared to the effect of antidepressants (Spedding, 2014). But, a separate meta-analysis did not support this evidence in adults and pointed out that the variability in methodological attributes of the studies included in the meta-analysis (differences in vitamin D doses, time of intervention duration, and assessment of depression) could influence the conclusions (Gowda et al., 2015). Despite all this uncertainty about the effects of vitamin D supplementation to treat depression, when the preventive effect of adequate concentrations of vitamin D was investigated in observational studies, the results are promising. Two systematic reviews

and metanalysis with population-based epidemiological studies (Ju et al., 2013; Li et al., 2019) showed an inverse association between serum 25(OH)D and the risk of depression and, in the pooled estimation analysis, an increase of 10 ng/mL in serum concentrations of vitamin D might have a protective effect against depression. The data from these two meta-analyses leads us to postulate that the monitoring of vitamin D during long periods of indoor activities associated with reduced time to sunlight exposure is a reasonable health measure, as well as the supplementation to maintain adequate vitamin D concentrations.

Vitamin D and COVID-19

A growing body of literature has been discussing a possible relationship between 25(OH)D and COVID-19, in which vitamin D may contribute to reducing the severity of illness caused by COVID-19 (Bergman, 2020; Jakovac, 2020; Marik et al., 2020; Mitchell, 2020; Panarese and Shahini, 2020). The main discussion is that Vitamin D could exert protective effects against respiratory infections, due to its immunomodulatory and anti-inflammatory roles, which have been highlighted in patients with community-acquired infections and acute respiratory failure (Zhou et al., 2019; Bergman, 2020; Mitchell, 2020; Panarese and Shahini, 2020). COVID-19 has been shown to affect the neuroendocrine-immune system wherein it suppresses its activity. The neuroendocrine-immune system has been implicated in stress response and coping strategies (Nami et al., 2020).

One study performed in vitro showed that the active form of Vitamin D, calcitriol, exhibits significant potent activity against SARS-CoV-2 in African green monkey kidney cells, human hepatoma cells, and human nasal epithelial cells (Mok et al., 2020). In fact, the interest in the field has been growing and some systematic reviews and meta-analysis were performed to measure the risk of infection and severity of covid-19 due to low levels of 25(OH)D in observational studies (Pereira et al., 2020; Kazemi et al., 2021; Liu et al., 2021; Petrelli et al., 2021; Teshome et al., 2021). Pereira et al (2020) reported that severe cases of COVID-19 present 64% (OR=1.64; 95% CI=1.30-2.09) of vitamin D deficiency and that insufficiency increased hospitalization (OR=1.81;95% CI=1.41-2.21) and mortality (OR=1.82; 95% CI=1.06-2.58). Kazemi et al., (2021) found that vitamin D deficiency was a higher risk of SARS-CoV-2 infection (OR=1.77; 95% CI=1.24-2.53) and presented a higher severity (OR=2.57; 95% CI=1.65-4.01). Liu et al (2021) showed

that vitamin D deficiency or insufficiency also was associated with an increased risk of COVID-19 (OR=1.43; 95% CI=1.00-2.05). Petrelli et al., (2021) revealed that deficient vitamin D values showed a higher risk of COVID-19 infection (OR=1.26; 95% CI=1.19-1.34) and worse severity (OR=2.6; 95% CI=1.84-3.67) and higher mortality (OR = 1.22; 95% CI, 1.04-1.43). Teshome et al., (2021) found that vitamin D deficiency was 80% more likely to acquire COVID-19 infection (OR=1.80; 95%CI=1.72-1.88).

Concerning clinical trials, only one systematic review and metanalysis were performed to identify the effect of vitamin D on Covid-19, and 32 clinical protocol was identified but only 3 studies have published results to-date and the results are controversial (Bassatne et al., 2021). In fact, there are some challenges in vitamin D research and some authors have provided recommendations for the design of randomized clinical trials of vitamin D supplementation to prevent COVID-19 and to provide evidence-based guidance for clinicians and public health leaders (Camargo and Martineau, 2020).

Conclusion

In the light of these evidence, it is possible to postulate that vitamin D deficiency could play a significant role in the elevation of stress-related depressive symptoms during the COVID-19 pandemic. It has been postulated that vitamin D is involved in the serotoninergic system, influencing serotonin metabolism and contributing to circadian rhythm maintenance, which are important aspects of the development of depressive symptoms. In order to reduce physical and mental health risks associated with vitamin D deficiency, it is suggested that vitamin D monitoring and, when deficiency is detected, supplementation could be considered as an important healthcare measure while lockdown and restrictive social isolation procedures last during the COVID19 pandemic.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author Contributions

All authors have contributed equally to this work.

Funding

No funding was received for this study.

Acknowledgments

Ceolin G receive PhD scholarship from Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES).

References

Alavi, N. M., Khademalhoseini, S., Vakili, Z., and Assarian, F. (2019). Effect of vitamin D supplementation on depression in elderly patients: A randomized clinical trial. *Clinical Nutrition* 38, 2065–2070. doi:10.1016/j.clnu.2018.09.011.

Alghamdi, S., Alsulami, N., Khoja, S., Alsufiani, H., Tayeb, H. O., and Tarazi, F. I. (2020). Vitamin D Supplementation Ameliorates Severity of Major Depressive Disorder. *J Mol Neurosci* 70, 230–235. doi:10.1007/s12031-019-01461-2.

Alpalhão, M., and Filipe, P. (2020). SARS-CoV-2 pandemic and Vitamin D deficiency—A double trouble. *Photodermatol Photoimmunol Photomed*. doi:10.1111/phpp.12579.

Amrein, K., Scherkl, M., Hoffmann, M., Neuwersch-Sommeregger, S., Köstenberger, M., Tmava Berisha, A., et al. (2020). Vitamin D deficiency 2.0: an update on the current status worldwide. *Eur J Clin Nutr*, 1–16. doi:10.1038/s41430-020-0558-y.

Bassatne, A., Basbous, M., Chakhtoura, M., Zein, O. E., Rahme, M., and Fuleihan, G. E.-H. (2021). The link between COVID-19 and VItamin D (VIVID): a systematic review and meta-analysis. *Metabolism*, 154753. doi:10.1016/j.metabol.2021.154753.

Bergman, P. (2020). The link between vitamin D and COVID-19: distinguishing facts from fiction. *J. Intern. Med.* doi:10.1111/joim.13158.

Berridge, M. J. (2017). Vitamin D and Depression: Cellular and Regulatory Mechanisms. *Pharmacol Rev* 69, 80–92. doi:10.1124/pr.116.013227.

Camargo, C. A., and Martineau, A. R. (2020). Vitamin D to prevent COVID-19: recommendations for the design of clinical trials. *The FEBS Journal* 287, 3689–3692. doi:https://doi.org/10.1111/febs.15534.

Caruso, G., Benatti, C., Blom, J. M. C., Caraci, F., and Tascedda, F. (2019). The Many Faces of Mitochondrial Dysfunction in Depression: From Pathology to Treatment. *Front Pharmacol* 10. doi:10.3389/fphar.2019.00995.

Ceolin, G., Matsuo, L. H., Confortin, S. C., D'Orsi, E., Rieger, D. K., and Moreira, J. D. (2020). Lower serum 25-hydroxycholecalciferol is associated with depressive symptoms in older adults in Southern Brazil. *Nutrition Journal* 19, 123. doi:10.1186/s12937-020-00638-5.

Chalcraft, J. R., Cardinal, L. M., Wechsler, P. J., Hollis, B. W., Gerow, K. G., Alexander, B. M., et al. (2020). Vitamin D Synthesis Following a Single Bout of Sun Exposure in Older and Younger Men and Women. *Nutrients* 12, 2237. doi:10.3390/nu12082237.

Chel, V. G. M., Ooms, M. E., Pavel, S., de Gruijl, F., Brand, A., and Lips, P. (2011). Prevention and treatment of vitamin D deficiency in Dutch psychogeriatric nursing home residents by weekly half-body UVB exposure after showering: a pilot study. *Age Ageing* 40, 211–214. doi:10.1093/ageing/afq159.

Di Nicola, M., Dattoli, L., Moccia, L., Pepe, M., Janiri, D., Fiorillo, A., et al. (2020). Serum 25-hydroxyvitamin D levels and psychological distress symptoms in patients with affective disorders during the COVID-19 pandemic. *Psychoneuroendocrinology* 122, 104869. doi:10.1016/j.psyneuen.2020.104869.

Ettman, C. K., Abdalla, S. M., Cohen, G. H., Sampson, L., Vivier, P. M., and Galea, S. (2020). Prevalence of Depression Symptoms in US Adults Before and During the COVID-19 Pandemic. *JAMA network open* 3, e2019686. doi:10.1001/jamanetworkopen.2020.19686.

Eyles, D. W., Smith, S., Kinobe, R., Hewison, M., and McGrath, J. J. (2005). Distribution of the Vitamin D receptor and 1α-hydroxylase in human brain. *Journal of Chemical Neuroanatomy* 29, 21–30. doi:10.1016/j.jchemneu.2004.08.006.

Gowda, U., Mutowo, M. P., Smith, B. J., Wluka, A. E., and Renzaho, A. M. N. (2015). Vitamin D supplementation to reduce depression in adults: Meta-analysis of randomized controlled trials. *Nutrition* 31, 421–429. doi:10.1016/j.nut.2014.06.017.

He, Y., Wu, Z., Lan, T., Wang, Y., Tian, Y., Chen, X., et al. (2020). The 25(OH)D/VDR signaling may play a role in major depression. *Biochemical and Biophysical Research Communications* 523, 405–410. doi:10.1016/j.bbrc.2019.12.071.

Holick, M. F., Binkley, N. C., Bischoff-Ferrari, H. A., Gordon, C. M., Hanley, D. A., Heaney, R. P., et al. (2011). Evaluation, Treatment, and Prevention of Vitamin D Deficiency: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab* 96, 1911–1930. doi:10.1210/jc.2011-0385.

Jakovac, H. (2020). COVID-19 and vitamin D—Is there a link and an opportunity for intervention? *American Journal of Physiology-Endocrinology and Metabolism* 318, E589–E589. doi:10.1152/ajpendo.00138.2020.

Jones, K. S., Assar, S., Harnpanich, D., Bouillon, R., Lambrechts, D., Prentice, A., et al. (2014). 25(OH)D2 half-life is shorter than 25(OH)D3 half-life and is influenced by DBP concentration and genotype. *J. Clin. Endocrinol. Metab.* 99, 3373–3381. doi:10.1210/jc.2014-1714.

Jones, K. S., Redmond, J., Fulford, A. J., Jarjou, L., Zhou, B., Prentice, A., et al. (2017). Diurnal rhythms of vitamin D binding protein and total and free vitamin D metabolites. *J Steroid Biochem Mol Biol* 172, 130–135. doi:10.1016/j.jsbmb.2017.07.015.

Jorde, R., Sneve, M., Hutchinson, M., Emaus, N., Figenschau, Y., and Grimnes, G. (2010). Tracking of serum 25-hydroxyvitamin D levels during 14 years in a population-based study and during 12 months in an intervention study. *Am. J. Epidemiol.* 171, 903–908. doi:10.1093/aje/kwq005.

Ju, S.-Y., Lee, Y.-J., and Jeong, S.-N. (2013). Serum 25-hydroxyvitamin D levels and the risk of depression: A systematic review and meta-analysis. *J Nutr Health Aging* 17, 447–455. doi:10.1007/s12603-012-0418-0.

Kaneko, I., Sabir, M. S., Dussik, C. M., Whitfield, G. K., Karrys, A., Hsieh, J.-C., et al. (2015). 1,25-Dihydroxyvitamin D regulates expression of the tryptophan hydroxylase 2 and leptin genes: implication for behavioral influences of vitamin D. *The FASEB Journal* 29, 4023–4035. doi:10.1096/fj.14-269811.

Kazemi, A., Mohammadi, V., Aghababaee, S. K., Golzarand, M., Clark, C. C. T., and Babajafari, S. (2021). Association of Vitamin D Status with SARS-CoV-2 Infection or COVID-19 Severity: A Systematic Review and Meta-analysis. *Adv Nutr*. doi:10.1093/advances/nmab012.

Kennel, K. A., Drake, M. T., and Hurley, D. L. (2010). Vitamin D deficiency in adults: when to test and how to treat. *Mayo Clin. Proc.* 85, 752–757; quiz 757–758. doi:10.4065/mcp.2010.0138.

Köhnke, C., Herrmann, M., and Berger, K. (2020). Associations of major depressive disorder and related clinical characteristics with 25-hydroxyvitamin D levels in middle-aged adults. *Nutritional Neuroscience* 0, 1–10. doi:10.1080/1028415X.2020.1843892.

Kontoangelos, K., Economou, M., and Papageorgiou, C. (2020). Mental Health Effects of COVID-19 Pandemia: A Review of Clinical and Psychological Traits. *Psychiatry Investig* 17, 491–505. doi:10.30773/pi.2020.0161.

Leonard, B., and Maes, M. (2012). Mechanistic explanations how cell-mediated immune activation, inflammation and oxidative and nitrosative stress pathways and their sequels and concomitants play a role in the pathophysiology of unipolar depression. *Neuroscience & Biobehavioral Reviews* 36, 764–785. doi:10.1016/j.neubiorev.2011.12.005.

Li, H., Sun, D., Wang, A., Pan, H., Feng, W., Ng, C. H., et al. (2019). Serum 25-Hydroxyvitamin D Levels and Depression in Older Adults: A Dose–Response Meta-Analysis of Prospective Cohort Studies. *The American Journal of Geriatric Psychiatry* 27, 1192–1202. doi:10.1016/j.jagp.2019.05.022.

Lippi, G., Ferrari, A., and Targher, G. (2021). Is COVID-19 lockdown associated with vitamin D deficiency? *European Journal of Public Health*. doi:10.1093/eurpub/ckab004.

Lips, P. (2007). Relative value of 25(OH)D and 1,25(OH)2D measurements. *J. Bone Miner. Res.* 22, 1668–1671. doi:10.1359/jbmr.070716.

Liu, N., Sun, J., Wang, X., Zhang, T., Zhao, M., and Li, H. (2021). Low vitamin D status is associated with coronavirus disease 2019 outcomes: a systematic review and meta-analysis. *Int J Infect Dis* 104, 58–64. doi:10.1016/j.ijid.2020.12.077.

Luo, J., Quan, Z., Lin, S., and Cui, L. (2018). The association between blood concentration of 25- hydroxyvitamin D and sarcopenia: a meta-analysis. *Asia Pac J Clin Nutr* 27, 1258–1270. doi:10.6133/apjcn.201811_27(6).0013.

Luo, M., Guo, L., Yu, M., Jiang, W., and Wang, H. (2020). The psychological and mental impact of coronavirus disease 2019 (COVID-19) on medical staff and general public – A systematic review and meta-analysis. *Psychiatry Res* 291, 113190. doi:10.1016/j.psychres.2020.113190.

Macdonald, H. M., Mavroeidi, A., Fraser, W. D., Darling, A. L., Black, A. J., Aucott, L., et al. (2011). Sunlight and dietary contributions to the seasonal vitamin D status of cohorts of healthy postmenopausal women living at northerly latitudes: a major cause for concern? *Osteoporos Int* 22, 2461–2472. doi:10.1007/s00198-010-1467-z.

Marik, P. E., Kory, P., and Varon, J. (2020). Does vitamin D status impact mortality from SARS-CoV-2 infection? *Medicine in Drug Discovery* 6, 100041. doi:10.1016/j.medidd.2020.100041.

Mehta, A., Soni, V. K., Sharma, K., Ratre, Y. K., Shukla, D., Singh, A. K., et al. (2021). Finding Horcrux of psychiatric symptoms in COVID-19: Deficiencies of amino acids and vitamin D. *Asian Journal of Psychiatry* 55, 102523. doi:10.1016/j.ajp.2020.102523.

Mitchell, F. (2020). Vitamin-D and COVID-19: do deficient risk a poorer outcome? *The Lancet Diabetes & Endocrinology* 8, 570. doi:10.1016/S2213-8587(20)30183-2.

Mocayar Marón, F. J., Ferder, L., Reiter, R. J., and Manucha, W. (2020). Daily and seasonal mitochondrial protection: Unraveling common possible mechanisms involving vitamin D and melatonin. *J. Steroid Biochem. Mol. Biol.* 199, 105595. doi:10.1016/j.jsbmb.2020.105595.

Mok, C. K., Ng, Y. L., Ahidjo, B. A., Lee, R. C. H., Loe, M. W. C., Liu, J., et al. (2020). Calcitriol, the active form of vitamin D, is a promising candidate for COVID-19 prophylaxis. *bioRxiv*, 2020.06.21.162396. doi:10.1101/2020.06.21.162396.

Morris, G., and Berk, M. (2015). The many roads to mitochondrial dysfunction in neuroimmune and neuropsychiatric disorders. *BMC Medicine* 13, 68. doi:10.1186/s12916-015-0310-y.

Muscogiuri, G., Barrea, L., Scannapieco, M., Di Somma, C., Scacchi, M., Aimaretti, G., et al. (2019). The lullaby of the sun: the role of vitamin D in sleep disturbance. *Sleep Med.* 54, 262–265. doi:10.1016/j.sleep.2018.10.033.

Nami, M., Gadad, B. S., Chong, L., Ghumman, U., Misra, A., Gadad, S. S., et al. (2020). The Interrelation of Neurological and Psychological Symptoms of COVID-19: Risks and Remedies. *J Clin Med* 9. doi:10.3390/jcm9082624.

Okereke, O. I., Reynolds, C. F., Mischoulon, D., Chang, G., Vyas, C. M., Cook, N. R., et al. (2020). Effect of Long-term Vitamin D3 Supplementation vs Placebo on Risk of Depression or Clinically Relevant Depressive Symptoms and on Change in Mood Scores: A Randomized Clinical Trial. *JAMA* 324, 471–480. doi:10.1001/jama.2020.10224.

Oliveri, B., Mastaglia, S. R., Brito, G. M., Seijo, M., Keller, G. A., Somoza, J., et al. (2015). Vitamin D3 seems more appropriate than D2 to sustain adequate levels of 25OHD: a pharmacokinetic approach. *Eur J Clin Nutr* 69, 697–702. doi:10.1038/ejcn.2015.16.

Panarese, A., and Shahini, E. (2020). Letter: Covid-19, and vitamin D. *Alimentary Pharmacology & Therapeutics* 51, 993–995. doi:10.1111/apt.15752.

Patrick, R. P., and Ames, B. N. (2015). Vitamin D and the omega-3 fatty acids control serotonin synthesis and action, part 2: relevance for ADHD, bipolar disorder, schizophrenia, and impulsive behavior. *The FASEB Journal* 29, 2207–2222. doi:10.1096/fj.14-268342.

Pereira, M., Dantas Damascena, A., Galvão Azevedo, L. M., de Almeida Oliveira, T., and da Mota Santana, J. (2020). Vitamin D deficiency aggravates COVID-19: systematic review and meta-analysis. *Crit Rev Food Sci Nutr*, 1–9. doi:10.1080/10408398.2020.1841090.

Petrelli, F., Luciani, A., Perego, G., Dognini, G., Colombelli, P. L., and Ghidini, A. (2021). Therapeutic and prognostic role of vitamin D for COVID-19 infection: A systematic review and meta-analysis of 43 observational studies. *J Steroid Biochem Mol Biol*, 105883. doi:10.1016/j.jsbmb.2021.105883.

Robb, C. E., de Jager, C. A., Ahmadi-Abhari, S., Giannakopoulou, P., Udeh-Momoh, C., McKeand, J., et al. (2020). Associations of Social Isolation with Anxiety and Depression During the Early COVID-19 Pandemic: A Survey of Older Adults in London, UK. *Front Psychiatry* 11. doi:10.3389/fpsyt.2020.591120.

Sabir, M. S., Haussler, M. R., Mallick, S., Kaneko, I., Lucas, D. A., Haussler, C. A., et al. (2018). Optimal vitamin D spurs serotonin: 1,25-dihydroxyvitamin D represses serotonin reuptake transport (SERT) and degradation (MAO-A) gene expression in cultured rat serotonergic neuronal cell lines. *Genes Nutr* 13. doi:10.1186/s12263-018-0605-7.

Santini, Z. I., Jose, P. E., York Cornwell, E., Koyanagi, A., Nielsen, L., Hinrichsen, C., et al. (2020). Social disconnectedness, perceived isolation, and symptoms of depression and anxiety among older Americans (NSHAP): a longitudinal mediation analysis. *Lancet Public Health* 5, e62–e70. doi:10.1016/S2468-2667(19)30230-0.

Smith, B. J., and Lim, M. H. (2020). How the COVID-19 pandemic is focusing attention on loneliness and social isolation. *Public Health Res Pract* 30. doi:10.17061/phrp3022008.

Song, B. M., Kim, H. C., Rhee, Y., Youm, Y., and Kim, C. O. (2016). Association between serum 25-hydroxyvitamin D concentrations and depressive symptoms in an older Korean population: A cross-sectional study. *J Affect Disord* 189, 357–364. doi:10.1016/j.jad.2015.09.043.

Spedding, S. (2014). Vitamin D and Depression: A Systematic Review and Meta-Analysis Comparing Studies with and without Biological Flaws. *Nutrients* 6, 1501–1518. doi:10.3390/nu6041501.

Teshome, A., Adane, A., Girma, B., and Mekonnen, Z. A. (2021). The Impact of Vitamin D Level on COVID-19 Infection: Systematic Review and Meta-Analysis. *Front Public Health* 9, 624559. doi:10.3389/fpubh.2021.624559.

Vellekkatt, F., Menon, V., Rajappa, M., and Sahoo, J. (2020). Effect of adjunctive single dose parenteral Vitamin D supplementation in major depressive disorder with concurrent vitamin D deficiency: A double-blind randomized placebo-controlled trial. *Journal of Psychiatric Research* 129, 250–256. doi:10.1016/j.jpsychires.2020.07.037.

Vidgren, M., Virtanen, J. K., Tolmunen, T., Nurmi, T., Tuomainen, T.-P., Voutilainen, S., et al. (2018). Serum Concentrations of 25-Hydroxyvitamin D and Depression in a General Middle-Aged to Elderly Population in Finland. *J Nutr Health Aging* 22, 159–164. doi:10.1007/s12603-017-0948-6.

Wacker, M., and Holick, M. F. (2013). Sunlight and Vitamin D: A global perspective for health. *Dermato-Endocrinology* 5, 51–108. doi:10.4161/derm.24494.

Wang, C., Pan, R., Wan, X., Tan, Y., Xu, L., Ho, C. S., et al. (2020). Immediate Psychological Responses and Associated Factors during the Initial Stage of the 2019 Coronavirus Disease (COVID-19) Epidemic among the General Population in China. *Int J Environ Res Public Health* 17. doi:10.3390/ijerph17051729.

Xiong, J., Lipsitz, O., Nasri, F., Lui, L. M. W., Gill, H., Phan, L., et al. (2020). Impact of COVID-19 pandemic on mental health in the general population: A systematic review. *J Affect Disord* 277, 55–64. doi:10.1016/j.jad.2020.08.001.

Yao, Y., Fu, S., Zhang, H., Li, N., Zhu, Q., Zhang, F., et al. (2018). The prevalence of depressive symptoms in Chinese longevous persons and its correlation with vitamin D status. *BMC Geriatrics* 18, 198. doi:10.1186/s12877-018-0886-0.

Zhou, Y.-F., Luo, B.-A., and Qin, L.-L. (2019). The association between vitamin D deficiency and community-acquired pneumonia: A meta-analysis of observational studies. *Medicine (Baltimore)* 98, e17252. doi:10.1097/MD.0000000000017252.

Zhu, C., Zhang, Y., Wang, T., Lin, Y., Yu, J., Xia, Q., et al. (2020). Vitamin D supplementation improves anxiety but not depression symptoms in patients with vitamin D deficiency. *Brain and Behavior* 10, e01760. doi:https://doi.org/10.1002/brb3.1760.

4.2.4 Artigo 5

LOWER SERUM 25-HYDROXYCHOLECALCIFEROL IS ASSOCIATED WITH DEPRESSIVE SYMPTOMS IN OLDER ADULTS IN SOUTHERN BRAZIL

Gilciane Ceolin[1], Luísa Harumi Matsuo[1], Susana Cararo Confortin[2], Eleonora d'Orsi[3], Débora Kurrle Rieger Venske[4], Júlia Dubois Moreira[4]

1 Postgraduate Program in Nutrition. Federal University of Santa Catarina, Florianopolis, Brazil.

2 Postgraduate Program in Public Health. Federal University of Maranhão, Maranhão, Brazil.

3 Postgraduate Program in Public Health. Department of Public Health. Federal University of Santa Catarina, Florianopolis, Brazil.

4 Translational Nutritional Neuroscience working group. Postgraduate Program in Nutrition. Department of Nutrition. Federal University of Santa Catarina, Florianopolis, Brazil.

Abstract

Background: Older adults are one of the most susceptible populations to depression, especially those living in low- and middle-income countries. As well, they are also considering a risk group for vitamin D deficiency. Low serum vitamin D has been associated with an increased risk of brain neuropsychiatry disorders. We aimed to investigate the association between serum 25-hydroxycholecalciferol concentrations and depressive symptoms in adults aged 60 years and over from southern Brazil. **Methods:** A cross-sectional analysis was performed using data collected during 2013-2014 from the populational-based longitudinal EpiFloripa Aging Study (n=1197). Serum 25-hydroxycholecalciferol concentrations were analyzed and classified according to the Endocrine Society reference values [sufficiency (≥ 30 ng/mL), insufficiency (21–29 ng/mL), and deficiency (≤ 20 ng/mL)]. Depressive symptoms were evaluated using the Geriatric Depression Scale (15-item GDS). Logistic regression was performed to assess depressive symptoms in each vitamin D category. The analysis was adjusted for sex, age, skin color, family income, leisure-time physical activities, social or religious groups attendance, morbidities, cognitive impairment, and dependence in activities of daily living. **Results:** A total of 557 participants with complete data for exposure and outcome were enrolled in the analysis. Most of the sample participants were female (63.1%), age-

range 60-69 years (42.2%), white skin color (85.1%), and vitamin D serum level samples were collected in autumn (50.7%). Depressive symptoms were present in 15.8% of the participants, and the prevalence was higher in individuals classified as deficient in vitamin D (23.2%, 95% confidence interval [CI]=15.6;32.9) and insufficiency (17.2%, 95%CI=11.0;25.9). The crude analysis showed that vitamin D deficient participants had 3.08 (CI=1.53;6.20) times higher odds to present depressive symptoms compared to vitamin D sufficiency. After adjusting, the association was maintained [OR 2.27 (95%CI=1.05;4.94). **Conclusions:** Serum 25-hydroxycholecalciferol deficiency was positively associated with depressive symptoms in older adults from southern Brazil.
Key Words: Vitamin D; aging; depressive symptoms; cohort study; mental health.

Introduction

Despite efforts to reduce the number of people with depressive disorders, their prevalence has increased, particularly in lower-income countries, and depression holds the third position globally in terms of years lived with disability (1,2). Besides being a debilitating disease for older adults, presenting a variety of emotional and physical problems, its treatment approach involves mainly implementation of preventive health habits and high-cost rehabilitation programs (3,4).

Depression in older adults living in low- and middle-income countries is associated with a higher risk of suicide and excess mortality, more frequent medical consultations and hospitalization, and a significant family burden, even though the number of depressive older adults is similar to that of adults (3,5,6). Additionally, depression is associated with significant adverse consequences ranging from poor quality of life, difficulties with daily living activities (DLA), physical comorbidities, and cognitive impairment (5). Environmental causes and lifestyle factors, such as obesity, exposure to physical and substance abuse, widowhood, the presence of chronic illnesses and sleep disorders, lack of education and social support, intimate partner, and physical activity have been related to depression (7). Several mechanisms have been studied in the neurobiology of depression, such as genetic factors, neurotransmitter systems, neuroendocrine systems, inflammation, functional and structural brain anatomy, and cognition (8,9). Some promising studies suggest the involvement of nutritional factors, such as vitamin D, in the development of depressive symptoms (10,11).

Vitamin D-related effects on homeostasis, neurotrophic, and neuroimmunomodulatory actions appear to be associated to depressive symptoms

prevention. However, the exact molecular mechanisms underlying this relationship are not well stablished (12). Vitamin D is considered a neurosteroid hormone because of its essential role in the central nervous system and connection to processes associated with cell differentiation, neurotrophic factor synthesis and release, neurotransmitter synthesis, intracellular calcium homeostasis, redox balance, neuronal metabolism, and cognitive function (13,14). Vitamin D signaling through the nuclear receptors vitamin D receptors (VDR) and the membrane receptor protein disulfide isomerase family member3 (PDIA3), and the presence of some key enzymes of Cytochrome P450, such as CYP27a1, CYP27b1 and CYP24a1, responsible to convert the inactive form of vitamin D to its active form in the brain cells, as well as its requirements for neuron cell cycle, initiated the investigation of vitamin D relevance for brain metabolism in health and disease (15–18).

One underlying mechanism proposed is that the vitamin D could regulate serotonin synthesis (19,20). Calcitriol (1,25-dihydroxyvitamin D3) is a key regulator of serotonin, inducing the TPH2 (tryptophan hydroxylase 2) gene expression, which is the enzyme involved on tryptophan metabolism in the brain to produce serotonin (19,21). Calcitriol also reduce serotonin reuptake transporter (SERT) expression., which is responsible to remove serotonin from synaptic cleft, and monoamine oxidase-A (MAO-A), which is responsible for serotonin catabolism (22). Calcium homeostasis is another possible mechanism associated to vitamin D neuroprotection. Its relevance in redox balance and inflammation could also be involved in the relationship between vitamin D and depression (23,24). Vitamin D stimulates the expression of many antioxidant genes, such as factor 2 related to the nuclear factor eritroid-2 (NRF2), g-glutamyl transpeptidase (g-GT), glutamate-cysteine ligase (GCLC), glutathione reductase (GR), glutathione peroxidase (Gpx)(23).

Aging process is associated to the reduced ability to sustain homeostasis and more susceptibility to pathological alterations, such as neuropsychiatric disorders ((25,26). Understanding the link between vitamin D concentration and depression in aging is required due to be a possible way to minimize the effects of depression. Given the complexity of the condition, more risk to mortality, difficulty in access to treatment, and including those older adults that are undiagnosed (6,27,28). Besides of being considered a risk group for depression, older adults are also one of the risk groups for vitamin D deficiency due to their reduced skin capacity to synthesize vitamin D, reduced sun exposure, and more significant complications related to low serum vitamin D concentrations (29,30). Some observational studies have investigated the relationship

between low serum vitamin D concentrations and depressive symptoms in adulthood or in adults and elderly population combined, and few included only older adults in the sample, as observed by a recently published meta-analyses (31–33).

Therefore, the present study aimed to investigate the association between low serum vitamin D concentrations and depressive symptoms in older adults living in Southern Brazil, as well as elucidate the prevalence of depressive symptoms in this population and the magnitude of the prevalence of vitamin D deficiency as well. We hypothesized that the low serum of 25(OH)D (<20ng/ml) could be associated with depressive symptoms and we intend to discuss the factors related this association in elderly.

Methods

Study population and design

We performed a cross-sectional analysis with data collected in the second wave (2013-2014) of the populational-based EpiFloripa Aging Study. Details about the sample and methodology have been previously published (34,35). Briefly, EpiFloripa Aging is a cohort study aiming to investigate health determinants and aspects of the older adult population living in Southern Brazil. Older adults of both sexes, aged 60 years or over at the time of the first interview, living in the sectors determined by the survey, were considered eligible at baseline, in 2009 (Figure 1). Older adults who were institutionalized (residing in long-term care institutions, hospitals, prisons) were excluded.

All the older adults in the follow-up (1197 interviews; retention rate of 70.2%) were invited to participate in the second wave of the study (2013-2015), which included biochemical blood analysis (retention rate of 50.5%; n = 604) (35). For this cross-sectional analysis, we enrolled 577 individuals, and the inclusion criteria were to present complete data for depressive symptoms and to be the evaluation of 25-hydroxycholecalciferol (Figure 1).

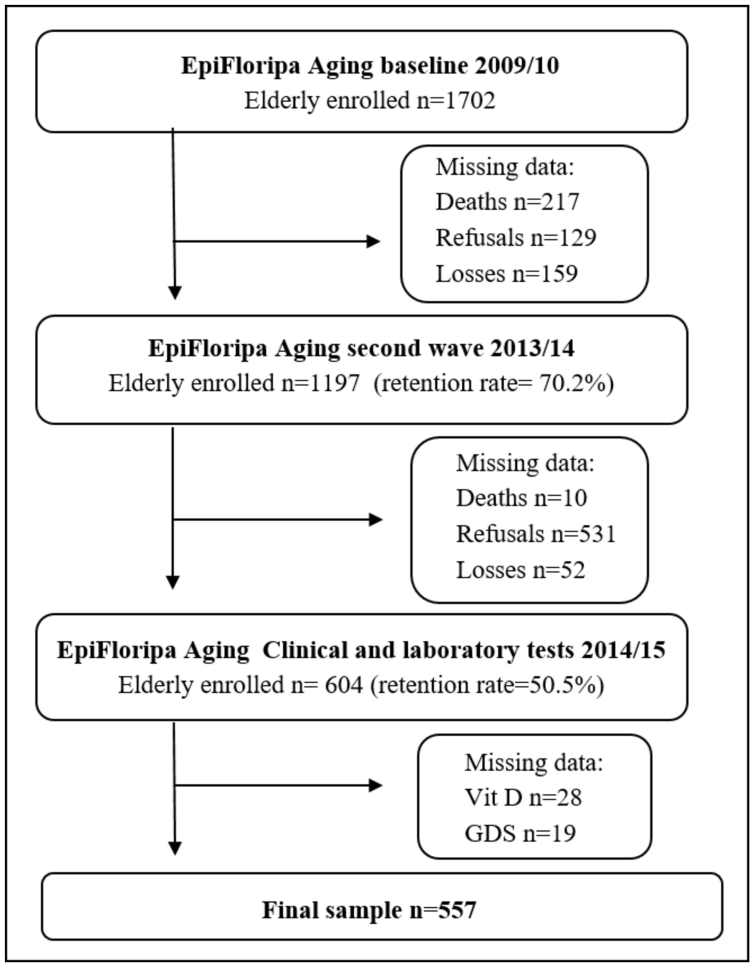


Fig. 1 EpiFloripa Aging Study Flowchart. (GDS: Geriatric Depression Scale).

The EpiFloripa Aging Study's second wave of follow-up was approved by the Human Research Ethics Committee of the Federal University of Santa Catarina (approval protocols numbers: 329.650 and 526.126). Voluntary participation of the individuals was obtained through the signing of the Informed Consent Form, after explaining the study objectives and collection procedures. The EpiFloripa Aging Study was conducted in accordance with the Declaration of Helsinki.

Data collection and Covariates

Trained interviewers conducted data collection at the participant's home. The face-to-face interviews were scheduled with the participants by phone. EpiFloripa Aging Study data were collected using a 15-block questionnaire with socioeconomic, demographic, and health aspects related to aging and prioritizing validated instruments translated and validated in Brazil for the composition of the questionnaire to guarantee the data quality control. The selected interviewers were health science graduates with research experience. Data were recorded in a netbook and transmitted directly to the

EpiFloripa database. Quality control was carried out by telephone, using a short version of the questionnaire in 10% of the samples.

Depressive symptoms

To evaluate the presence of depressive symptoms, we applied the 15-item Geriatric Depression Scale (15-item GDS). We used the cut-off points suggested by Almeida and Almeida, we classified participants into two groups: those with the presence of depressive symptoms (≥ 6 points) and those with the absence of depressive symptoms (≤ 5 points) (36,37).

The GDS-15 is recommended by the Brazilian Ministry of Health, and is a useful alternative for the rapid assessment of the presence of depressive symptoms in the elderly (38). The GDS-15 was translated and validated in Brazil according to ICD-10 criteria for research and DSM-IV with outpatients aged 60 or over who met criteria for depressive disorder (current or in remission) (36,39). The cutoff point 5/6 (not case/case) produced sensitivity indexes of 85.4% and specificity of 73.9% according to ICD-10 and 90.9% of sensitivity and 64.5% of specificity according to the DSM-IV and the internal consistency using Cronbach's alpha coefficient revealed reliability indexes of 0.81 (39). Moreover, in the test-retest reliability when the outpatient was evaluated twice in 48 to 72 hours, and GDS-15 scores were reasonably stable, as assessed by paired Wilcoxon ($z=1.60$, $p=0.109$) and Spearman's correlation coefficient ($rho=0.86$, $p<0,001$) and weighted Kappa (Kappa = 0.64) (36).

Serum vitamin D (25-hydroxycholecalciferol) concentrations

For the measurement of 25-hydroxycholecalciferol [25(OH)D] blood samples were collected at the University Laboratory for Metabolism and Dietetics, between 7-10 a.m., with the required minimum of 8 hour fasting period before the procedure (35). Blood samples were centrifuge (3.500 rpm) for 10 min. Serum samples used to detect 25(OH)D were immediately processed using LIASON® 25 OH vitamin D assay (Diasorin, São Paulo, Brazil) accordingly to manufacture (Functional Sensitivity: ≤ 2.0 ng/mL; (inter-assay imprecision <20%), which is considered s a rapid, accurate, and precise assay (40). Briefly, an antibody specific to vitamin D was coated on magnetic particles, and 25-OHD conjugated to an isoluminol derivative and diluted in phosphate buffer (pH 7.4). In the first incubation period, 25-OHD dissociated from the binding protein, and it interacts with the antibody. After the second incubation with the tracer reagent, microplate is washed with the buffer and starter reagents are added to generate the chemiluminescent signal,

which is measured by a photomultiplier. Serum 25(OH)D concentrations were measured using the Microparticle Chemiluminescence method/LIAISON (41). Subsequently, we categorized serum 25(OH)D concentrations according to the Endocrine Society Reference values (42) into: sufficiency (≥30 ng/mL), insufficiency (21-29 ng/mL), and deficiency (≤20 ng/mL).

Covariates

For characterization of the samples, we analyzed sociodemographic variables, such as sex (male/female), skin color (white/not white), the season during blood collection (summer/autumn/winter/spring), age range (aged 60-69/70-79/≥80 years), education (no formal education/1-4/5-8/9-11/≥12 years), per capita family income in minimal wages according to the values in 2013 (R$ 678.00) and 2014 (R$ 724.00) (≤1/>1 to ≤ 3/>3 to ≤ 5/>5 to ≤10/>10), retired (no/yes), living arrangements (live with another/alone) and marital status (married/single/divorced/widowed). Behavioral modified factors were included in the analysis, such as belonging to a social or religious group (no/yes), smoking (no/yes), alcohol consumption (no/yes) collected by Alcohol Use Disorder Identification Test (43). Leisure-time physical activity (insufficiently active <150 minutes or sufficiently active ≥150 minutes) collected by the International Physical Activity Questionnaire (44,45).

Health status-related information included dependence in the activities of daily living (ADLs) [no disability, low disability (any level of disability in 1 to 3 activities), and moderate/severe disability (any level of disability in ≥4 activities)] collected by the scale of daily basic and instrumental activities (46). Screening for cognitive impairment was evaluated using the Mini-Mental State Examination (absence/presence–considering schooling, using the cut-off points 19/20 for illiterate and 23/24 for any level of education) (47,48). The number of comorbidities were assessed [zero/1/≥2 (sum of diagnosed diseases: spine or back pain, arthritis, cancer, diabetes, bronchitis, cardiovascular or renal conditions, tuberculosis, cirrhosis, stroke, osteoporosis, hypertension, and depression)]. Nutritional status was assessed by body mass index (underweight <22 kg/m²; healthy weight 22-27 kg/m²; overweight >27 kg/m²), according to the Nutrition Screening Initiative (49). Information about antidepressant drug use and vitamin D supplement use was collected by consulting all boxes of medicines prescribed for and used by the participant. The Anatomical Therapeutic Chemical Classification codes from the World

Health Organization Collaborating Centre for Drug Statistic Methodology were applied for codification in the database (50).

Statistical analysis

Descriptive analysis of the data was presented as absolute and relative frequency, prevalence, and respective 95% confidence intervals (CI) for the total sample based on the presence of depressive symptoms. The distribution of the covariates was determined using the chi-square test. We performed Student's t-test to verify the mean differences between sex and depressive symptoms in serum 25(HO)D concentrations.

Logistic regression was used to evaluate the odds ratio (OR) for depressive symptoms in each 25(HO)D category and the respective CI in the crude and adjusted association models. The covariates were included following a hierarchical model (first socioeconomic covariates, followed by behavioral covariates, and finally, health covariates). Model 1 was adjusted for demographic and socioeconomic variables (sex, skin color, age range, and family income). Model 2 included demographic, socioeconomic, and behavioral variables (leisure-time physical activities and social or religious groups attendance). Model 3 included demographic, socioeconomic, behavioral, and health variables (morbidities, cognitive impairment, dependence in activities of daily living).

The analysis was performed using Stata 14.0 software (StataCorp, College Station, TX, USA). Due to the sampling design (two-stage cluster) of the EpiFloripa Aging Study, sample weights were used in all the analyses, using the "svy" command. *P*-value <0.05 was used to define statistical significance for all reports.

Results

Of the 604 older adults who participated in clinical and laboratory tests in 2014-2015, 577 individuals met the criteria and presented complete data to be included in the analysis (Figure 1). Sample characteristics are summarized according to the prevalence of depressive symptoms in Table 1. For the total sample, the prevalence of depressive symptoms was 15.8%, and the prevalence of 25(OH)D was 39.4% and 25.5% in insufficiency and deficiency cases, respectively.

Individuals with presence of depressive symptoms were mostly women (18.2% *P*=0.006), aged ≥80 years (22.2%; *P*=0.009), with ≤4 years of formal education (19.5;17.5%; *P*=0.016), lower per capita family income ≤1 minimum wage (22.4%; *P*=0.002), insufficient leisure-time physical activity (19.3%; *P*<0.001), more dependency

in ADLs (30.8%; *P*<0.001), presence of cognitive impairment (34.0%; *P*<0.001); and reported 2 or more comorbidities (19.5% *P*<0.001). Considering the Endocrinology Society reference values for 25(OH)D, a higher prevalence of depressive symptoms was observed in those with vitamin D deficiency than in those with sufficiency (23.8% vs. 8.9% respectively; *P* = 0.006).

Table 1 Prevalence of depressive symptoms according to demographic, socioeconomic, behavioral, and health characteristics.

Characteristics (n=557)	**Total**		**Presence of depressive symptoms**		
	n	**%**	**%**	**95%CI**	***P*-value**
Sex					0.006
Men	194	36.9	11.7	6.4;20.6	
Women	363	63.1	18.2	13.5;24.0	
Skin Color					0.077
White	468	85.1	14.1	9.9;19.7	
Not white	89	14.9	25.5	16.6;37.0	
Season (Vit. D collection)					0.791
Summer	55	9.1	14.4	6.7;28.0	
Autumn	276	50.7	18.1	11.4;27.5	
Winter	145	23.6	14.8	10.2;21.0	
Spring	81	16.6	11.1	5.1;22.5	
Age range (years)					0.009*
60-69	236	42.2	12.4	7.2;20.5	
70-79	235	41.8	16.8	11.6;23.8	
≥ 80	86	16,0	22.2	14.3;32.9	
Education (years)					0.016
No formal education	35	5.5	17.5	8.4;32.9	
1-4	199	33.7	19.5	13.3;27.5	
5-8	100	19.2	14.9	8.4;25.2	
9-11	86	17.8	18.5	7.8;38.0	
≥ 12	137	23.8	8.9	4.3;17.7	
Per capita family income (n=539)					0.002*
≤ 1 mw	40	6.4	22.4	11.8;38.6	
>1 and ≤ 3 mw	156	30.3	20.6	13.7;29.7	
>3 and ≤ 5 mw	108	17.5	19.3	11.1;31.3	
>5 and ≤ 10 mw	136	26.4	10.9	5.6;20.1	
>10 mw	99	19.4	9.9	4.8;19.2	
Retirement (n=521)					0.152
No	102	19.9	21.8	11.5;37.1	
Yes	419	80.1	14.4	10.8;19.0	

Living arrangements					0.547
Live with another/others	445	78.7	16.0	12.0;21.0	
Live alone	112	21.3	15.2	8.3;26.1	
Marital Status					0.095
Married	317	56.5	11.6	7.7;17.2	
Single	33	6.1	20.9	7.0;48.3	
Divorced	45	9.3	27.1	14.5;44.8	
Widowed	162	28.1	19.4	13.4;17.3	
Social and religious groups attendance					0.114
No	298	56.3	18.2	13.1;24.8	
Yes	259	43.7	12.7	8.6;18.4	
Alcohol Consumption					<0.001
No	319	56.0	19.0	13.8;25.7	
Yes	238	44.0	11.7	6.7;19.6	
Smoking					0.307
No	351	58.6	17.0	12.2;23.3	
Yes	206	41.4	14.1	10.1;19.3	
Leisure-time physical activity (n=556)					<0.001
Insufficiently active	395	70.7	19.3	14.7;24.8	
Sufficiently active	161	29.3	7.4	3.5;14.8	
Dependence in ADLs (n=554)					<0.001*
None	202	38.1	6.4	3.2;12.4	
Low	217	37.5	15.1	9.7;22.7	
Moderate/severe	135	24.4	30.8	21.4;42.1	
Cognitive impairment (n=554)					<0.001
Absent	442	79.6	10.9	7.3;15.9	
Present	112	20.4	34.0	23.6;46.1	
Number of comorbidities					<0.001
Zero	34	6,0	13.5	2.8;46.2	
1	96	18.6	1.4	0.3;5.7	
≥ 2	427	75.4	19.5	15.1;24.9	
Nutritional status (n=554)					0.061
Underweight	45	8.2	23.3	12.3;39.7	
Healthy Weight	256	44.3	11.8	7.7;17.8	
Overweight	253	47.5	18.0	12.6;25.1	
Antidepressant use (n=529)					0.048
No	449	85.4	15.4	11.2;20.7	
Yes	80	14.6	21.4	12.4;34.4	
Vitamin D supplement use (n=521)					0.232

No	464	90.6	16.6	12.1;22.2	
Yes	57	9.4	11.5	4.8;25.1	
Serum 25(OH)D					0.006*
Sufficiency	188	35.1	8.9	4.8;15.9	
Insufficiency	226	39.4	17.2	11.0;25.9	
Deficiency	143	25.5	23.2	15.6;32.9	
Depressive Symptoms					
Absent	467	84.2	-		
Present	90	15.8	-		

mw, minimum wage; ADLs, activities of daily living; BMI, Body Mass Index; CI confidence interval; *P*-value, statistical significance; * *P*-value of chi-square test for trend.

On average, women presented lower serum 25(OH)D concentrations than men (*P*=0.001), and individuals with depressive symptoms also showed lower concentrations (*P*=0.005) (Table 2).

Table 2. Serum 25(OH)D concentrations according to sex and depressive symptoms.

	Serum 25(OH)D (ng/mL)		
	Mean	95%CI	*P-value*
Sex			<0.001
Men	28.7	27.3;30.2	
Women	25.4	24.5;26.2	
Depressive Symptom			0.005
Absent	27.0	26.2;27.8	
Present	24.1	22.2;26.0	

CI, Confidence interval; *P*-value, statistical significance using Student's T-Test.

In Table 3, we present the crude and adjusted association analysis between serum 25(OH)D concentrations and depressive symptoms. In the crude analysis, we found that vitamin D-deficient individuals presented 3.08 times higher OR (CI 95% = 1.53; 6.20) of depressive symptoms than those with sufficient concentrations. After adjusting for demographic, socioeconomic, behavioral, and health covariates (model 3), vitamin D-deficient individuals presented 2.27 times higher OR (CI 95%= 1.05; 4.94) of depressive symptoms than those considered sufficient.

Table 3. Crude and adjusted measures of association between serum 25(OH)D concentrations and depressive symptoms.

Serum	**Crude Analysis**			**Model 1[2]**			**Model 2[3]**			**Model 3 (final)[4]**		
25(OH)D[1]	OR	95%CI	p	OR	95%CI	p	OR	95%CI	p	OR	95%CI	p

Sufficiency	1						1			1		
Insufficiency	2.12	0.95;4.74	0.067	1.86	0.77;4.52	0.166	1.78	0.71;4.50	0.217	2.08	0.78;5.50	0.138
Deficiency	3.08	1.53;6.20	0.002	2.82	1.37;5.81	0.005	2.61	1.22;5.60	0.014	2.27	1.05;4.94	0.038

[1]References by the Endocrine Society; [2]Model 1 was adjusted by demographic and socioeconomic factors (sex, skin color, age range, family income); [3]Model 2 was adjusted by demographic, socioeconomic, and behavioral factors (leisure-time physical activities and social or religious groups attendance); [4]Model 3 was adjusted by demographic, socioeconomic, behavioral, and health factors (morbidities, cognitive impairment, dependence in activities of daily living). OR, odds ratio; CI, confidence interval.

Discussion

In the present study, we observed a statistically significant association between serum 25(OH)D deficiency and depressive symptoms in the older adult population living in one capital of southern Brazil, even after adjustments for potential confounding factors related to demographic, socioeconomic, behavioral, and health variables. Vitamin D deficient individuals had 2.7 times higher odds of depressive symptoms. We also found that 15.8% of the population enrolled in the analysis presented depressive symptoms, using the 15-item GDS; thus, showing the importance of screening for depression symptoms in this population.

There is little evidence published in the literature about vitamin D deficiency in older adults and its relationship with neuropsychiatric disorders, especially studies that used a population-based sample, as presented here. Until May 2020, we found 10 other studies with cross-sectional analysis performed with older adults (51–60), one of these with longevous individuals (aged >100 years) [42], and two were conducted only with men (57,58). We identified 13 cross-sectional studies conducted with a mixed population of adults and older adults (61–73). Only two studies were performed in low- and middle-income countries (61,72), which are the most affected by depression accordingly to World Health Organization (1). We concluded that there is a gap in the literature about investigations involving depressive symptoms in low- and middle-income countries. This was a relevant aspect because socioeconomic covariates, such as low per capita family income and fewer years of formal education, were related to a higher prevalence of depressive symptoms in our sample, and were a universal life situation for the populations living in low- and middle-income countries (74,75).

Older adults are considered a risk group for hypovitaminosis D due to the reduction in vitamin D absorption and synthesis, modification in food intake that could reduce vitamin D ingestion, and reduced outdoor activity that favors sunlight-derived

vitamin D synthesis (29,76–78). A study comparing two cohorts from the Longitudinal Aging Study Amsterdam (LASA), one with adults aged 55-65 years (n=737) and other with older adults aged 65 years or older (n=1,282), found a higher 25(OH)D concentrations in the younger group, better physical functioning, fewer chronic diseases, and they were more physically active compared with the older ones (73).

In our sample, 70.7% of the participants who reported reduced leisure physical activity and 19% of those who presented with depressive symptoms were classified as vitamin D insufficient (data not shown). These data were consistent with the literature review. A recent meta-analysis showed that people with depression were less physically active than the corresponding controls, and about 80% of people with depression were unable to achieve the recommended weekly physical activity (79). A previous study found that less physical activity was associated with reduced vitamin D concentrations and modestly attenuated the OR for depression in the adjusted analysis (52). Another study provided evidence for the potential mediating role of physical functioning in the relationship between low 25(OH)D levels and increasing of depressive symptoms (73).

We found a relationship between sex and the mean 25(OH)D concentration. Women presented lower levels than men, but we could not perform a stratified analysis by sex due to the small number of observations in the variable categories for men. However, we included sex as an adjustment variable in the investigation. Previous studies described sex differences showing generally lower 25(OH)D concentrations in women than in men (51–53,55,73,80). The sex difference is not yet clearly understood, but is considered to be related to sunscreen use and body fat mass (78,81,82). In our study (data not shown), overweight was found to have a higher prevalence in women (68.8% *vs.* 31.2% women and men, respectively; P=0.012) and those with hypovitaminosis D (43.9%, 29.6% and 26.5% in insufficiency, deficiency, and sufficiency, respectively, P=0.001).

In our study, we observed a prevalence of ~15% for depressive symptoms, which was considered a high prevalence (1). Other studies that evaluated depressive symptoms using the GDS screening tool, also showed higher prevalence: 27.9% in South Korea (sample included individuals aged ≥65 years; n=2853) (53); 25.2% in England (sample included those aged ≥65 years; n=2070) (54), and 32.2% in China (n=940) (56). One study performed in the Netherlands found 7% prevalence (sample included individuals aged ≥65 years; n=2839) (59). In our study, women presented a higher prevalence (18%) of depressive symptoms, which could indicate this group's greater vulnerability for

depression. The studies mentioned above also showed a higher prevalence 30.9 % *vs.* 21,9% (53), 35.6% *vs*. 17.7% (56), and 40,6% *vs.* 23.8% in women vs. men, respectively, the last one being an Italian sample (individuals aged ≥65 years; n= 1.675) (40).

The prevalence of depressive symptoms presented an inverse trend in 25(OH)D concentrations with 8.9% of individuals with levels ≥30 ng/mL, 17.2% with 21-29 ng/mL, and 23.2% with ≤20 ng/mL. Our findings were lower than those of a previous study. We determined 22.6% with levels <30 ng/mL, 25.8% with <20 ng/mL, and 35.0% with <10 ng/mL levels of serum concentration (54); however, they followed the same trend. In general, studies demonstrated that a lower serum vitamin D level was associated with a higher prevalence of depressive symptoms, even when other reference values were used [6% with >71.7 nmol/L; 4.6% with 53.4-71.7 nmol/L; 5% with 36.7-53 nmol/L; and 11% with <36.7 nmol/L (59); as well as 7.8% with ≥30.0 ng/mL; 27.4% with 20.0-29.9 ng/mL; 50.1% with 10.0-19.9 ng/mL; and 14.7% with <10.0 ng/mL (53).

The higher chance of depressive symptoms in older adults with low 25(OH)D concentrations was consistent with previous cross-sectional studies' results (51,54,56,59,60). In Amsterdam, the Netherlands, in a population-based sample (≥65 years; n=1282), the severity of depressive symptoms evaluated using the Center for Epidemiologic Studies Depression Scale (CES-D) was associated with decreased serum 25(OH)D concentrations (B=9.6; 95%CI=16.9;2.4; p=0.01) (51). In England, in a Health Survey with older adults (≥65 years; n=2070), depressive symptoms evaluated by 10-item GDS were associated with clinical vitamin D deficiency (25(OH)D levels <10 ng/mL (OR=1.46; 95%CI=1.02;2.08; p=0.04) (54). Data from the English Longitudinal Study of Aging (≥50 years; n=5870) showed a significant association between low 25(OH)D concentrations and depressive symptoms (CES-D) [OR=1.58; 95% CI=1.20–2.07 for the lowest quartile; OR=1.45, 95%CI=1.15.1.83 for ≤ 30- nmol/L cut-off and OR=1.34, 95%CI=1.10–1.62 for the ≤50 nmol/L cut-off)] (63).

Although depression has well-studied pathophysiology, the biochemical mechanisms involved in the relationship between vitamin D and depression are still not well elucidated. Some mechanisms of vitamin D have been suggested, such as changes in glutamatergic neurotransmitter and monoaminergic systems, interactions with inflammatory processes, and control of the expression of those genes that are responsible for maintaining both Ca2+ and reactive oxygen species homeostasis (23). Additionally, VDR was found in the prefrontal cortex and parts of the limbic system, and these brain areas had been implicated in the pathophysiology of depression (17).

Another interesting finding in our study was that 21.4% (*P*=0.048) of older individuals who used antidepressant drugs were classified as having depressive symptoms. Some studies discussed that around 10%-30% of individuals with depression presented resistance in drug therapy, not responding to treatment with at least two antidepressants (9,83–85). Alternatively, the available antidepressants are commonly accompanied by unpleasant side effects and may cause treatment to be discontinued (33). Additionally, sometimes unintentional non-adherence, such as forgetting and inability to follow treatment instructions because of poor understanding or physical problems (poor eyesight or impaired manual dexterity), was found to be responsible for treatment discontinuation (86).

In our study we did not perform an evaluation about the influence of antidepressant in 25(OH)D concentration, but some findings point to a relationship in antidepressant use and low level of vitamin D (87,88). The mechanism is not well explained, but there are a hypothesis that tricyclic antidepressant may dampen 1-α-hydroxylase activity and induce the activity of 1,25-(OH)2 vitamin D3 24-hydroxylase (87). If this hypothesis is verified, perhaps this influence of the antidepressant on the level of vitamin D could lead to a risk of depression.

Furthermore, only 9.4% of older adults diagnosed with vitamin D insufficiency or deficiency (39.4% and 25.5%, for insufficiency and deficiency, respectively) were using vitamin D supplements. At the same time, the prevalence of hypovitaminosis (<30 ng/mL) was present in >50% of the total sample. These results offer crucial evidence for the lack of vitamin D supplementation in this population.

A growing body of literature has investigated the potential effect of vitamin D on depression and its promising results, such as its prospective role as an adjuvant in drug therapy (89–92). This issue is still controversial and may be explained by several methodological differences, such as self-reported diagnosis for depression, different vitamin D reference values used, and various methods for serum vitamin D analysis (33,93–95). Further studies are needed to confirm these findings, and vitamin D supplementation may become a convenient and low-cost treatment (33,91). Moreover, depression is a disease requiring high treatment costs; therefore, there is a substantial gap in the necessity and availability of therapy; consequently, a significant population of depressed individuals are left untreated in low- and middle-income countries (28,96). Prevention has the potential to reduce not only recurrences, but also initial episodes, thus reducing the prevalence of period and in a lifetime (97).

Our study presented some limitations. It is essential to mention that the blood tests were performed with a part of the total EpiFloripa Study sample, and this may have limited some of the analyses, such as sex stratification. Clinical and biochemical examinations were conducted at the university, which could select individuals with relatively better health conditions than those from the general population. Although important, the cross-sectional analyzes should be considered with caution due to their methodological limitations inherent in obtaining data. In addition, longitudinal analysis of this data is in progress for a future study.

As for the strengths of this study, we consider that selecting a sample that includes only older adults is one of them because the population is distinct, considering metabolic alterations and life cycle aspects. Aging is a particular physiological phase of the life cycle, in which people reduce their metabolic ability to sustain homeostasis, which renders them highly susceptible to pathological alterations, especially concerning neuropsychiatric disorders (25,26). Additionally, we analyzed covariates, such as skin color, ethnicity, and the season in which the blood was collected. The 15-item GDS, which evaluates depressive symptoms, is one of the most widely used screening tools in similar studies and has been validated for application in the Brazilian population. Our study followed a highly accurate method for the quality of the data (trained and supervised interviewers, pilot study, face-to-face interviews, and interview quality control).

Conclusion

In summary, our findings showed that lower serum 25(OH)D concentrations were independently associated with depressive symptoms in older adults living in Southern Brazil, even after adjusting for demographic, socioeconomic, behavioral, and health variables. These findings are relevant, given the high prevalence of hypovitaminosis D established among this population. We observed that few older adults classified as vitamin D insufficient/deficient were using supplements, pointing to the necessity of serum vitamin D monitoring and prescription, when necessary, for prevention of not only depressive symptoms, but also other well-known conditions, such as compromised bone health. To better elucidate this relationship, a future longitudinal analysis would also be important and should be validated in more detail animal and cell experiments.

Abbreviations

25(OH)D: 25-hydroxyvitamin D; BMI: Body mass index; OR: Odds ratio; CI: Confidence interval; MW: minimum wage; ADLs: activities of daily living; VDR: vitamin D receptors; GDS: Geriatric Depression Scale; CES-D: Center for Epidemiologic Studies Depression Scale.

Acknowledgments

We are grateful to the participants, interviewers, and researchers from the EpiFloripa Aging Study.

Author contributions

All authors contributed to the study conception and design and takes responsibility for the integrity of the data and the accuracy of the data analysis. Data collection were performed by [ED], [SCC], [JDM], and analysis were performed by [GC]. Material preparation and the first draft of the manuscript was written by [GC] and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Funding

This study was supported by partnerships established with the Federal University of Santa Catarina (UFSC), other research projects, and assistance from students and teachers involved in the research. All the infrastructure and instruments needed to carry out the research were made available by the proposing institution, UFSC, with the exception of the netbooks used for data collection that were provided by the Oswaldo Cruz Foundation (FIOCRUZ) in Rio de Janeiro. The stage of collecting clinical and laboratory exams was financed by the *Conselho Nacional de Desenvolvimento Científico e Tecnológico* (CNPq), process number 475.904 / 2013-3, and developed within the scope of the Postgraduate Program in Collective Health at UFSC. This study was financed in part by the *Coordenação de Aperfeiçoamento de Pessoal de Nível Superior* – CAPES/Brasil (Finance Code 001).

Availability of data and materials

The datasets during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing of Interest

The authors declare that they have no competing of interest.

Ethics approval and consent to participate

The study was conducted according to the guidelines laid down in the Declaration of Helsinki and was approved by the Ethics Committee of the Federal University of Santa Catarina (protocol approval numbers 329.650 and 526.126). All participants provided informed consent prior to participation.

Consent for publication

All authors read and approved the final manuscript.

References

1. World Health Organization. Depression and Other Common Mental Disorders: Global Health Estimates [Internet]. Geneva: World Health Organization; 2017 [citado 31 de julho de 2019] p. 27. Disponível em: http://www.who.int/mental_health/management/depression/prevalence_global_health_estimates/en/

2. James SL, Abate D, Abate KH, Abay SM, Abbafati C, Abbasi N, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. The Lancet. 10 de novembro de 2018;392(10159):1789–858.

3. Chisholm D, Sweeny K, Sheehan P, Rasmussen B, Smit F, Cuijpers P, et al. Scaling-up treatment of depression and anxiety: a global return on investment analysis. Lancet Psychiatry. 1o de maio de 2016;3(5):415–24.

4. DiLuca M, Olesen J. The cost of brain diseases: a burden or a challenge? Neuron. 18 de junho de 2014;82(6):1205–8.

5. Avasthi A, Grover S. Clinical Practice Guidelines for Management of Depression in Elderly. Indian J Psychiatry. fevereiro de 2018;60(Suppl 3):S341–62.

6. Brandão DJ, Fontenelle LF, da Silva SA, Menezes PR, Pastor-Valero M. Depression and excess mortality in the elderly living in low- and middle-income countries: Systematic review and meta-analysis. Int J Geriatr Psychiatry. 1o de janeiro de 2019;34(1):22–30.

7. Köhler CA, Evangelou E, Stubbs B, Solmi M, Veronese N, Belbasis L, et al. Mapping risk factors for depression across the lifespan: An umbrella review of evidence from meta-analyses and Mendelian randomization studies. J Psychiatr Res. 1o de agosto de 2018;103:189–207.

8. Kaltenboeck A, Harmer C. The neuroscience of depressive disorders: A brief review of the past and some considerations about the future. Brain Neurosci Adv. 1o de janeiro de 2018;2:2398212818799269.

9. Otte C, Gold SM, Penninx BW, Pariante CM, Etkin A, Fava M, et al. Major depressive disorder. Nat Rev Dis Primer. 15 de setembro de 2016;2:16065.

10. Camargo A, Dalmagro AP, Rikel L, da Silva EB, Simao da Silva KAB, Zeni ALB. Cholecalciferol counteracts depressive-like behavior and oxidative stress induced by repeated corticosterone treatment in mice. Eur J Pharmacol. 15 de agosto de 2018;833:451–61.

11. Fedotova J, Dudnichenko T, Kruzliak P, Puchavskaya Z. Different effects of vitamin D hormone treatment on depression-like behavior in the adult ovariectomized female rats. Biomed Pharmacother Biomedecine Pharmacother. dezembro de 2016;84:1865–72.

12. Menon V, Kar SK, Suthar N, Nebhinani N. Vitamin D and Depression: A Critical Appraisal of the Evidence and Future Directions. Indian J Psychol Med. 6 de janeiro de 2020;42(1):11–21.

13. Eyles DW, Burne THJ, McGrath JJ. Vitamin D, effects on brain development, adult brain function and the links between low levels of vitamin D and neuropsychiatric disease. Front Neuroendocrinol. 1o de janeiro de 2013;34(1):47–64.

14. Mayne PE, Burne THJ. Vitamin D in Synaptic Plasticity, Cognitive Function, and Neuropsychiatric Illness. Trends Neurosci. 1o de abril de 2019;42(4):293–306.

15. Eyles DW, Smith S, Kinobe R, Hewison M, McGrath JJ. Distribution of the Vitamin D receptor and 1α-hydroxylase in human brain. J Chem Neuroanat. 1o de janeiro de 2005;29(1):21–30.

16. Stumpf WE, Sar M, Clark SA, DeLuca HF. Brain target sites for 1,25-dihydroxyvitamin D3. Science. 12 de março de 1982;215(4538):1403–5.

17. DeLuca GC, Kimball SM, Kolasinski J, Ramagopalan SV, Ebers GC. Review: The role of vitamin D in nervous system health and disease. Neuropathol Appl Neurobiol. 1o de agosto de 2013;39(5):458–84.

18. Landel V, Stephan D, Cui X, Eyles D, Feron F. Differential expression of vitamin D-associated enzymes and receptors in brain cell subtypes. J Steroid Biochem Mol Biol. 1o de março de 2018;177:129–34.

19. Patrick RP, Ames BN. Vitamin D and the omega-3 fatty acids control serotonin synthesis and action, part 2: relevance for ADHD, bipolar disorder, schizophrenia, and impulsive behavior. FASEB J. 24 de fevereiro de 2015;29(6):2207–22.

20. Alghamdi S, Alsulami N, Khoja S, Alsufiani H, Tayeb HO, Tarazi FI. Vitamin D Supplementation Ameliorates Severity of Major Depressive Disorder. J Mol Neurosci. 1o de fevereiro de 2020;70(2):230–5.

21. Kaneko I, Sabir MS, Dussik CM, Whitfield GK, Karrys A, Hsieh J-C, et al. 1,25-Dihydroxyvitamin D regulates expression of the tryptophan hydroxylase 2 and leptin genes: implication for behavioral influences of vitamin D. FASEB J. 2015;29(9):4023–35.

22. Sabir MS, Haussler MR, Mallick S, Kaneko I, Lucas DA, Haussler CA, et al. Optimal vitamin D spurs serotonin: 1,25-dihydroxyvitamin D represses serotonin reuptake transport (SERT) and degradation (MAO-A) gene expression in cultured rat serotonergic neuronal cell lines. Genes Nutr [Internet]. 11 de julho de 2018 [citado 1o de outubro de 2020];13. Disponível em: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6042449/

23. Berridge MJ. Vitamin D and Depression: Cellular and Regulatory Mechanisms. Pharmacol Rev. 1o de abril de 2017;69(2):80–92.

24. Berk M, Williams LJ, Jacka FN, O'Neil A, Pasco JA, Moylan S, et al. So depression is an inflammatory disease, but where does the inflammation come from? BMC Med. 12 de setembro de 2013;11:200.

25. Sibille E. Molecular aging of the brain, neuroplasticity, and vulnerability to depression and other brain-related disorders. Dialogues Clin Neurosci. março de 2013;15(1):53–65.

26. Pomatto LCD, Davies KJA. The role of declining adaptive homeostasis in ageing. J Physiol. 2017;595(24):7275–309.

27. World Health Organization. Depression [Internet]. 2020 [citado 13 de fevereiro de 2020]. Disponível em: https://www.who.int/news-room/fact-sheets/detail/depression

28. Lopes CS, Hellwig N, e Silva G de A, Menezes PR. Inequities in access to depression treatment: results of the Brazilian National Health Survey – PNS. Int J Equity Health. dezembro de 2016;15(1):154.

29. MacLaughlin J, Holick MF. Aging decreases the capacity of human skin to produce vitamin D3. J Clin Invest. outubro de 1985;76(4):1536–8.

30. Arabi A, El Rassi R, El-Hajj Fuleihan G. Hypovitaminosis D in developing countries—prevalence, risk factors and outcomes. Nat Rev Endocrinol. outubro de 2010;6(10):550–61.

31. Ju S-Y, Lee Y-J, Jeong S-N. Serum 25-hydroxyvitamin D levels and the risk of depression: A systematic review and meta-analysis. J Nutr Health Aging. 1o de maio de 2013;17(5):447–55.

32. Li H, Sun D, Wang A, Pan H, Feng W, Ng CH, et al. Serum 25-Hydroxyvitamin D Levels and Depression in Older Adults: A Dose–Response Meta-Analysis of Prospective Cohort Studies. Am J Geriatr Psychiatry. 1o de novembro de 2019;27(11):1192–202.

33. Wong SK, Ima-Nirwana* K-YC and S. Vitamin D and Depression: The Evidence from an Indirect Clue to Treatment Strategy [Internet]. Current Drug Targets. 2018 [citado 7 de julho de 2019]. Disponível em: http://www.eurekaselect.com/155568/article

34. Schneider IJC, Confortin SC, Bernardo C de O, Bolsoni CC, Antes DL, Pereira KG, et al. EpiFloripa Aging cohort study: methods, operational aspects, and follow-up strategies. Rev Saúde Pública [Internet]. 2017 [citado 29 de abril de 2019];51. Disponível em: http://www.scielo.br/scielo.php?script=sci_abstract&pid=S0034-89102017000100290&lng=en&nrm=iso&tlng=en

35. Confortin SC, Schneider IJC, Danielewicz AL, Fassula AS, Souza BB de, Santos CES dos, et al. Estudo Longitudinal EpiFloripa Idoso – Rotinas de organização e protocolos referentes à coleta, análise e armazenamento de material biológico, exames de imagem e capacidade físico-funcional. Cad Saúde Coletiva. junho de 2019;27(2):210–24.

36. Almeida OP, Almeida SA. Confiabilidade da versão brasileira da Escala de Depressão em Geriatria (GDS) versão reduzida. Arq Neuropsiquiatr. junho de 1999;57(2B):421–6.

37. Paradela EMP, Lourenço RA, Veras RP. Validation of geriatric depression scale in a general outpatient clinic. Rev Saúde Pública. dezembro de 2005;39(6):918–23.

38. BRASIL. Ministério da Saúde. CADERNOS DE ATENÇÃO BÁSICA 19 - Envelhecimento e saúde da pessoa idosa [Internet]. DF: Mnistério da Saúde; 2006. Disponível em: http://bvsms.saude.gov.br/bvs/publicacoes/evelhecimento_saude_pessoa_idosa.pdf

39. Almeida OP, Almeida SA. Short versions of the geriatric depression scale: a study of their validity for the diagnosis of a major depressive episode according to ICD-10 and DSM-IV. Int J Geriatr Psychiatry. 1o de outubro de 1999;14(10):858–65.

40. Ersfeld DL, Rao DS, Body J-J, Sackrison JL, Miller AB, Parikh N, et al. Analytical and clinical validation of the 25 OH vitamin D assay for the LIAISON® automated analyzer. Clin Biochem. 1o de outubro de 2004;37(10):867–74.

41. Bianchi S, Maffei S, Prontera C, Battaglia D, Vassalle C. Preanalytical, analytical (DiaSorin LIAISON) and clinical variables potentially affecting the 25-OH Vitamin D estimation. Clin Biochem. 1o de dezembro de 2012;45(18):1652–7.

42. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, et al. Evaluation, Treatment, and Prevention of Vitamin D Deficiency: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 1o de julho de 2011;96(7):1911–30.

43. Babor TF, Higgins-Biddle JC, Saunders JB, Monteiro MG. The alcohol use disorders identification test: guidelines for use in primary care. 2001;(2):41.

44. Benedetti TB, Mazo GZ, Barros MVG de. Application of the International Physical Activity Questionnaire (IPAQ) for evaluation of elderly women: concurrent validity and test-retest reprodutibility. Rev Bras Ciênc Mov. 2004;12(1):25–34.

45. Benedetti TRB, Antunes P de C, Rodriguez-Añez CR, Mazo GZ, Petroski ÉL. Reproducibility and validity of the International Physical Activity Questionnaire (IPAQ) in elderly men. Rev Bras Med Esporte. fevereiro de 2007;13(1):11–6.

46. Rosa TE da C, Benício MHD, Latorre M do RD de O, Ramos LR. Determinant factors of functional status among the elderly. Rev Saúde Pública. fevereiro de 2003;37(1):40–8.

47. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. novembro de 1975;12(3):189–98.

48. Almeida OP. The Mini-Mental State Examination and the Diagnosis of Dementia in Brazil. Arq Neuropsiquiatr. setembro de 1998;56(3B):605–12.

49. American Academy of Family Physicians, American Dietetic Association, National Concil On The Aging. Nutrition screening and intervention resources for healthcare professionals working with older adults. Nutrition Screening Initiative. Washington DC: American Dietetic Association; 2002.

50. World Health Organization, Collaborating Centre for Drug Statistics Methodology, Norwegian Institute of Public Health. WHOCC - ATC/DDD Index [Internet]. [citado 20 de dezembro de 2019]. Disponível em: https://www.whocc.no/atc_ddd_index/

51. Hoogendijk WJG, Lips P, Dik MG, Deeg DJH, Beekman ATF, Penninx BWJH. Depression Is Associated With Decreased 25-Hydroxyvitamin D and Increased Parathyroid Hormone Levels in Older Adults. Arch Gen Psychiatry. 1o de maio de 2008;65(5):508–12.

52. Imai CM, Halldorsson TI, Eiriksdottir G, Cotch MF, Steingrimsdottir L, Thorsdottir I, et al. Depression and serum 25-hydroxyvitamin D in older adults living at northern latitudes – AGES-Reykjavik Study. J Nutr Sci [Internet]. 20 de novembro de 2015 [citado 24 de fevereiro de 2020];4. Disponível em: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4678766/

53. Song BM, Kim HC, Rhee Y, Youm Y, Kim CO. Association between serum 25-hydroxyvitamin D concentrations and depressive symptoms in an older Korean population: A cross-sectional study. J Affect Disord. 1o de janeiro de 2016;189:357–64.

54. Stewart R, Hirani V. Relationship Between Vitamin D Levels and Depressive Symptoms in Older Residents From a National Survey Population. Psychosom Med. setembro de 2010;72(7):608.

55. Toffanello ED, Sergi G, Veronese N, Perissinotto E, Zambon S, Coin A, et al. Serum 25-hydroxyvitamin d and the onset of late-life depressive mood in older men and women: the Pro.V.A. study. J Gerontol A Biol Sci Med Sci. dezembro de 2014;69(12):1554–61.

56. Yao Y, Fu S, Zhang H, Li N, Zhu Q, Zhang F, et al. The prevalence of depressive symptoms in Chinese longevous persons and its correlation with vitamin D status. BMC Geriatr. 29 de agosto de 2018;18(1):198.

57. Almeida OP, Hankey GJ, Yeap BB, Golledge J, Flicker L. Vitamin D concentration and its association with past, current and future depression in older men: The Health In Men Study. Maturitas. maio de 2015;81(1):36–41.

58. Chan R, Chan D, Woo J, Ohlsson C, Mellström D, Kwok T, et al. Association between serum 25-hydroxyvitamin D and psychological health in older Chinese men in a cohort study. J Affect Disord. 1o de abril de 2011;130(1):251–9.

59. Brouwer-Brolsma EM, Dhonukshe-Rutten RAM, van Wijngaarden JP, van der Zwaluw NL, Sohl E, In't Veld PH, et al. Low vitamin D status is associated with more depressive symptoms in Dutch older adults. Eur J Nutr. junho de 2016;55(4):1525–34.

60. Lapid MI, Cha SS, Takahashi PY. Vitamin D and depression in geriatric primary care patients. Clin Interv Aging. 2013;8:509–14.

61. Sherchand O, Sapkota N, Chaudhari RK, Khan SA, Baranwal JK, Pokhrel T, et al. Association between vitamin D deficiency and depression in Nepalese population. Psychiatry Res. 2018;267:266–71.

62. Vidgren M, Virtanen JK, Tolmunen T, Nurmi T, Tuomainen T-P, Voutilainen S, et al. Serum Concentrations of 25-Hydroxyvitamin D and Depression in a General Middle-

Aged to Elderly Population in Finland. J Nutr Health Aging. 1o de janeiro de 2018;22(1):159–64.

63. de Oliveira C, Hirani V, Biddulph JP. Associations Between Vitamin D Levels and Depressive Symptoms in Later Life: Evidence From the English Longitudinal Study of Ageing (ELSA). J Gerontol Ser A. 11 de setembro de 2018;73(10):1377–82.

64. Jovanova O, Aarts N, Noordam R, Carola-Zillikens M, Hofman A, Tiemeier H. Vitamin D serum levels are cross-sectionally but not prospectively associated with late-life depression. Acta Psychiatr Scand. 2017;135(3):185–94.

65. Lee S-H, Suh E, Park K-C, Haam J-H, Kim K, Koo HS, et al. Association of serum 25-hydroxyvitamin D and serum total cholesterol with depressive symptoms in Korean adults: the Fifth Korean National Health and Nutrition Examination Survey (KNHANES V, 2010-2012). Public Health Nutr. julho de 2017;20(10):1836–43.

66. Shin Y-C, Jung C-H, Kim H-J, Kim E-J, Lim S-W. The associations among vitamin D deficiency, C-reactive protein, and depressive symptoms. J Psychosom Res. novembro de 2016;90:98–104.

67. Rabenberg M, Harisch C, Rieckmann N, Buttery AK, Mensink GBM, Busch MA. Association between vitamin D and depressive symptoms varies by season: Results from the German Health Interview and Examination Survey for Adults (DEGS1). J Affect Disord. 1o de novembro de 2016;204:92–8.

68. Józefowicz O, Rabe-Jabłońska J, Woźniacka A, Strzelecki D. Analysis of vitamin D status in major depression. J Psychiatr Pract. setembro de 2014;20(5):329–37.

69. Milaneschi Y, Hoogendijk W, Lips P, Heijboer AC, Schoevers R, van Hemert AM, et al. The association between low vitamin D and depressive disorders. Mol Psychiatry. abril de 2014;19(4):444–51.

70. Lee DM, Tajar A, O'Neill TW, O'Connor DB, Bartfai G, Boonen S, et al. Lower vitamin D levels are associated with depression among community-dwelling European men. J Psychopharmacol (Oxf). 1o de outubro de 2011;25(10):1320–8.

71. Nanri A, Mizoue T, Matsushita Y, Poudel-Tandukar K, Sato M, Ohta M, et al. Association between serum 25-hydroxyvitamin D and depressive symptoms in Japanese: analysis by survey season. Eur J Clin Nutr. dezembro de 2009;63(12):1444–7.

72. Pan A, Lu L, Franco OH, Yu Z, Li H, Lin X. Association between depressive symptoms and 25-hydroxyvitamin D in middle-aged and elderly Chinese. J Affect Disord. 1o de novembro de 2009;118(1):240–3.

73. de Koning EJ, Elstgeest LEM, Comijs HC, Lips P, Rijnhart JJM, van Marwijk HWJ, et al. Vitamin D Status and Depressive Symptoms in Older Adults: A Role for Physical Functioning? Am J Geriatr Psychiatry. 1o de novembro de 2018;26(11):1131–43.

74. Lotfaliany M, Hoare E, Jacka FN, Kowal P, Berk M, Mohebbi M. Variation in the prevalence of depression and patterns of association, sociodemographic and lifestyle factors in community-dwelling older adults in six low- and middle-income countries. J Affect Disord. 15 de maio de 2019;251:218–26.

75. Lorant V, Deliège D, Eaton W, Robert A, Philippot P, Ansseau M. Socioeconomic Inequalities in Depression: A Meta-Analysis. Am J Epidemiol. 15 de janeiro de 2003;157(2):98–112.

76. Holick MF. Vitamin D Deficiency. N Engl J Med. 19 de julho de 2007;357(3):266–81.

77. Hayes DP. Vitamin D and ageing. Biogerontology. 1o de fevereiro de 2010;11(1):1–16.

78. Boucher BJ. The Problems of Vitamin D Insufficiency in Older People. Aging Dis. 6 de junho de 2012;3(4):313–29.

79. Schuch FB, Vancampfort D, Firth J, Rosenbaum S, Ward PB, Silva ES, et al. Physical Activity and Incident Depression: A Meta-Analysis of Prospective Cohort Studies. Am J Psychiatry. 25 de abril de 2018;175(7):631–48.

80. Milaneschi Y, Shardell M, Corsi AM, Vazzana R, Bandinelli S, Guralnik JM, et al. Serum 25-hydroxyvitamin D and depressive symptoms in older women and men. J Clin Endocrinol Metab. julho de 2010;95(7):3225–33.

81. Wortsman J, Matsuoka LY, Chen TC, Lu Z, Holick MF. Decreased bioavailability of vitamin D in obesity. Am J Clin Nutr. 1o de setembro de 2000;72(3):690–3.

82. Snijder MB, van Dam RM, Visser M, Deeg DJH, Dekker JM, Bouter LM, et al. Adiposity in Relation to Vitamin D Status and Parathyroid Hormone Levels: A Population-Based Study in Older Men and Women. J Clin Endocrinol Metab. 1o de julho de 2005;90(7):4119–23.

83. Al-Harbi KS. Treatment-resistant depression: therapeutic trends, challenges, and future directions. Patient Prefer Adherence. 1o de maio de 2012;6:369–88.

84. Jaffe DH, Rive B, Denee TR. The humanistic and economic burden of treatment-resistant depression in Europe: a cross-sectional study. BMC Psychiatry. 7 de agosto de 2019;19(1):247.

85. Johnston KM, Powell LC, Anderson IM, Szabo S, Cline S. The burden of treatment-resistant depression: A systematic review of the economic and quality of life literature. J Affect Disord. 1o de janeiro de 2019;242:195–210.

86. Horne R. Representations of medication and treatment: Advances in theory and measurement. In: Perceptions of health and illness: Current research and applications. Amsterdam, Netherlands: Harwood Academic Publishers; 1997. p. 155–88.

87. Oude Voshaar RC, Derks WJ, Comijs HC, Schoevers RA, de Borst MH, Marijnissen RM. Antidepressants differentially related to 1,25-(OH)2 vitamin D3 and 25-(OH) vitamin D3 in late-life depression. Transl Psychiatry. abril de 2014;4(4):e383.

88. Fond G, Faugere M, Faget-Agius C, Cermolacce M, Richieri R, Boyer L, et al. Hypovitaminosis D is associated with negative symptoms, suicide risk, agoraphobia, impaired functional remission, and antidepressant consumption in schizophrenia. Eur Arch Psychiatry Clin Neurosci. 1o de dezembro de 2019;269(8):879–86.

89. Vellekkatt F, Menon V. Efficacy of vitamin D supplementation in major depression: A meta-analysis of randomized controlled trials. J Postgrad Med. 2019;65(2):74–80.

90. Alavi NM, Khademalhoseini S, Vakili Z, Assarian F. Effect of vitamin D supplementation on depression in elderly patients: A randomized clinical trial. Clin Nutr. 1o de outubro de 2019;38(5):2065–70.

91. Singh S, Sharma P, Gautam V. Role of vitamin D supplementation as adjunctive therapy to escitalopram in patients of major depressive disorder: a 8 week prospective, randomized, interventional, clinical study. Int J Basic Clin Pharmacol. 23 de julho de 2019;8(8):1713–6.

92. Khoraminya N, Tehrani-Doost M, Jazayeri S, Hosseini A, Djazayery A. Efeitos terapêuticos da vitamina D como terapia adjuvante à fluoxetina em pacientes com transtorno depressivo maior. Aust N Z J Psychiatry. 1o de março de 2013;47(3):271–5.

93. Spedding S. Vitamin D and Depression: A Systematic Review and Meta-Analysis Comparing Studies with and without Biological Flaws. Nutrients. abril de 2014;6(4):1501–18.

94. de Koning EJ, Lips P, Penninx BWJH, Elders PJM, Heijboer AC, den Heijer M, et al. Vitamin D supplementation for the prevention of depression and poor physical function in older persons: the D-Vitaal study, a randomized clinical trial. Am J Clin Nutr. 01 de 2019;110(5):1119–30.

95. Jorde R, Kubiak J. No improvement in depressive symptoms by vitamin D supplementation: results from a randomised controlled trial. J Nutr Sci. 2018;7:e30.

96. Wang PS, Aguilar-Gaxiola S, Alonso J, Angermeyer MC, Borges G, Bromet EJ, et al. Worldwide Use of Mental Health Services for Anxiety, Mood, and Substance Disorders: Results from 17 Countries in the WHO World Mental Health (WMH) Surveys. Lancet. 8 de setembro de 2007;370(9590):841–50.

97. Ormel J, Cuijpers P, Jorm A, Schoevers RA. What is needed to eradicate the depression epidemic, and why. Ment Health Prev. 1o de março de 2020;17:200177.

4.3 CAPÍTULO 3 - ESTÁGIO DE DOUTORADO SANDUÍCHE NO EXTERIOR

Com o intuito de fortalecer o vínculo com instituições internacionais, promover a visibilidade da ciência brasileira, bem como aprimorar as técnicas e estudo para realização dos artigos da tese, realizou-se o estágio de doutorado sanduiche no exterior, com bolsa do programa de Doutorado Sanduíche no Exterior (PDSE) da CAPES no período de fevereiro a julho de 2022. O estágio foi realizado no departamento de psiquiatria do *Kingston General Hospital* (KGH), associado ao *Centre for Neuroscience Studies* (CNS), da *Queen's University*, Kingston, Ontário, Canadá, sob supervisão da Profa. Dra. Elisa Brietzke.

Neste capítulo são apresentados os artigos:

Artigo 6 - "*Lower vitamin D concentration is associated with depressive symptoms over 2 to 5-year follow-up: the EpiFloripa Aging Cohort Study"* (páginas 218 a 234).
Artigo a ser submetido: formatado de acordo com as normas da revista *Brazilian Journal of Psychiatry* (Qualis Capes B1, fator de impacto 6.328).

Artigo 7 - *"Association between adiposity and emergent depressive symptoms in a 10-years cohort of older adults: the EpiFloripa Aging Study"* (páginas 235 a 255).
Artigo em apreciação: *Journal of Affective Disorders* (Qualis Capes A1, Fator de impacto 6.533).

4.3.1 Artigo 6

Lower vitamin D concentration is associated with depressive symptoms over 2 to 5-year follow-up: the EpiFloripa Aging Cohort Study

Gilciane Ceolin[1,2,3], Anna Quialheiro[4], Antônio Augusto Moura Silva[5], Eleonora d'Orsi[6], Débora Kurrle Rieger[3,7], Júlia Dubois Moreira[3,7], Elisa Brietzke[2,8]

1. Postgraduate Program in Nutrition, Federal University of Santa Catarina, Florianopolis, SC, Brazil.
2. Centre for Neuroscience Studies (CNS), Queen's University, Kingston, ON, Canada.
3. Translational Nutritional Neuroscience working group. Federal University of Santa Catarina, Florianopolis, Brazil.
4. Life and Health Sciences Research Institute, Medical School, University of Minho, Portugal
5. Postgraduation Program of Collective Health. Department of Public Health. Federal University of Maranhão, São Luís, Brazil.
6. Department of Public Health, Federal University of Santa Catarina, Florianopolis, SC, Brazil.
7. Department of Nutrition, Federal University of Santa Catarina, Brazil.
8. Department of Psychiatry, Queen's University School of Medicine, Kingston, ON, Canada.

Abstract

Objective: To evaluate the longitudinal association between Vitamin D and depressive symptoms in older adults.

Methods: Data from the second (2013-2015) and third (2017-2019) waves of the EpiFloripa Aging Cohort Study were used. Depressive symptoms were assessed by the 15-item Geriatric Depression Scale (GDS-15) and the severity was classified as ≥6 points. Vitamin D serum concentration [25(OH)D, 25-hydroxycolecalciferol] was measured using the microparticle chemiluminescence method. Logistic regression was used to assess the association between 25(OH)D and the change in GDS-15 over a 3 to 5-year follow-up. The analysis was adjusted by sex, age, income, alcohol use,

multimorbidity, body fat percentage, leisure-time physical activity, and use of the antidepressants.

Results: We analyze data from 574 older adults. From wave 2 to wave 3, 12.6% showed an increase in the severity of depressive symptoms, 7.1% presented a decrease, and 5.0% kept the severity of depressive symptoms over two years. In the adjusted analysis, those in the lowest quartile of 25(OH)D (4 to 20.6 ng/ml) presented high risk to have severity of depressive symptoms in wave 3 (OR=2.90; CI95%: 1.14-7.34, p = 0.025), compared to those in the highest quartile (32.1 a 50 ng/ml).

Conclusions: Lower 25(OH)D concentration was prospectively associated with the severity of depressive symptoms in older adults.

Keywords: Vitamin D; Aging; Depressive Symptoms; Longitudinal Studies.

1. Introduction

A growing body of literature has investigated the association between lower (<20 ng/ml) vitamin D concentration and depression in older adults in different scenarios as in cross-sectional, longitudinal, and clinical studies since both conditions are highly prevalent in this population[1]. The combined worldwide prevalence of depression in older adults was estimated at 28.4%[2], while the deficiency of vitamin D (<20 ng/ml) is estimated between 17–87%[3]. Also, both are implicated in an increased risk of frailty, disabilities, and mortality in the older population [4–8].

Depression is a multifactorial disorder, also linked with the impact of many aging processes in brain structures and functions of the neurotransmitter levels and neuroendocrine systems that have been implicated as a target to vitamin D metabolites [9,10]. Due to the presence of nuclear and membrane receptors of vitamin D and some enzymes responsible for converting the metabolites of vitamin D in the central nervous system, many other studies have investigated the possible role of 25(OH)D on the pathophysiology of depression[11–15]. Some of the mechanisms proposed that link 25(OH)D to depression are the maintenance of Ca^{2+} homeostasis, activation of the expression of many antioxidant genes regulating the formation of serotonin and dopamine, and reducing inflammation by reducing the expression of inflammatory cytokines[11–15].

Although with published promising preclinical studies, the relationship is not fully understood from a clinical and observational studies. In the literature, at this point, only

six longitudinal studies were carried out, including only older adults (≥60 years). The results vary due to methodological differences, in that studies have not found an effect on depression[16–19], and some have found [20,21]. Further, there is a lack of longitudinal studies evaluating the observational association between vitamin D and depressive symptoms in older adults from low and middle-income countries[1], which are known to be both lower levels of 25(OH)D and high prevalence of depression[22,23]. This study aimed to analyze the prospective association between vitamin D and depressive symptoms in a 2 to 5-year follow-up cohort study with older adults from southern Brazil.

2. Methods

Design, sample, and data collection

To this analysis we used data from the second (2013–2015) and third (2017–2019) waves of the "Conditions of the health of the older adults in the Florianopolis - EpiFloripa Aging Cohort Study," a population-based study. The design, methods, and sample details were described in previous publications [24,25]. Briefly, the inclusion criteria at baseline were males and females aged ≥60 years and living in an urban area in Florianopolis, Santa Catarina, Brazil; those living in long-term care institutions, hospitals, and prisons were excluded. All older adults who initially participated in the study's first wave (2009–2010) were invited to participate in the second and third waves. A face-to-face interview was conducted through a structured questionnaire on a laptop by trained interviewers at participants' homes. In the second wave, the older adults of the follow-up were invited to do a complementary examinations collection including blood sample collection [25] (**Figure 1**). The complementary examinations were carried out at the *Federal University of Santa Catarina* (UFSC), and the mean time between blood sample collection and the interview in the third wave was 3.7 year (standard deviation of 0.5; minimum of 2.7 and maximum of 5.7). The study's consistency analysis and quality control were conducted by telephone through a reduced questionnaire version applied to 10% of randomly selected participants [24].

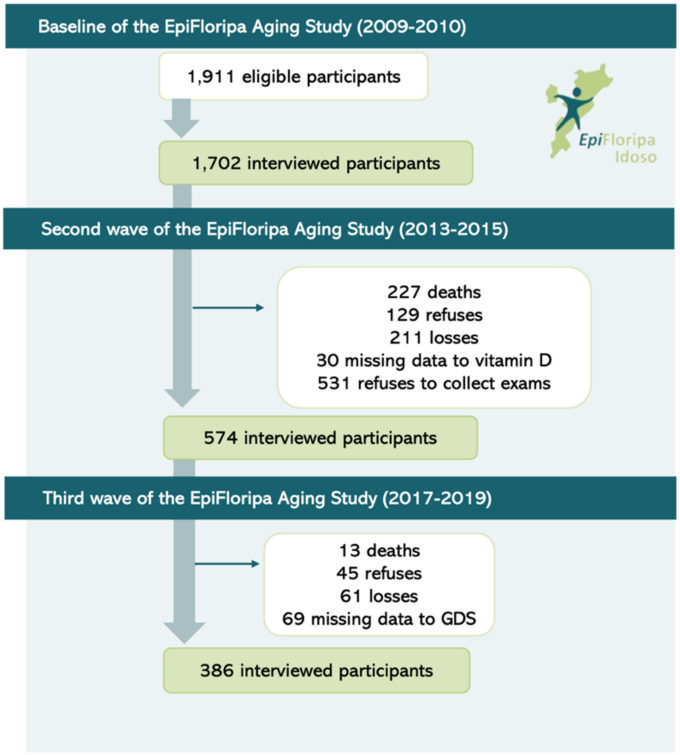


Figure 1. Flowchart of EpiFloripa Aging Study.

Measurements

Vitamin D

Blood samples were collected at the Laboratory for Metabolism and Dietetics of the UFSC and analyzed at the laboratory of clinical analysis of the *Polydoro Ernani de São Thiago* University Hospital [25]. Participants were asked to fast for 8–10 h before blood collection, and 30 mL of peripheral venous blood was collected from each participant.

Serum 25(OH)D concentrations (ng/mL) were measured using the microparticle chemiluminescence method. The blood samples were centrifuged at 3,500 rpm for 10 min to collect serum. Serum samples used to detect 25(OH)D were immediately processed according to the manufacturer's instructions using LIAISON® (DiaSorin, São Paulo, SP, Brazil)[26]. In this method, an antibody specific to vitamin D was coated with magnetic particles, and 25(OH)D was conjugated to an isoluminol derivative and diluted in phosphate buffer (pH 7.4). In the first incubation period, 25(OH)D was dissociated from the binding protein and interacted with the antibody. During the second incubation period with the tracer reagent, the microplate was washed with the

buffer, and starter reagents were added to generate the chemiluminescent signal, measured using a photomultiplier[26].

LIAISON® is a rapid, accurate, and precise assay (functional sensitivity, ≤ 2.0 ng/mL; inter-assay imprecision, < 20%) [26]. Since 2014, the LIAISON® has received certification for a total of 25-hydroxyvitamin D assays from the Vitamin D Standardization Certification Program by the Center for Disease Control and Prevention [27]. The 25(OH)D was categorized into quartiles (Quartile 1: 4 to 20.6 ng/ml; Quartile 2: 20.7 to 26.5 ng/ml; Quartile 3: 26.6 to 32 ng/ml; Quartile 4: 32.1 a 50 ng/ml).

Severity of depressive symptoms

The GDS-15 was used to evaluate depressive symptoms. In Brazil, the GDS-15 is recommended by the Brazilian Ministry of Health[28] as useful due to a rapid screening of depressive symptoms in the older adult in primary health care centers. The GDS-15 was translated to Portuguese and validated in a Brazilian sample according to the International Classification of Diseases (ICD-10)[29] criteria for research and the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), with outpatients aged 60 or over who met the criteria for depressive disorder (current or in remission)[31,32].

In this study, it was followed the cut-off points suggested by Almeida and Almeida (1980), of ≥ 6 points for individuals with severity in depressive symptoms[31,33]. For the change between waves, it was categorized as: Low severity (Kept low severity with ≤ 5 points in both waves + decreased severity from ≤ 6 points in wave 2 to ≤ 5 points in wave 3); Severity (Kept ≥ 6 points in both waves + increased severity from ≤ 5 points in wave 2 to ≥ 6 points in wave 3).

The Almeida and Almeida's cut-off points presented a sensitivity of 85.4% and a specificity of 73.9% according to ICD-10, and 90.9% of sensitivity and 64.5% of specificity according to the DSM-IV. The internal consistency as assessed by Cronbach's alpha revealed a reliability coefficient of 0.81[32]. In the test-retest reliability, when the outpatient was evaluated for the second time 48 to 72 hours after the first assessment, the GDS-15 scores were reasonably stable, as assessed by paired Wilcoxon ($z=1.60$, $p=0.109$) and Spearman's correlation coefficients ($rho=0.86$, $p<0.001$), and Cohen's weighted kappa ($kappa=0.64$)[32].

Covariates

A directed acyclic graph (DAG, or causal Bayesian networks) was constructed to represent the theoretical model and elucidate the involvement of covariates in the longitudinal association between 25(OH)D and depressive symptoms (**Figure 2**). The DAG was built using DAGitty software (version 3.0; Nijmegen, GE, The Netherlands)[34]. The graphical criteria for selecting the adjusted covariates were used to define the minimum set of covariates and reduce variable selection bias[35,36].

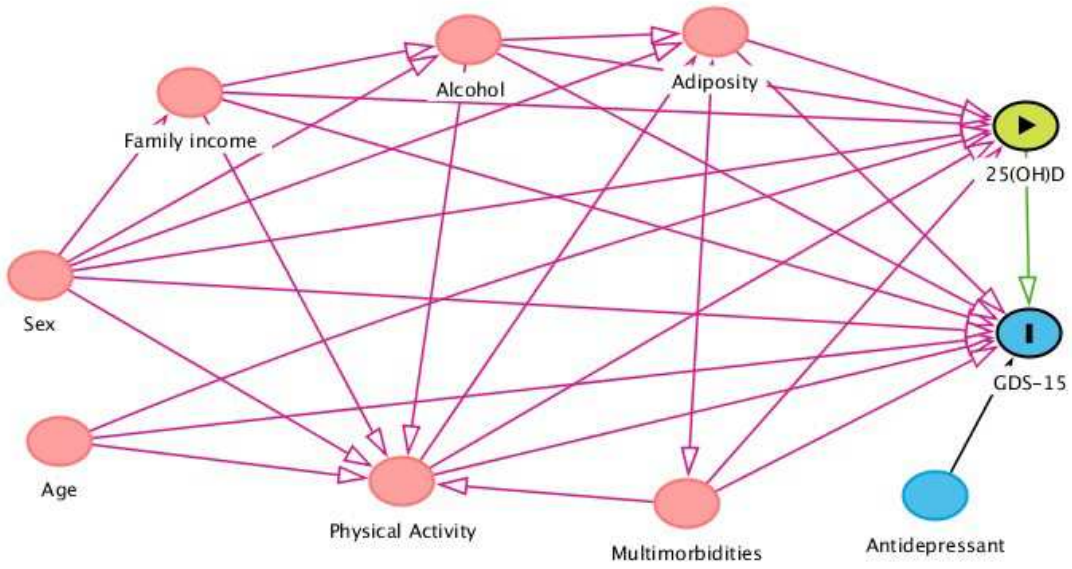


Figure 2. DAG of the minimum set of covariates to adjust for confounding in the association between Vitamin D concentration and severity of depressive symptoms. The arrows in pink represent the biasing path and in green the causal path. The variable with play bottom is the exposure, and the stop bottom is the outcome. GDS-15, 15-items Geriatric Depressive Scale. 25(OH)D, concentration of 25-hydroxycholecalciferol.

The minimum set of covariates selected to adjust for confounding using the backdoor criteria in the DAG were sociodemographic variables, such as sex (male/female), age (years), and per capita family income in minimal wages (categories: ≤1; >1 and ≤3; >3 and ≤5; >5 and ≤10; >10 minimal wages) according to the values in second wave, 2013 (R$ 678.00) and 2014 (R$ 724.00). Behavioral modified factors, such as alcohol consumption (no/yes) collected using the Alcohol Use Disorder Identification Test[37]; leisure-time physical activity (LTPA, assessed by the International Physical Activity Questionnaire, classified as insufficiently active <150 min; and active ≥150 min)[38,39].

As health variables included the number of medical comorbidities (sum of diagnosed medical conditions: spine or back disorders, arthritis, cancer, diabetes, bronchitis, cardiovascular disease, renal disease, tuberculosis, cirrhosis, stroke, osteoporosis, hypertension, and depression); the adiposity, measured by the body fat percentage (%Fat), was performed using Dual Energy X-ray Absorptiometry (DXA, Lunar Prodigy Advance, General Electric, Madison, WI, USA) following the manufacturer's instructions[40], and was classified into terciles (Tercile 1: 5 to 33.2%; Tercile 2: 33.6 to 41.7%; Tercile 3: 41.9 to 57.8%. The use of antidepressants was not suggested by the backdoor criteria, but we choose to include them in the model. Information about antidepressant use was collected by consulting prescription sheets and vials/bottles of medications prescribed by a physician in the participant's house. The medication was codified in the database using the Anatomical Therapeutic Chemical Classification codes from the World Health Organization Collaborating Centre for Drug Statistic Methodology [41].

Statistical analysis

Descriptive analysis of the data is presented as absolute and relative frequencies. To analyze the longitudinal association between 25(OH)D and the change of GDS categories between waves two and three, logistic regression was used to evaluate the odds ratio (OR) and the respective confidence intervals of 95% (CI) in the crude and adjusted models. As the reference, we choose those who had low severity of depressive symptoms (≤ 5 points). The covariates suggested by DAG were used in the adjusted model.

All analysis were performed using Stata 14.0 software (StataCorp, College Station, TX, USA). We considered the effect of the sample design by conglomerates and the sample weight using the command "*svy"*. For all analyses, we considered the level of statistical significance of 5%. The power of the sample size (1 − β error probability) was calculated a posteriori (post hoc) using G*Power (version 3.1.9.7, Düsseldorf, Germany) [42], establishing as parameters the logistic regression with an odds ratio of 3.5, and the number of the sample size of 386 (power=0.99).

Ethical Approval

The EpiFloripa Aging cohort study was conducted following the Declaration of Helsinki [43]. The second and third waves were approved by the Human Research Ethics

Committee of the UFSC (approval numbers second wave: 329.650 and 526.126, and third wave: 1.957.977). All participants voluntarily agreed to participate in the study and signed the informed consent form.

3. Results

A total of 574 participants were enrolled in this analysis, with a final sample from third wave of 386 participants (**Table 1**). The most of participants were female (63.1%), aged between 60–69 (42.4%), inactive in the LTPA (53.2%), and have 2 or more medical comorbidities (75.6%), 25.1% presented lower levels of vitamin D (< 20 ng/ml). Regarding the GDS classification between waves, 75.4% did not have changes, which means, kept low severity depressive symptoms over two years (≤ 5 points); 12.6% presented an increase (from ≤ 5 waves 2 to ≥ 6 wave 3); 7.1% presented a decrease (from ≥6 wave 2 to ≥ 5 wave 3); and 5.0% kept the severity of depressive symptoms (≥ 6 points) over two years.

Table 1. Sample characterization according to demographic, socioeconomic, and health characteristics of the older adults from EpiFloripa Aging Cohort Study (2013-2019).

Participants' characteristic (n=*574)*	N	%	95% CI
Sex			
Male	199	36.9	32.0–42.0
Female	375	63.1	58.0–68.0
Age			
60-69 years	243	42.4	36.6–48.4
70-79 years	239	41.3	36.2–46.6
≥80 years	92	16.3	12.9–20.5
Education (n=573)			
≤ 4 years	244	39.7	33.0–47.0
5 to 11 years	104	19.3	15.2–24.2
≥ 12 years	225	40.9	34.3–47.9
Family income (n=554)			
≤3 minimum wage	203	37.1	32.0–42.6
>3 and ≤5 minimum wages	113	17.6	13.4–22.7
≥5 minimum wages	238	45.3	38.9–51.9
Alcohol consumption			

No	332	56.4	50.0–62.6
Yes	242	43.6	37.4–50.0
Leisure-time PA (n=573)			
Inactive	311	53.2	47.8–58.4
Insufficiently active ≤150 min/week	100	18.2	14.9–22.0
Active >150 min/week	162	28.7	23.6–34.3
Number of medical comorbidities			
None	35	6.0	4.0–8.7
1 comorbidity	98	18.4	14.7–22.8
2 or more comorbidities	441	75.6	71.2–79.6
%Fat (n=571)			
Tercile 1 (5 to 33.2%)	191	33.4	29.7–37.4
Tercile 2 (33.6 to 41.7%)	190	33.3	29.5–37.3
Tercile 3 (41.9 to 57.8%)	190	33.3	29.5–37.3
Antidepressant use			
No	494	86.3	83.1–89.1
Yes	80	13.7	10.9–16.9
25(OH)D in quartiles			
Quartile 1 (4 to 20.6 ng/ml)	144	25.1	21.7–28.8
Quartile 2 (20.7 to 26.5 ng/ml)	144	25.1	21.7–28.8
Quartile 3 (26.6 to 32 ng/ml)	147	25.6	22.2–29.4
Quartile 4 (32.1 a 50 ng/ml)	139	24.2	20.1–27.9
Change in GDS (n=386)			
Low severity in wave 3 (≤ 5 points)	322	82.4	76.2–87.3
Severity in wave 3 (≥ 6 points)	64	17.6	12.7–23.8

N, number of participants; 95%CI, 95% of confidence interval; PA, physical activity; %Fat, fat body percentage; 25(OH)D, 25-hydroxycholecalciferol concentration; GDS, Geriatric Depression Scale.

In the crude analysis (**Table 2**), those in the lowest quartile of 25(OH)D (4 to 20.6 ng/ml) presented higher risk (OR = 3.40, 95%CI: 1.34–8.62) to have severity of depressive symptoms (≥ 6 points) in wave 3 compared to those in the highest quartile (32.1 a 50 ng/ml). The same was observed in the adjusted analysis (OR = 2.90, 95%CI: 1.14–7.34).

Table 2. Associations between 25(OH)D and change in depressive symptoms over 3 to 5-years follow-up in the older adults from EpiFloripa Aging Cohort Study (2013-2019).

25(OH)D in quartiles	**Crude**			**Adjusted***		
	OR	95%CI	p	OR	95%CI	p
Q4 (32.1 a 50 ng/ml)	1	-	-	1	-	-
Q3 (26.6 to 32 ng/ml)	0.87	0.32–2.33	0.788	0.84	0.31–2.37	0.727
Q2 (20.7 to 26.5 ng/ml)	1.76	0.63–4.90	0.276	1.77	0.51–6.10	0.361
Q1 (4 to 20.6 ng/ml)	3.40	1.34–8.62	0.011	2.90	1.14–7.34	0.025

Adjusted by sex, age, income, alcohol use, multimorbidity, body fat percentage, leisure-time physical activity, and antidepressant. GDS, Geriatric Depressive Scale; Q, quartile; OR, odds ratio;

4. Discussion

In this study, our results showed that 17.6% of the older adults presented severity in depressive symptoms in wave 3. The analysis revealed that those with lower levels of vitamin D (Quartile 1: 4 to 20.6 ng/ml) were more likely to present severity in depressive symptoms evaluated by GDS-15 over 3 to 5-year follow-up, even after controlling for covariates.

Few studies carried out with only older adults (≥60 years) have been developed [16–21]. The results of this study are in line with two previous studies. One study from the United States, in that the cut-off points are similar and the participants with <20ng/mL were at greater risk of developing depression (HR= 1.65; 95%CI:1.23–2.22) over 4 years of follow-up compared with those with ≥30ng/mL[20]. And another study from Italy, using the same cut-off point of <50 nmol/L (<20 ng/mL), however comparing to those ≥50 nmol/L (≥20 ng/mL), only women presented a high risk to develop a depressive mood in follow-up (women: HR= 2.0; 95% CI: 1.2–3.2)[21]. The studies that did not find a longitudinal association were carried out only with depressed older adults[16]; or have stratified the analysis by sex[18]; or carried out the analysis with men only and just found a cross-sectional association[17,19]. We also found in our sample a cross-sectional association between low levels of vitamin D and depressive symptoms[44].

Previous studies have mixed older adults and adults in the analyses in both cross-sectional and longitudinal studies on the association between vitamin D and depressive/symptoms depression[1]. However, it is known that older adults are in a distinct life cycle due to the aging process being associated with a reduced ability to sustain homeostasis, which could make them more susceptible to pathological alterations, including low circulating levels of vitamin D and neuropsychiatric disorders[45,46]. Women in menopausal transition present a higher risk of experiencing

depressive symptoms due to a lot of changes (i.e. stressful events in life, hormone fluctuations)[47]. Moreover, older adults with depression present a higher risk of mortality[4], especially in low- and middle-income countries, where that are low treatment access and more undiagnosed cases[48,49].

An interesting point is that from the second wave, the prevalence of low levels in the smallest quartile (Q1, ≤ 20.6 ng/ml) was 25.1%, however only 6.0% of this sample reported the use of vitamin D supplements, from the third wave only 8.5% reported the use of vitamin D supplements (data not shown). Although we did not measure the 25(OH)D in the third wave and the half-life stability in the blood is short (15 ~ 25 days)[50], the vitamin D deficiency (≤ 20ng/ml) is common a highly prevalent in this population[3,51], and we could assume that it can reflect inadequate levels in this sample and just a small part was treated.

Vitamin D adequate levels is not only important to bone health in older adults, but also have been related to a lot of functions due to the spread presence of its receptors and enzymes responsible to its conversion in a lot of other tissues, organs and systems [15,52–54]. It is known that depression is a complex disease, that could be triggered to a lot of mechanisms, and since preclinical studies have been demonstrating some ways that vitamin D could be linked to depression[1,11], it's important to keep adequate levels.

A possible limitation can be due to the clinical and biochemical examinations conducted at the university, which could select individuals with relatively better health conditions than those from the general population. Due to the logistics of data collection of blood samples were not collected at the same time as the interview and were not able to be repeated in wave 3 which can limit the options of analysis. Although we use a technique certified by the CDC/VDSCP for a total of 25-hydroxyvitamin D assays to measure the 25(OH)D, it is wise to consider that it has differences from the gold standard [55].

As for the strengths of this study, we considered that the sample includes only the older adults since it is a population at risk for low levels of vitamin D and is quite different considering metabolic changes and aspects of the life cycle. The study followed a highly accurate method for quality of the data including trained and supervised interviewers, conducting a face-to-face interview, and quality control of the interviews, and a recommended way to define the minimum set of variables and reduce bias using DAG.

In conclusion, this study supports the hypothesis of a prospective association between lower vitamin D and the severity of depressive symptoms in older adults. Those with lower 25(OH)D are likely to have higher severity of depressive symptoms over 3 to 5-year follow-up. It is known that depression is a complex and multifactorial disorder, and the vitamin D can be involved in some psychopathological ways according to the background at this point. Also is important to plan actions to prevent and treat lower levels of 25(OH)D in the older adult population that still prevalent and is also important to prevent bone issues.

Acknowledgments

We would like to thank the Florianopolis Health Authority staff for their help with the practical aspects of the study.

Funding

This study was supported by partnerships established with the UFSC and assistance from students and teachers involved in this research. All the infrastructure and instruments needed to carry out the research were made available by the UFSC, except for the netbooks used for data collection that was provided by the Oswaldo Cruz Foundation, Rio de Janeiro. The process of collecting clinical and laboratory examinations was financed by the *Conselho Nacional de Desenvolvimento Científico e Tecnológico* (process number 475.904/2013-3) and developed within the scope of the Postgraduate Program in Collective Health at UFSC. Wave 3 was supported by the Economic and Social Research Council (ESRC/UK) (contract ESRC-UK/UFSC/FAPEU 75/2017). Gilciane Ceolin has received research support from *Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES/Brazil)* Finance Code 001.

Disclosure

The authors declare that don’t have any conflict of interest.

References

1 Ceolin G, Antunes L da C, Moretti M, Rieger DK, Moreira JD. VITAMIN D AND DEPRESSION IN OLDER ADULTS: LESSONS LEARNED FROM

OBSERVATIONAL AND CLINICAL STUDIES. Nutrition Research Reviews. 2022:1–63.

2 Hu T, Zhao X, Wu M, Li Z, Luo L, Yang C, et al. Prevalence of depression in older adults: A systematic review and meta-analysis. Psychiatry Research. 2022;311:114511.

3 Palacios C, Gonzalez L. Is vitamin D deficiency a major global public health problem? The Journal of Steroid Biochemistry and Molecular Biology. 2014;144 Pt A:138–45.

4 Brandão DJ, Fontenelle LF, da Silva SA, Menezes PR, Pastor-Valero M. Depression and excess mortality in the elderly living in low- and middle-income countries: Systematic review and meta-analysis. International Journal of Geriatric Psychiatry. 2019;34:22–30.

5 James SL, Abate D, Abate KH, Abay SM, Abbafati C, Abbasi N, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. The Lancet. 2018;392:1789–858.

6 Soysal P, Veronese N, Thompson T, Kahl KG, Fernandes BS, Prina AM, et al. Relationship between depression and frailty in older adults: A systematic review and meta-analysis. Ageing Res Rev. 2017;36:78–87.

7 Dudenkov DV, Mara KC, Petterson TM, Maxson JA, Thacher TD. Serum 25-Hydroxyvitamin D Values and Risk of All-Cause and Cause-Specific Mortality: A Population-Based Cohort Study. Mayo Clin Proc. 2018;93:721–30.

8 Marcos-Pérez D, Sánchez-Flores M, Proietti S, Bonassi S, Costa S, Teixeira JP, et al. Low Vitamin D Levels and Frailty Status in Older Adults: A Systematic Review and Meta-Analysis. Nutrients. 2020;12:2286.

9 Kaltenboeck A, Harmer C. The neuroscience of depressive disorders: A brief review of the past and some considerations about the future. Brain and Neuroscience Advances. 2018;2:2398212818799269.

10 Otte C, Gold SM, Penninx BW, Pariante CM, Etkin A, Fava M, et al. Major depressive disorder. Nature Reviews Disease Primers. 2016;2:1–20.

11 Berridge MJ. Vitamin D and Depression: Cellular and Regulatory Mechanisms. Pharmacol Rev. 2017;69:80–92.

12 Kesby JP, Eyles DW, Burne THJ, McGrath JJ. The effects of vitamin D on brain development and adult brain function. Molecular and Cellular Endocrinology. 2011;347:121–7.

13 Mayne PE, Burne THJ. Vitamin D in Synaptic Plasticity, Cognitive Function, and Neuropsychiatric Illness. Trends in Neurosciences. 2019;42:293–306.
14 Smaga I, Niedzielska E, Gawlik M, Moniczewski A, Krzek J, Przegaliński E, et al. Oxidative stress as an etiological factor and a potential treatment target of psychiatric disorders. Part 2. Depression, anxiety, schizophrenia and autism. Pharmacol Rep. 2015;67:569–80.
15 Landel V, Stephan D, Cui X, Eyles D, Feron F. Differential expression of vitamin D-associated enzymes and receptors in brain cell subtypes. The Journal of Steroid Biochemistry and Molecular Biology. 2018;177:129–34.
16 van den Berg KS, Marijnissen RM, van den Brink RHS, Naarding P, Comijs HC, Oude Voshaar RC. Vitamin D deficiency, depression course and mortality: Longitudinal results from the Netherlands Study on Depression in Older persons (NESDO). J Psychosom Res. 2016;83:50–6.
17 Almeida OP, Hankey GJ, Yeap BB, Golledge J, Flicker L. Vitamin D concentration and its association with past, current and future depression in older men: The Health In Men Study. Maturitas. 2015;81:36–41.
18 Toffanello ED, Sergi G, Veronese N, Perissinotto E, Zambon S, Coin A, et al. Serum 25-hydroxyvitamin d and the onset of late-life depressive mood in older men and women: the Pro.V.A. study. J Gerontol A Biol Sci Med Sci. 2014;69:1554–61.
19 Chan R, Chan D, Woo J, Ohlsson C, Mellström D, Kwok T, et al. Association between serum 25-hydroxyvitamin D and psychological health in older Chinese men in a cohort study. Journal of Affective Disorders. 2011;130:251–9.
20 Williams JA, Sink KM, Tooze JA, Atkinson HH, Cauley JA, Yaffe K, et al. Low 25-Hydroxyvitamin D Concentrations Predict Incident Depression in Well-Functioning Older Adults: The Health, Aging, and Body Composition Study. J Gerontol A Biol Sci Med Sci. 2015;70:757–63.
21 Milaneschi Y, Shardell M, Corsi AM, Vazzana R, Bandinelli S, Guralnik JM, et al. Serum 25-Hydroxyvitamin D and Depressive Symptoms in Older Women and Men. J Clin Endocrinol Metab. 2010;95:3225–33.
22 Cashman KD, Sheehy T, O'Neill CM. Is vitamin D deficiency a public health concern for low middle income countries? A systematic literature review. Eur J Nutr. 2019;58:433–53.

23 Patel V, Burns JK, Dhingra M, Tarver L, Kohrt BA, Lund C. Income inequality and depression: a systematic review and meta-analysis of the association and a scoping review of mechanisms. World Psychiatry. 2018;17:76–89.
24 Schneider IJC, Confortin SC, Bernardo C de O, Bolsoni CC, Antes DL, Pereira KG, et al. EpiFloripa Aging cohort study: methods, operational aspects, and follow-up strategies. Revista de Saúde Pública. 2017;51.
25 Confortin SC, Schneider IJC, Danielewicz AL, Fassula AS, Souza BB de, Santos CES dos, et al. Estudo Longitudinal EpiFloripa Idoso – Rotinas de organização e protocolos referentes à coleta, análise e armazenamento de material biológico, exames de imagem e capacidade físico-funcional. Cadernos Saúde Coletiva. 2019;27:210–24.
26 Ersfeld DL, Rao DS, Body J-J, Sackrison JL, Miller AB, Parikh N, et al. Analytical and clinical validation of the 25 OH vitamin D assay for the LIAISON® automated analyzer. Clinical Biochemistry. 2004;37:867–74.
27 Centers for Disease Control and Prevention. Laboratory Quality Assurance and Standardization Programs. 2021. Available at https://www.cdc.gov/labstandards/hs_certified_participants.html Accessed March 8, 2021.
28 BRASIL. Ministério da Saúde. CADERNOS DE ATENÇÃO BÁSICA 19 - Envelhecimento e saúde da pessoa idosa. DF: Mnistério da Saúde; 2006.
29 World Health Organization. International Statistical Classification of Diseases and Related Health Problems - ICD-10. 1990. Available at https://icd.who.int/browse10/2019/en#/ Accessed June 8, 2022.
30 Guze SB. Diagnostic and Statistical Manual of Mental Disorders, 4th ed. (DSM-IV). AJP. 1995;152:1228–1228.
31 Almeida OP, Almeida SA. Short versions of the geriatric depression scale: a study of their validity for the diagnosis of a major depressive episode according to ICD-10 and DSM-IV. Int J Geriat Psychiatry. 1999;14:858–65.
32 Almeida OP, Almeida SA. Reliability of the Brazilian version of the Geriatric Depression Scale (GDS) short form. Arquivos de Neuro-Psiquiatria. 1999;57:421–6.
33 Paradela EMP, Lourenço RA, Veras RP. Validation of geriatric depression scale in a general outpatient clinic. Revista de Saúde Pública. 2005;39:918–23.
34 Textor J, van der Zander B, Gilthorpe MS, Liśkiewicz M, Ellison GTH. Robust causal inference using directed acyclic graphs: the R package 'dagitty.' Int J Epidemiol. 2017:dyw341.

35 Shrier I, Platt RW. Reducing bias through directed acyclic graphs. BMC Med Res Methodol. 2008;8:70.
36 Hernán MA, Robins JM. Causal Inference: What If. Chapman & Hall/CRC; 2020.
37 Babor TF, Higgins-Biddle JC, Saunders JB, Monteiro MG. The alcohol use disorders identification test: guidelines for use in primary care. 2001:41.
38 Benedetti TB, Mazo GZ, Barros MVG de. Application of the International Physical Activity Questionnaire (IPAQ) for evaluation of elderly women: concurrent validity and test-retest reprodutibility. Rev bras ciênc mov. 2004;12:25–34.
39 Benedetti TRB, Antunes P de C, Rodriguez-Añez CR, Mazo GZ, Petroski ÉL. Reproducibility and validity of the International Physical Activity Questionnaire (IPAQ) in elderly men. Revista Brasileira de Medicina Do Esporte. 2007;13:11–6.
40 Genton L, Hans D, Kyle UG, Pichard C. Dual-Energy X-ray absorptiometry and body composition: differences between devices and comparison with reference methods. Nutrition. 2002;18:66–70.
41 World Health Organization. WHOCC - ATC/DDD Index. 2022. Available at https://www.whocc.no/atc_ddd_index/ Accessed December 20, 2019.
42 Faul F, Erdfelder E, Lang A-G, Buchner A. G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav Res Methods. 2007;39:175–91.
43 The World Medical Association. Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects. 2013.
44 Ceolin G, Matsuo LH, Confortin SC, D'Orsi E, Rieger DK, Moreira JD. Lower serum 25-hydroxycholecalciferol is associated with depressive symptoms in older adults in Southern Brazil. Nutrition Journal. 2020;19:123.
45 Sibille E. Molecular aging of the brain, neuroplasticity, and vulnerability to depression and other brain-related disorders. Dialogues Clin Neurosci. 2013;15:53–65.
46 Pomatto LCD, Davies KJA. The role of declining adaptive homeostasis in ageing. The Journal of Physiology. 2017;595:7275–309.
47 Soares CN, Shea AK. The Midlife Transition, Depression, and Its Clinical Management. Obstetrics and Gynecology Clinics of North America. 2021;48:215–29.
48 World Health Organization. Depression. 2020. Available at https://www.who.int/news-room/fact-sheets/detail/depression Accessed February 13, 2020.

49 Lopes CS, Hellwig N, e Silva G de A, Menezes PR. Inequities in access to depression treatment: results of the Brazilian National Health Survey – PNS. Int J Equity Health. 2016;15:154.
50 Altieri B, Cavalier E, Bhattoa HP, Pérez-López FR, López-Baena MT, Pérez-Roncero GR, et al. Vitamin D testing: advantages and limits of the current assays. European Journal of Clinical Nutrition. 2020;74:231–47.
51 Pereira-Santos M, Santos JYG dos, Carvalho GQ, Santos DB dos, Oliveira AM. Epidemiology of vitamin D insufficiency and deficiency in a population in a sunny country: Geospatial meta-analysis in Brazil. Critical Reviews in Food Science and Nutrition. 2019;59:2102–9.
52 Abbas MA. Physiological functions of Vitamin D in adipose tissue. The Journal of Steroid Biochemistry and Molecular Biology. 2017;165:369–81.
53 Boyan BD, Chen J, Schwartz Z. Mechanism of Pdia3-dependent 1α,25-dihydroxy vitamin D3 signaling in musculoskeletal cells. Steroids. 2012;77:892–6.
54 Bouillon R, Carmeliet G, Verlinden L, van Etten E, Verstuyf A, Luderer HF, et al. Vitamin D and Human Health: Lessons from Vitamin D Receptor Null Mice. Endocr Rev. 2008;29:726–76.
55 Elsenberg EHAM, ten Boekel E, Huijgen H, Heijboer AC. Standardization of automated 25-hydroxyvitamin D assays: How successful is it? Clinical Biochemistry. 2017;50:1126–30.

4.3.1 Artigo 7

ASSOCIATION BETWEEN ADIPOSITY AND EMERGENT DEPRESSIVE SYMPTOMS IN A 10-YEARS COHORT OF OLDER ADULTS: THE EPIFLORIPA AGING STUDY

Gilciane Ceolin[1,2], Vitor Breda[2,3], Bruna Cunha Mendes[1], Fabiano Alves Gomes[2,3], Rodrigo Barbachan Mansur[4], Eleonora d'Orsi[5], Débora Kurrle Rieger[6], Júlia Dubois Moreira[6], Elisa Brietzke[2,3]

1. Postgraduate Program in Nutrition, Universidade Federal de Santa Catarina, Florianopolis, SC, Brazil.
2. Centre for Neuroscience Studies (CNS), Queen's University, Kingston, ON, Canada.
3. Department of Psychiatry, Queen's University School of Medicine, Kingston, ON, Canada.
4. Mood Disorders Psychopharmacology Unit, University Health Network, Toronto, Ontario, Canada. Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada.
5. Department of Public Health, Universidade Federal de Santa Catarina, Florianopolis, SC, Brazil.
6. Department of Nutrition, Universidade Federal de Santa Catarina, Brazil.

Highlights

- Older adults present a stability in the probability to change their BMI over 10 years
- Obesity had a high incident rate ratio to increase depressive symptoms over 10 years
- Association between body mass index and depressive symptoms followed a U-shaped curve
- Association between waist circumference and depressive symptoms followed a J-shaped curve

Abstract

Background: The association between obesity and depressive symptoms has been described in the literature, but there is a scarcity of longitudinal data. This study aimed to verify the association between body mass index (BMI) and waist circumference and the incidence of depressive symptoms over a 10-years follow-up in a cohort of older adults.

Methods: Data from the first (2009-2010), second (2013-2014), and third (2017-2019) waves of the EpiFloripa Aging Cohort Study were used. Depressive symptoms were assessed by the 15-items Geriatric Depression Scale (GDS-15). The Generalized Estimating Equations model was used to estimate the longitudinal association between BMI and waist circumference and depressive symptoms across a 10-years follow-up.

Results: The incidence of depressive symptoms (N= 580) was 9.9%. The relationship between BMI and incidence of depressive symptoms in older adults followed a U-shaped curve. Older adults with obesity had an incidence relative ratio of 76% (IRR=1.24, p=0.035) for increasing the score of depressive symptoms after 10 years, compared to those with overweight. The higher category of waist circumference (Male: ≥102; Female: ≥88 cm) was associated with depressive symptoms (IRR=1.09, p=0.033), only in a non-adjusted analysis.

Limitations: Relatively high follow-up dropout rate; Few individuals in the underweight BMI category; BMI must be considered with caution, because it does not measure only adiposity.

Conclusions: Obesity was associated with the incidence of depressive symptoms when compared with overweight in older adults.

Keywords: Depressive Symptoms; Longitudinal Studies; Aging; Adiposity.

1. Introduction

Major Depressive Disorder (MDD) in older adults is a common condition, with a recent meta-analysis estimating a worldwide prevalence of 31.7% and even higher rates in developing countries (40.8% *vs* 17.1% in developed countries)[1]. In this age group, MDD is associated with an increased risk of frailty, cognitive decline, disabilities, and mortality[2–5]. From a biological perspective, aging has been defined as a result of the impact of the accumulation of a wide variety of molecular and cellular damage over time[6]. This accumulated damage can lead to a gradual decrease in physical and mental capacity, and an increase in fat mass[7,8].

Depression is a multifactorial disorder, but the pathophysiology of MDD in the elderly has been linked to the impact of aging processes in brain structures and functions through mechanisms such as neurotransmitter levels and neuroendocrine systems[9,10]. A reduction in dopaminergic transmission, the presence of a persistent low-grade inflammation, oxidative stress imbalances, and reduced mitochondrial functioning are some age-related factors that have been associated with depression[11].

Aging has also been associated with changes in body composition, especially a decrease in lean mass and bone density, and an increase in fat mass[7,8]. Interestingly, the medical literature indicates that obesity and MDD are intrinsically linked and share some clinical, neurobiological, genetic, and environmental factors[12]. Most studies support a bidirectional association between body mass index (BMI) and depressive symptoms in adults and in the elderly[13,14], especially for the melancholic and atypical subtypes[15,16]. However, most evidence on this topic comes from cross-sectional observations, which do not inform about the temporal sequence of factors. Only a few longitudinal studies investigated both the effect of BMI and/or waist circumference on the incidence of depressive symptoms/MDD in older adults. Preliminary findings have indicated an increased risk of developing depression in those with both obesity and underweight, and lower risk in those with overweight, especially women[17–24]. Furthermore, there is a lack of data on low-income populations, which are known to have a higher risk for both obesity and depression[25–27].

This study aimed to investigate the longitudinal association between BMI and waist circumference, with the incidence of depressive symptoms over 10 years of follow-up in a population and home-based cohort of older adults.

2. Materials & Methods

Design, sample, and data collection

This longitudinal post-hoc analysis was carried out with data from the 10-year follow-up of the "Conditions of the Health of the Older Adults in the Florianopolis - EpiFloripa Aging Cohort Study", which is a population-based, home-based, longitudinal cohort study with a representative sample of Florianopolis. The details of the design, methods, and sample were described elsewhere[28]. Briefly, the inclusion criteria at baseline were males and females aged ≥60 years and living in an urban area in the city of Florianopolis/SC, in southern Brazil; those living in long-term care institutions, hospitals, and prisons were excluded[28]. Data collection was carried out by trained interviewers through face-to-face interviews at participants' homes using a structured questionnaire on a laptop. The consistency analysis and quality control of the study was carried out by telephone through a reduced questionnaire version applied to 10% of randomly selected participants.

For this specific analysis to estimate the incidence of depressive symptoms, individuals who already had significant depressive symptoms at baseline, operationalized

by a GDS-15 score ≥ 6, were excluded (N=401). Individuals taking antidepressants for other indications (e.g.: pain, sleep, appetite) were included in the sample if their GDS-15 score was below 6. All older adults who participated in the baseline study (2009-2010, N=1,234) and collected data in the second wave (2013-2014, N=877) were invited to participate in the third wave of the study (2017-2019, N=583). We used repeated measures from the three periods (Figure 1).

Measurements

Body Mass Index

The BMI was calculated to assess nutritional status[29] according to the World Health Organization (WHO): Underweight <18.5 kg/m², Normal weight 18.5-24.9 kg/m², Overweight 25-29.9 kg/m², and Obesity ≥30 kg/m²[30]. Anthropometric data were measured by a portable stadiometer and a digital scale with a resolution of 100 grams[28].

Waist circumference

Waist circumference was measured using a flexible and inelastic measuring tape with a resolution of 1 mm (total of 160 cm). The measurement was undertaken at the narrowest part of the trunk. For those with a non-apparent waist, the measurement was made at the midpoint between the iliac crest and the lowest rib[29]. Waist circumference was categorized according to the WHO cut-off points to the risk of metabolic complications and according to sex (M: male, F: female): normal M: <94, F: <80; increased M: 94-101, F: 80-87; substantially increased M: ≥102 F: ≥88[30].

Presence and Severity of depressive symptoms

The GDS-15 was used to evaluate the presence and severity of depressive symptoms. The GDS-15 is recommended by the Brazilian Ministry of Health[31] as a useful alternative for the rapid assessment of depressive symptoms in the elderly in primary health care centers. The GDS-15 was translated to Portuguese and validated in Brazil according to the International Classification of Diseases (ICD-10)[32] criteria for research and the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)[33] with outpatients aged 60 or over who met criteria for depressive disorder (current or in remission)[34,35].

We used cut-off points as suggested by Almeida and Almeida, to categorize the sample into two groups: individuals with significant depressive symptoms severity (≥ 6

points) and those without significant depressive symptoms severity (≤ 5 points)[34,36]. This cut-off points produced a sensitivity of 85.4% and a specificity of 73.9% according to ICD-10, and 90.9% of sensitivity and 64.5% of specificity according to the DSM-IV. The internal consistency as assessed by Cronbach's alpha revealed a reliability coefficient of 0.81[35]. In the test-retest reliability, when the outpatient was evaluated for the second time 48 to 72 hours after the first assessment, the GDS-15 scores were reasonably stable, as assessed by paired Wilcoxon (z=1.60, p=0.109) and Spearman's correlation coefficients (rho=0.86, p<0.001), and Cohen's weighted kappa (kappa=0.64)[35].

Statistics

Selection of Covariates

A directed acyclic graph (DAG, or causal Bayesian networks) was constructed to represent the theoretical model and elucidate the involvement of covariates in the longitudinal association between BMI and depressive symptoms (Figure S1, supplementary material), and between waist circumference and depressive symptoms (Figure S2, supplementary material). The DAG was built using DAGitty software (version 3.0; Nijmegen, GE, The Netherlands)[37]. The graphical criteria for selecting the adjusted covariates were used to define the minimum set of covariates and reduce variable selection bias[38,39].

The covariates suggested by the DAG were sex (observed by the interviewer: male/female); age (in years, 60-69, 70-79, ≥80); family income (in minimum wages classified as ≤ 3, 4 and 5, and ≥ 6, based on one minimum wage at the interview time as wave 1: R$465 in 2009, R$510 in 2010; wave 2: R$678,00 in 2013, R$724,00 in 2014; wave 3: R$937,00 in 2017, R$954,00 in 2018, and R$998,00 in 2019); alcohol consumption (no/yes, assessed through the Alcohol Use Disorder Identification Test)[40]; leisure-time physical activity (assessed by the International Physical Activity Questionnaire, classified as insufficiently active <150 min; and active ≥150 min)[41,42]; and the number of medical comorbidities (sum of diagnosed medical conditions: spine or back disorders, arthritis, cancer, diabetes, bronchitis, cardiovascular disease, renal disease, tuberculosis, cirrhosis, stroke, osteoporosis, hypertension, and depression).

Information about antidepressant use was collected by consulting prescription sheets and vials/bottles of medications prescribed for the participant. The Anatomical Therapeutic Chemical Classification codes from the World Health Organization

Collaborating Centre for Drug Statistic Methodology were applied for codification in the database[43].

Analysis

The analysis was performed using Stata 14.0 software (StataCorp, College Station, TX, USA), considering the sample weights. Descriptive analysis of the data was presented as absolute and relative frequency, prevalence, and respective 95% confidence intervals (CI) for the total sample based on the incidence of depressive symptoms. The distribution of the covariates was determined by Pearson's chi-squared and Fisher's exact tests with a level of significance of 5%. We estimated the transition probabilities in BMI over time using the "*xttrans*" Stata command.

A longitudinal analysis model with Generalized Estimating Equations was used to estimate the effect of BMI on depressive symptoms across the ten-year follow-up using repeated measures from the three periods. The time was considered as a variable, and the database was changed from "wide" to "long" to permit analysis of within-subject missing data. The command "*reshape*" was used to change the dataset to the "long" format indicating the identification variable as a key variable and "wave" as a time variable. The command "*xtgee*" was used to analyze the data using the Poisson family since our outcome has a Poisson distribution and is a countable variable. Two models were analyzed: raw or adjusted to covariates. The incident rate ratios (IRR) were obtained by the command "*eform*" with the respective 95% confidence intervals (95%CI) considering a level of significance of < 0.05. The category of BMI of 25 to 29.9 kg/m^2 was used as the reference category.

Ethical procedures

The EpiFloripa Aging cohort study protocol complied with the principles from the National Health Council and the Declaration of Helsinki[45]. The EpiFloripa Aging Cohort Study was approved by the Human Research Ethics Committee of the *Universidade Federal de Santa Catarina* (approval numbers 352/2008 and 1.957.977). After the explanation of study objectives and collection procedures, all participants voluntarily agreed to participate and to be interviewed at home, and all participants provided written informed consent.

3. Results

Table 1 shows participants' characteristics in waves 1 and 3, and the incidence of depressive symptoms. The incidence of significant depressive symptoms was 9.9%. We observed a higher proportion of female in the baseline (62.5%) and follow-up (65.7%). In wave 3, the incidence of GDS score ≥6 (n=54) was higher in female (11.3%). Most participants in both baseline and follow-up were overweight or had obesity and substantially increased waist circumference. In wave 3, those with incident depressive symptoms presented higher proportion in the age range of ≥ 80 years (13.9%); had 2 or more medical comorbidities (12.0%); were not taking antidepressants (24.0%) (all $P<0.05$).

Table 2 presents the transitions in the BMI categories over time. The probability of remaining in the same BMI category, over a ten-year follow-up was 77.0% for those with obesity, 82.1% for overweight, and 76.2% for normal weight. Those with obesity had probabilities of 10.5% and 12.2% to become overweight and normal weight over time, respectively. Those with overweight had probability of 17.4% to become obesity. Those with normal weight had a probability of 20.2 % of becoming obesity.

Analysis by sex showed that male with overweight had a higher probability to turn obesity when compared to female. Female with obesity had a higher probability to becoming overweight and normal weight when compared to male. Both male and female in the normal weight category had a similar probability of becoming obesity. Regarding waist circumference (Table S1, supplementary material), the only category stable was the higher waist circumference with a probability of 86.2% of remaining in the same category. Of those in the intermediate category, 18% decreased and 40.2% increased their waist circumference.

The crude and adjusted analysis of the association between BMI and incidence of depressive symptoms over ten years of follow-up are shown in Table 3 and Figure 2. The crude analysis showed that compared with those in the 25-29.9 kg/m^2 category, those with BMI in all categories presented a risk to present a higher score of depressive symptoms, following a discrete U-shaped curve (Figure 2). However, the statistically difference was observed only in those with obesity (≥30 kg/m^2). The finding remained the same when adjusted for covariates, representing an incidence relative ratio of 76% for an increased score of depressive symptoms after 10 years.

4. Discussion

Taken together the results of this study expand the knowledge on the relationship between BMI and geriatric depression using longitudinal data from a home-based sample. In our study, the incidence of significant depressive symptoms was 9.9%. Most individuals had overweight or obesity at baseline, and the probability of changes in BMI categories in older adults was low over the ten-year follow-up. Our results suggest that the association between BMI and incident depressive symptoms in older adults follows a U-shaped curve with obesity representing the higher relative risk compared to those overweight (Figure 2). After controlling for socio-demographic, behavioral and health variables, the relative risk of 76% for an increased score of depressive symptoms in 10 years to those with obesity. Regarding waist circumference, those with ≥102cm for male and ≥88cm for female, had a higher relative risk when compared with those with 94-101cm for male and 80-87 cm for female, which, however, was not significant after controlling for socio-demographic, behavioral and health variables.

Our results are partially in line with evidence from other geographic regions supporting a complex association between higher BMI and risk for geriatric depression [18–21,23,24]. However the studies used the regular cut-off point as the reference to analysis, and did find that those with obesity was likely to have depression in follow-up[19,24], and also some find that those with obesity were likely to have depression[17,22]. Interestingly, a study conducted with waist circumference, over 5 years observed that middle- and older-aged men with waist circumference ≥85 cm were less likely to develop depressive symptoms than those classified as having <85 cm (HR = 0.775; 95%CI = 0.64-0.93)[22]. A meta-analysis showed in a subgroup analysis with longitudinal studies (n=3), a protective effect of overweight/obesity on depression compared with normal weight, however was not significantly different, just in the pooled analysis (cross-sectional + longitudinal) odds ratio of 0.85 (95%CI=0.79-0.91, P < 0.001) for overweight, and of 0.80 (95%CI=0.66-0.96, P = 0.017) for obesity[46], what happened with our data to those with overweight, when we changed the cut-off point to normal as reference, however without statistically significance (data not shown).

A possible reason for this apparent protective effect of overweight could be the underestimation of adiposity by BMI measures in older adults, which suggests that a possible change in the cut-off point for the ideal BMI in this population (i.e.: 23–29 kg/m^2) might be appropriate[44]. Furthermore, this was the motivation to use a BMI cut-off point of overweight as a reference in our analysis. It is known that fat body composition is not fully captured by BMI and changes in their parameters are expected

to change with aging, such as a decrease in lean and an increase in fat mass, and muscle fat infiltration[47]. Regarding the increased risk for depression in those with low BMI, other studies have also found an association between being underweight and the presence of depression or depressive symptoms severity in the elderly[21,48]. A possible explanation is that changes in appetite, lifestyle, and other health factors (e.g.: alcohol consumption, presence of chronic diseases) are related to both low weight and depression[49].

Our data suggest the existence of a U-shaped curve for the relationship between BMI categories and depressive symptoms and a J-shaped curve for the relationship between waist circumference and depression. These findings are in line with previous studies that pointed towards a higher BMI cut-off point to be healthier in older adults, showing both a U-shaped curve to BMI, and a J-shaped curve to waist circumference, where the extreme categories were associated with increased risk of frailty and mortality[50–52]. Our results also indicate that age range, alcohol use, number of comorbidities, and antidepressant use were associated with incident depressive symptoms in the follow-up. These findings are consistent with a growing body of evidence describing advanced age, number of comorbidities, and alcohol consumption, especially in men, as risk factors for depression in older adults[1,53].

The results of this study should be considered in light of some limitations. First, the dropout rate due to losses over the ten years of follow-up may have affected the association between the low BMI category and depressive symptoms, due to a lower final number of individuals in this category compared to the other categories. Second, BMI is limited in assessing obesity, as shown above, because it represents a combined measure of fat with other tissues, like bone and muscles, but is easily obtainable, especially for clinical practice. Finally, in this study we included the current antidepressant use in the baseline as a covariate instead of excluding those individuals. Regarding use of antidepressants, we made the decision to adopt an agnostic approach, not focusing on the reason why the individual was taking them, because these medications are often used in pain control in this population. As for the strengths of this study, we should cite our representative sample of older adults, a distinct population considering metabolic alterations and life cycle aspects; the implementation of adequate methods to guarantee the high quality of the data (trained and supervised interviewers, pilot study, face-to-face interviews, and interview quality control); and finally, the longitudinal design and statistical methods used that allows establishing the temporal relationship with the exposure preceding the outcome.

5. Conclusion

Using overweight BMI as reference category in the analysis revealed that obesity had a higher incidence rate of depressive symptoms in older adults over ten years of follow-up even after adjustments, showing a U-shaped curve of this association. Although not significant after adjustments, we observed a similar pattern of association between waist circumference and depressive symptoms. Future studies should adopt longitudinal designs and include more accurate adiposity measures, such as the dual-energy X-ray absorptiometry, as well as behavioral and biological variables to disentangle the relationship between weight, fitness, metabolic profile, and depressive symptoms across the lifespan.

Contributors

Gilciane Ceolin: Conceptualization, Formal analysis, Investigation, Visualization, Writing - original draft; Writing - review & editing; **Vitor Breda**: Visualization, Writing - review & editing; **Bruna Cunha Mendes**: Writing - review & editing; **Fabiano Alves Gomes**: Writing - review & editing; **Rodrigo Barbachan Mansur**: Formal analysis, Writing - review & editing; **Eleonora d'Orsi**: Funding acquisition; Investigation, Project administration, Resource, Supervision, Writing - review & editing; **Débora Kurrle Rieger**: Supervision, Writing - review & editing; **Júlia Dubois Moreira**: Investigation, Supervision, Writing - review & editing; **Elisa Brietzke**: Formal analysis, Supervision, Writing - review & editing.

Role of the Funding Source

This work was supported by the Brazilian National Council for Scientific and Technological Development (CNPq) (grant number 569834/2008-2); the Economic and Social Research Council (ESRC/UK) (contract ESRC-UK/UFSC/FAPEU 75/2017); Gilciane Ceolin has received research support from Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES/Brazil) Finance Code 001.

Acknowledgements

We would like to thank the Brazilian Institute of Geography and Statistics (IBGE) and the Florianopolis Health Authority staff for their help with the practical aspects of the study.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

1. Zenebe Y, Akele B, W/Selassie M, Necho M. Prevalence and determinants of depression among old age: a systematic review and meta-analysis. *Annals of General Psychiatry*. 2021;20(1):55. doi:10.1186/s12991-021-00375-x

2. Brandão DJ, Fontenelle LF, da Silva SA, Menezes PR, Pastor-Valero M. Depression and excess mortality in the elderly living in low- and middle-income countries: Systematic review and meta-analysis. *International Journal of Geriatric Psychiatry*. 2019;34(1):22-30. doi:10.1002/gps.5008

3. James SL, Abate D, Abate KH, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *The Lancet*. 2018;392(10159):1789-1858. doi:10.1016/S0140-6736(18)32279-7

4. Soysal P, Veronese N, Thompson T, et al. Relationship between depression and frailty in older adults: A systematic review and meta-analysis. *Ageing Res Rev*. 2017;36:78-87. doi:10.1016/j.arr.2017.03.005

5. Zhu Y, Li C, Xie W, Zhong B, Wu Y, Blumenthal JA. Trajectories of depressive symptoms and subsequent cognitive decline in older adults: a pooled analysis of two longitudinal cohorts. *Age Ageing*. 2022;51(1):afab191. doi:10.1093/ageing/afab191

6. World Health Organization. Ageing and health. Published 2021. Accessed June 7, 2022. https://www.who.int/news-room/fact-sheets/detail/ageing-and-health

7. JafariNasabian P, Inglis JE, Reilly W, Kelly OJ, Ilich JZ. Aging human body: changes in bone, muscle and body fat with consequent changes in nutrient intake. *Journal of Endocrinology*. 2017;234(1):R37-R51. doi:10.1530/JOE-16-0603

8. Ponti F, Santoro A, Mercatelli D, et al. Aging and Imaging Assessment of Body Composition: From Fat to Facts. *Front Endocrinol (Lausanne)*. 2020;10. doi:10.3389/fendo.2019.00861

9. Kaltenboeck A, Harmer C. The neuroscience of depressive disorders: A brief review of the past and some considerations about the future. *Brain and Neuroscience Advances*. 2018;2:2398212818799269. doi:10.1177/2398212818799269

10. Otte C, Gold SM, Penninx BW, et al. Major depressive disorder. *Nature Reviews Disease Primers*. 2016;2(1):1-20. doi:10.1038/nrdp.2016.65

11. Rutherford BR, Taylor WD, Brown PJ, Sneed JR, Roose SP. Biological Aging and the Future of Geriatric Psychiatry. *J Gerontol A Biol Sci Med Sci*. 2017;72(3):343-352. doi:10.1093/gerona/glw241

12. Mansur RB, Brietzke E, McIntyre RS. Is there a "metabolic-mood syndrome"? A review of the relationship between obesity and mood disorders. *Neurosci Biobehav Rev*. 2015;52:89-104. doi:10.1016/j.neubiorev.2014.12.017

13. Luppino FS, de Wit LM, Bouvy PF, et al. Overweight, obesity, and depression: a systematic review and meta-analysis of longitudinal studies. *Arch Gen Psychiatry*. 2010;67(3):220-229. doi:10.1001/archgenpsychiatry.2010.2

14. Pan A, Sun Q, Czernichow S, et al. Bidirectional association between depression and obesity in middle-aged and older women. *Int J Obes (Lond)*. 2012;36(4):595-602. doi:10.1038/ijo.2011.111

15. Ottino C, Strippoli MPF, Gholam M, et al. Short-term and long-term effects of major depressive disorder subtypes on obesity markers and impact of sex on these associations. *Journal of Affective Disorders*. 2022;297:570-578. doi:10.1016/j.jad.2021.10.057

16. Silva DA, Coutinho E da SF, Ferriani LO, Viana MC. Depression subtypes and obesity in adults: A systematic review and meta-analysis. *Obes Rev*. 2020;21(3):e12966. doi:10.1111/obr.12966

17. Chang HH, Yen ST. Association between obesity and depression: Evidence from a longitudinal sample of the elderly in Taiwan. *Aging & Mental Health*. 2012;16(2):173-180. doi:10.1080/13607863.2011.605053

18. Dearborn PJ, Robbins MA, Elias MF. Challenging the "jolly fat" hypothesis among older adults: High body mass index predicts increases in depressive symptoms over a 5-year period. *J Health Psychol*. 2018;23(1):48-58. doi:10.1177/1359105316675209

19. Godin O, Elbejjani M, Kaufman JS. Body mass index, blood pressure, and risk of depression in the elderly: a marginal structural model. *Am J Epidemiol*. 2012;176(3):204-213. doi:10.1093/aje/kws003

20. Goes VF, Wazlawik E, D'Orsi E, González-Chica DA. Severe obesity increases the prevalence but not the incidence of depressive symptoms in the elderly-population-based cohort in Southern Brazil. *International Psychogeriatrics*. 2017;29(8):1307-1316. doi:10.1017/S1041610216002246

21. Huang C, Kogure M, Tomata Y, et al. Association of serum adiponectin levels and body mass index with worsening depressive symptoms in elderly individuals: a 10-year longitudinal study. *Aging & Mental Health*. 2020;24(5):725-731. doi:10.1080/13607863.2019.1584877

22. Luo H, Li J, Zhang Q, et al. Obesity and the onset of depressive symptoms among middle-aged and older adults in China: evidence from the CHARLS. *BMC Public Health*. 2018;18:909. doi:10.1186/s12889-018-5834-6

23. Sachs-Ericsson N, Burns AB, Gordon KH, et al. Body Mass Index and Depressive Symptoms in Older Adults: The Moderating Roles of Race, Sex, and Socioeconomic Status. *The American Journal of Geriatric Psychiatry*. 2007;15(9):815-825. doi:10.1097/JGP.0b013e3180a725d6

24. Vogelzangs N, Kritchevsky SB, Beekman AT, et al. Obesity and Onset of Significant Depressive symptoms. *J Clin Psychiatry*. 2010;71(4):391-399. doi:10.4088/JCP.08m04743blu

25. Evans-Lacko S, Aguilar-Gaxiola S, Al-Hamzawi A, et al. Socio-economic variations in the mental health treatment gap for people with anxiety, mood, and substance use disorders: Results from the WHO World Mental Health (WMH) Surveys. *Psychol Med*. 2018;48(9):1560-1571. doi:10.1017/S0033291717003336

26. Kim TJ, von dem Knesebeck O. Income and obesity: what is the direction of the relationship? A systematic review and meta-analysis. *BMJ Open*. 2018;8(1):e019862. doi:10.1136/bmjopen-2017-019862

27. Patel V, Burns JK, Dhingra M, Tarver L, Kohrt BA, Lund C. Income inequality and depression: a systematic review and meta-analysis of the association and a scoping review of mechanisms. *World Psychiatry*. 2018;17(1):76-89. doi:10.1002/wps.20492

28. Schneider IJC, Confortin SC, Bernardo C de O, et al. EpiFloripa Aging cohort study: methods, operational aspects, and follow-up strategies. *Revista de Saúde Pública*. 2017;51. doi:10.11606/s1518-8787.2017051006776

29. Lohmann TG, Roche AF, Martorell R. *Anthropometric Standardization Reference Manual*. Human Kinetics Books, Champaign, Ill.; 1988.

30. World Health Organization. Obesity : preventing and managing the global epidemic : report of a WHO Consultation on Obesity. Published online 1998. Accessed October 18, 2020. https://www.who.int/nutrition/publications/obesity/WHO_TRS_894/en/

31. BRASIL. Ministério da Saúde. *CADERNOS DE ATENÇÃO BÁSICA 19 - Envelhecimento e saúde da pessoa idosa*. Mnistério da Saúde; 2006. http://bvsms.saude.gov.br/bvs/publicacoes/evelhecimento_saude_pessoa_idosa.pdf

32. World Health Organization. International Statistical Classification of Diseases and Related Health Problems - ICD-10. Published 1990. Accessed June 8, 2022. https://icd.who.int/browse10/2019/en#/

33. Guze SB. Diagnostic and Statistical Manual of Mental Disorders, 4th ed. (DSM-IV). *AJP*. 1995;152(8):1228-1228. doi:10.1176/ajp.152.8.1228

34. Almeida OP, Almeida SA. Short versions of the geriatric depression scale: a study of their validity for the diagnosis of a major depressive episode according to ICD-10 and DSM-IV. *Int J Geriat Psychiatry*. 1999;14(10):858-865. doi:10.1002/(SICI)1099-1166(199910)14:10<858::AID-GPS35>3.0.CO;2-8

35. Almeida OP, Almeida SA. Reliability of the Brazilian version of the Geriatric Depression Scale (GDS) short form. *Arquivos de Neuro-Psiquiatria*. 1999;57(2B):421-426. doi:10.1590/S0004-282X1999000300013

36. Paradela EMP, Lourenço RA, Veras RP. Validation of geriatric depression scale in a general outpatient clinic. *Revista de Saúde Pública*. 2005;39(6):918-923. doi:10.1590/S0034-89102005000600008

37. Textor J, van der Zander B, Gilthorpe MS, Liśkiewicz M, Ellison GTH. Robust causal inference using directed acyclic graphs: the R package 'dagitty.' *Int J Epidemiol*. Published online January 15, 2017:dyw341. doi:10.1093/ije/dyw341

38. Hernán MA, Robins JM. *Causal Inference: What If*. Chapman & Hall/CRC; 2020. https://www.hsph.harvard.edu/miguel-hernan/causal-inference-book/

39. Shrier I, Platt RW. Reducing bias through directed acyclic graphs. *BMC Med Res Methodol*. 2008;8(1):70. doi:10.1186/1471-2288-8-70

40. Babor TF, Higgins-Biddle JC, Saunders JB, Monteiro MG. The alcohol use disorders identification test: guidelines for use in primary care. 2001;(2):41.

41. Benedetti TB, Mazo GZ, Barros MVG de. Application of the International Physical Activity Questionnaire (IPAQ) for evaluation of elderly women: concurrent validity and test-retest reprodutibility. *Rev bras ciênc mov*. 2004;12(1):25-34.

42. Benedetti TRB, Antunes P de C, Rodriguez-Añez CR, Mazo GZ, Petroski ÉL. Reproducibility and validity of the International Physical Activity Questionnaire (IPAQ) in elderly men. *Revista Brasileira de Medicina do Esporte*. 2007;13(1):11-16. doi:10.1590/S1517-86922007000100004

43. World Health Organization. WHOCC - ATC/DDD Index. Published 2022. Accessed December 20, 2019. https://www.whocc.no/atc_ddd_index/

44. Ben-Yacov L, Ainembabazi P, Stark AH. Is it time to update body mass index standards in the elderly or embrace measurements of body composition? *Eur J Clin Nutr*. 2017;71(9):1029-1032. doi:10.1038/ejcn.2017.39

45. The World Medical Association. Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects. Published online 2013. Accessed June 21, 2022. https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/

46. Yu M, Shi Y, Gu L, Wang W. "Jolly fat" or "sad fat": a systematic review and meta-analysis of the association between obesity and depression among community-dwelling older adults. *Aging & Mental Health*. 2022;26(1):13-25. doi:10.1080/13607863.2020.1857687

47. García-Esquinas E, José García-García F, León-Muñoz LM, et al. Obesity, fat distribution, and risk of frailty in two population-based cohorts of older adults in Spain. *Obesity*. 2015;23(4):847-855. doi:10.1002/oby.21013

48. Jung SJ, Woo HT, Cho S, et al. Association between body size, weight change and depression: systematic review and meta-analysis. *Br J Psychiatry*. 2017;211(1):14-21. doi:10.1192/bjp.bp.116.186726

49. Geoffroy MC, Li L, Power C. Depressive symptoms and body mass index: co-morbidity and direction of association in a British birth cohort followed over 50 years. *Psychological Medicine*. 2014;44(12):2641-2652. doi:10.1017/S0033291714000142

50. de Hollander EL, Bemelmans WJ, Boshuizen HC, et al. The association between waist circumference and risk of mortality considering body mass index in 65- to 74-year-olds: a meta-analysis of 29 cohorts involving more than 58 000 elderly persons. *International Journal of Epidemiology*. 2012;41(3):805-817. doi:10.1093/ije/dys008

51. Winter JE, MacInnis RJ, Wattanapenpaiboon N, Nowson CA. BMI and all-cause mortality in older adults: a meta-analysis. *Am J Clin Nutr*. 2014;99(4):875-890. doi:10.3945/ajcn.113.068122

52. Yuan L, Chang M, Wang J. Abdominal obesity, body mass index and the risk of frailty in community-dwelling older adults: a systematic review and meta-analysis. *Age and Ageing*. 2021;50(4):1118-1128. doi:10.1093/ageing/afab039

53. Choi NG, DiNitto DM. Heavy/binge drinking and depressive symptoms in older adults: gender differences. *Int J Geriatr Psychiatry*. 2011;26(8):860-868. doi:10.1002/gps.2616

Table 1. Sociodemographic characteristics and health variables of participants according to waves and depressive symptoms incidence in the EpiFloripa Aging Cohort Study.

Characteristics	Baseline (Wave 1) 2009-2010 (N=1,234)		Follow-up (Wave 3) 2017-2019 (N=529)		Depressive symptoms incidence (Wave 3) (N=54)			
	N	%	N	%	N	%	95%CI	P
Sex								
Male	474	39.6	203	39.0	17	7.4	4.5-12.0	0.550
Female	760	60.4	380	61.0	37	11.3	7.7-16.3	
Age								
60-69 years	652	53.7	83	13.3	7	7.9	3.6-16.3	0.012*
70-79 years	448	36.2	305	54.2	20	8.1	5.1-12.7	
≥ 80 years	133	10.1	195	32.5	27	13.9	8.8-21.4	
Family income								
≤ 3 MW	417	33.5	223	37.2	25	11.4	7.2-17.6	0.215*
4 and 5 MW	217	16.9	103	16.9	9	12.6	6.2-11.9	
≥ 6 MW	561	49.6	246	45.9	17	6.7	3.7-11.9	
Alcohol use								
Yes	487	40.1	246	42.9	10	4.4	2.2-8-6	<0.001*
No	747	59.9	337	57.1	44	14.1	10.2-19.2	
Leisure-time physical activity								
Active	631	53.0	150	25.8	9	5.4	2.7-10.5	0.124*
Insufficiently active	603	47.0	427	74.2	45	11.5	8.2-15.9	
Number of medical comorbidities								
None	107	9.4	51	11.0	1	1.8	0.2-12.5	0.027*
1	238	19.4	95	17.6	5	6.4	2.3-16.7	
≥ 2	889	71.1	437	71.4	48	12.0	8.7-16.4	
Current Antidepressant use								0.023
Yes	118	8.8	73	12.8	11	8.2	5.8-11.5	
No	1116	91.2	510	87.2	43	24.0	12.7-40.8	
BMI (kg/m^2)								0.037*
Underweight <18.5	18	1.6	10	1.8	3	35.9	10.2-73.5	

Normal Weight 18.5-24.9	327	25.1	143	23.4	17	12.8	6.9-22.4	
Overweight 25-29.9	558	46.7	251	46.4	18	7.1	3.8-12.8	
Obesity ≥30	315	26.6	153	28.4	16	11.0	5.4-20.9	
Waist Circumference (cm)								0.121*
M: <94 F: <80	331	26.7	104	18.1	15	16.5	9.0-28.4	
M: 94-101 F: 80-87	336	27.3	124	22.8	11	10.9	5.4-20.8	
M: ≥102 F: ≥88	548	46.1	324	59.1	27	7.7	4.4-13.0	
Incidence of Depressive symptoms								
≤5 points/	-	-	475	90.1	-	-	-	
≥6 points	-	-	54	9.9	-	-	-	

*Fisher's exact test. MW, minimum wages. BMI, body mass index. F, female. M, male. NSI, Nutrition Screening Initiative.

Table 2. Transitions of BMI categories over time from the EpiFloripa Aging Cohort Study.

	Probability of remaining in the same condition (%)	Probability of turning underweight (%)	Probability of turning normal weight (%)	Probability of turning overweight (%)	Probability of turning obesity (%)
BMI (kg/m^2; n= 1,432)					
Underweight <18.5	50.0	-	50.0	0.0	0.0
Normal Weight 18.5-24.9	76.2	2.3	-	1.3	20.2
Overweight 25-29.9	82.1	0.3	0.3	-	17.4
Obesity ≥30	77.0	0.3	12.2	10.5	-
Male (n=522)					
Underweight <18.5	50.0	-	50.0	0.0	0.0
Normal Weight 18.5-24.9	79.6	0.6	-	0.6	19.2
Overweight 25-29.9	74.2	0.0	0.0	-	25.8
Obesity ≥30	81.5	0.4	9.8	8.3	-
Female (n=899)					
Underweight <18.5	50.0	-	50.0	0.0	0.0
Normal Weight 18.5-24.9	73.6	3.7	-	1.9	20.8
Overweight 25-29.9	85.4	0.4	0.4	-	13.8

Obesity ≥30	74.0	0.3	13.8	11.9	-

Analysis using generalization of tabulate. BMI, body mass index.

Table 3. Unadjusted and adjusted analysis of the association between BMI and incidence of depressive symptoms in the EpiFloripa Aging Cohort Study.

	Unadjusted analysis			Adjusted analysis		
BMI (kg/m^2)	IRR	95%CI	P	IRR	95%CI	P
Overweight 25-29.9	1	-	-	1	-	-
Underweight <18.5	1.86	0.87-3.94	0.106	1.16	0.60-2.23	0.651
Normal Weight 18.5-24.9	1.21	0.98-1.49	0.077	1.03	0.86-1.26	0.711
Obesity ≥30	1.38	1.11-1.70	**0.003**	1.24	1.01-1.51	**0.035**
Waist Circumference (cm)						
M: 94-101 F: 80-87	1	-	-	1	-	-
M: <94 F: <80	1.03	0.93-1.13	0.592	1.03	0.94-1.13	0.536
M: ≥102 F: ≥88	1.09	1.01-1.17	**0.033**	1.07	0.99-1.15	0.085

Adjusted by sex, age, familiar income, alcohol use, physical activity, number of medical comorbidities, antidepressant use, and time. BMI, body mass index. IRR, incidence rate ratio estimated using a generalized estimating equation model. F, female. M, men. 95%CI, 95% confidence interval.

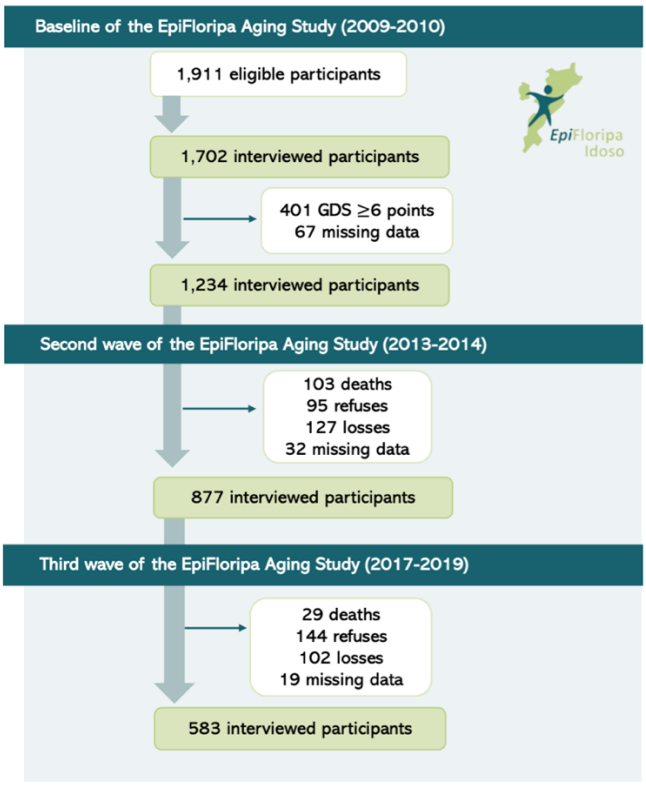


Figure 1. EpiFloripa Aging Study Flowchart.

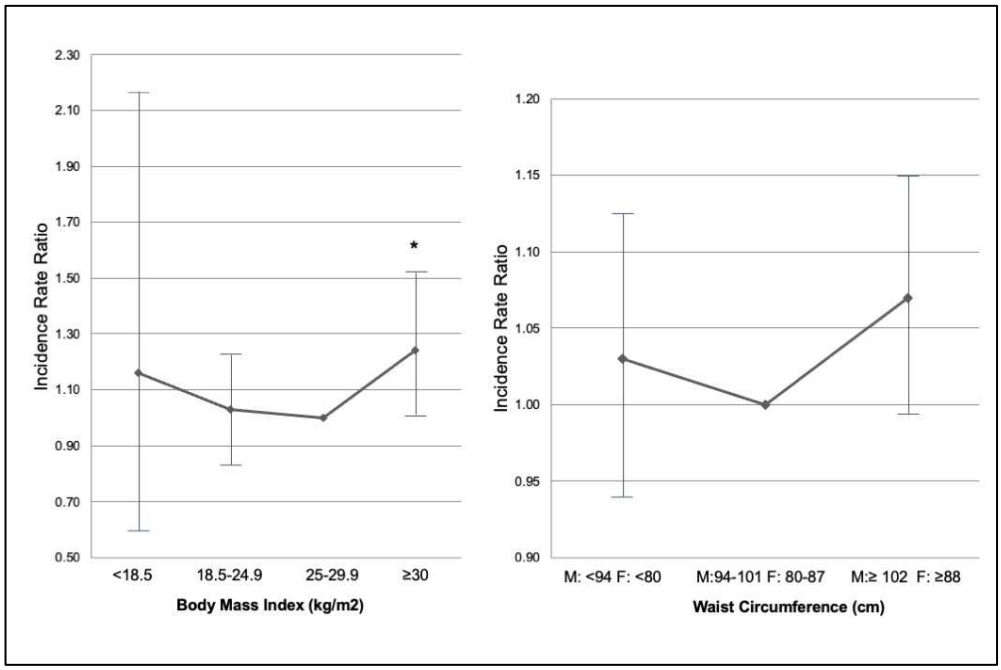


Figure 2. The curve of Incidence Rate Ratio of association between body mass index/ waist circumference and depressive symptoms.
Adjusted by sex, age, familiar income, alcohol use, physical activity, number of medical comorbidities, antidepressant use, and time. F, female. M, male. *P>0.05

Supplementary material

Table of contents

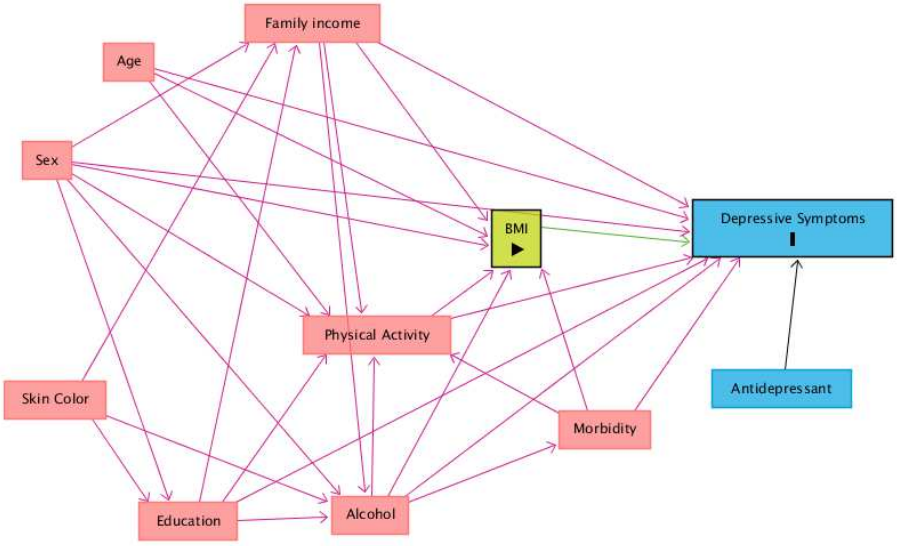


Figure S1. Theoretical model of the minimum set of adjustment covariates indicated by the DAG of the association between body mass index and depressive symptoms.

The directed acyclic graph (DAG) used to determine the minimum set of adjustments covariates was constructed based on literature associations between variables to test the directed effect of the exposure variable body mass index (BMI) on the outcome variable Depressive Symptoms. The variables identified by the red color are the ancestors of exposure and outcome; the blue color are the ancestors of outcome. The lines in pink are the biasing path, and in green are the causal path between exposure and outcome.

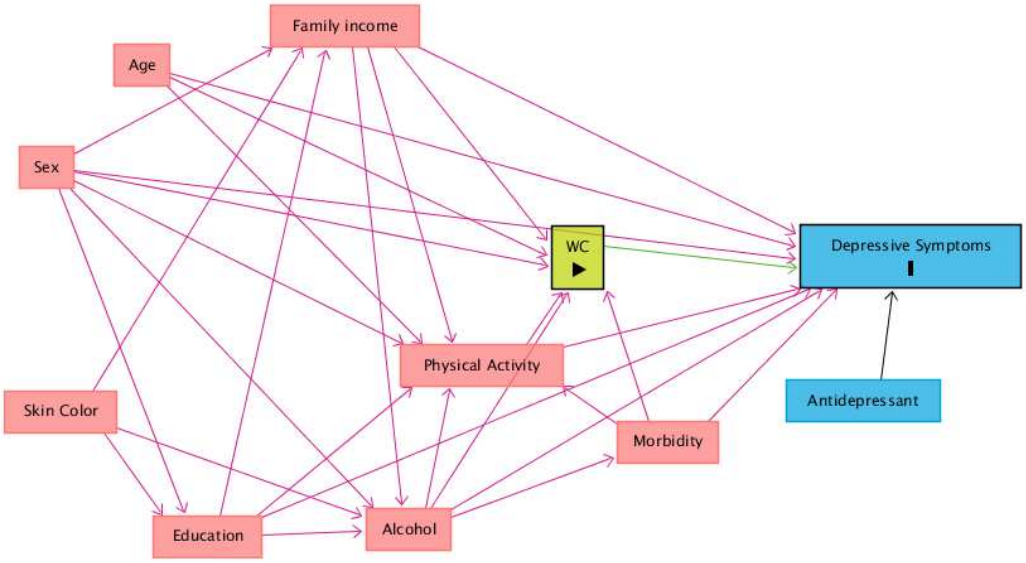


Figure S2. Theoretical model of the minimum set of adjustment covariates indicated by the DAG of the association between waist circumference and depressive symptoms.

The directed acyclic graph (DAG), used to determine to minimum set of adjustments covariates, was constructed based on literature associations between variables to test the directed effect of the exposure variable Waist Circumference (WC) on the outcome variable Depressive Symptoms. The variables identified by red color are the ancestors of exposure and outcome; the blue color are the ancestors of outcome. The lines in pink are the biasing path, and in green are the causal path between exposure and outcome.

Table S1. Transitions of waist circumference categories over time among older adults from the EpiFloripa Aging Cohort Study.

	Probability of remaining with same category (%)	**Probability of turn to 1st category (%)**	**Probability of turn to 2nd category (%)**	**Probability of turn to 3rd category (%)**
Waist Circumference (cm, n= 1,438)				
M:<94 F:<80cm	67.3	-	26.7	6.0
M:94/102 F:80/88 cm	41.8	18.0	-	40.2
M:>102 F:>88 cm	86.2	1.7	12.1	-

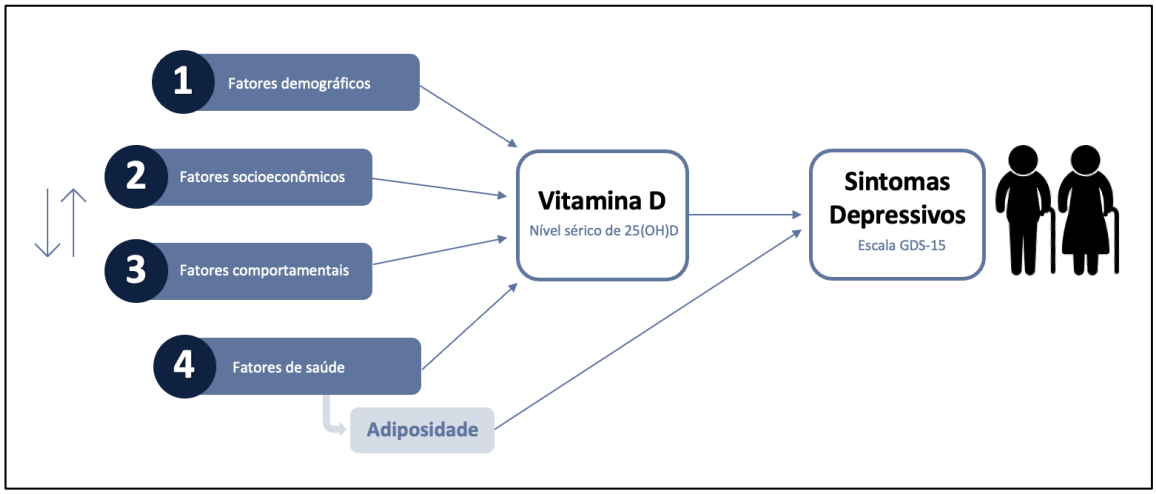
Analysis using generalization of tabulate. M, male. F, female.

5. CONSIDERAÇÕES FINAIS

Conclusões dos estudos

A presente tese de doutorado utilizou diferentes abordagens metodológicas e estatísticas com o objetivo de identificar os determinantes das concentrações séricas da vitamina D e avaliar a sua associação com sintomas depressivos, e da adiposidade e sintomas depressivos em idosos de Florianópolis-SC utilizando dados das três ondas de pesquisa do estudo EpiFloripa Idoso. Os estudos de revisão embasaram a perspectiva teórica do tema e a partir dos estudos empíricos desta tese, foi possível delinear uma linha entrelaçando os resultados evidenciados, iniciando pela exploratória dos determinantes da vitamina D, evidenciando que a adiposidade se associou tanto com o baixo nível sérico da vitamina D, quando com os sintomas depressivos clinicamente significativos, e que o baixo nível sérico da vitamina D se associou tanto com sintomas depressivos de maneira transversal quanto longitudinal, levando em consideração fatores demográficos, socioeconômicos, comportamentais e de saúde, em idosos de Florianópolis-SC (Figura 9).

Figura 9 - Diagrama de relação entre os estudos da tese



Fonte: elaborado pelos autores

Para a identificação dos determinantes das concentrações séricas da vitamina D, foi possível desenvolver dois produtos, um de caráter exploratório, encontrando resultados de vão de encontro a estudos prévios, identificando uma prevalência importante de hipovitaminose D em idosos e os principais fatores relacionados, como

sexo, colesterol LDL, obesidade, dependência em atividades da vida diária, e atividade física. A partir desses achados, o outro estudo com análise estatística mais robusta evidenciou que atividade física moderada a vigorosa teve efeito positivo, e que a obesidade teve efeito negativo no nível sérico da vitamina D, além da relação entre atividade física e vitamina D ser parcialmente mediado pela adiposidade. Tanto a atividade física quanto a adiposidade são fatores importantes durante o processo de envelhecimento. Tendo em vista o cenário de elevada prevalência de hipovitaminose D, também evidenciada na amostra de idosos de Florianópolis, tais achados são importantes para o planejamento de estratégias para prevenção de hipovitaminose D e as consequências comuns possíveis como risco de quedas e fraturas ocasionados pelos efeitos da do baixo nível sérico da vitamina D na saúde esquelética.

Considerando os resultados obtidos da relação entre vitamina D e sintomas depressivos em idosos, os resultados dos estudos de revisão evidenciaram uma falta de estudos longitudinais com amostra de estudos de base populacional e apenas com idosos, uma vez que essa fase da vida tem características distintas das demais. Há um potencial de efeito da vitamina D nos sintomas depressivos/depressão, mas ainda não é possível dizer se pode atuar como prevenção ou tratamento coadjuvante. Foi evidenciado uma maquinaria robusta para transformação e uso da vitamina D à nível cerebral, entretanto devido a divergência metodológica dos estudos em relação a métodos de mensuração no nível sérico de vitamina D, classificação e mensuração de sintomas depressivos, divergência no tipo de amostra, ainda não foi possível chegar a resultados conclusivos.

Em relação os estudos com dados dos idosos de Florianópolis, foi possível observar uma associação entre o baixo nível sérico de vitamina D e sintomas depressivos em idosos de maneira transversal e longitudinal, sendo que aqueles com o nível sérico menor, apresentam maior chance de ter sintomas depressivos clinicamente significativos. É um achado que vai de encontro a maioria dos estudos realizados internacionalmente. Sabe-se que a depressão é uma condição complexa, desencadeada por diversos mecanismos, e de acordo com os estudos pré-clínicos, há a possibilidade de a vitamina D atuar em algumas dessas vias que desencadeiam a depressão.

Ademais, foi possível verificar a relação longitudinal de medidas de IMC e Circunferência da cintura nos sintomas depressivos em idosos, contribuindo para a hipótese do efeito negativo da obesidade na depressão, além da associação da curva em U para o IMC, como ocorre em demais condições em idosos. Apesar de não se manter significativo após ajustes a circunferência da cintura apresentou uma curva em J.

Evidenciando que possivelmente a redução da obesidade seria benéfico não somente para a vitamina D conforme o estudo dos determinantes, mas também para a presença de sintomas depressivos clinicamente relevantes.

A partir dos resultados produzidos nessa tese, pode-se elencar **implicações teóricas e práticas**. No ponto de vista teórico, foi possível contribuir com dados de uma amostra de estudo brasileiro, que são escassos, tanto para a literatura nacional quando a internacional. Priorizou-se publicações em periódicos internacionais para dar visibilidade ampla a estudos nacionais, contribuindo tanto para achados que já estão mais consolidados como os dos fatores associados ao nível sérico de vitamina D, quanto para temas que ainda não estão estabelecidos, como a associação da vitamina D e adiposidade com sintomas depressivos.

Do ponto de vista prático, devido a elevada prevalência de hipovitaminose D, pode sugerir o monitoramento mais frequente dessa população de risco, quando o incentivo a prática de atividade física de lazer para aqueles que ainda não praticam, como incentivo de programas acessíveis na rede básica de saúde para redução da adiposidade, que consequentemente beneficia outras condições de saúde, como os sintomas depressivos. Além disso, um monitoramento mais frequente da vitamina D nessa população pode contribuir para a adequação do nível sérico em casos que necessite suplementação, e da redução do risco de apresentar sintomas depressivos, bem como outras condições comuns em idosos relacionados ao baixo nível sérico. A partir da busca de artigos para a revisão narrativa, identificou-se uma lacuna nos estudos de suplementação em relação a dose e tempo de suplementação, com metodologias diversas, não sendo possível ainda afirmar se a suplementação poderia ser benéfica como coadjuvante no tratamento da depressão.

Por fim, acrescentam-se as parcerias formalizadas ao longo da produção destes resultados, que envolveu a multidisciplinariedade, contanto com profissionais locais, nacionais e internacionais, e contribuiu para a discussão ampliada de cada resultado encontrado, além de cada produto desenvolvido ter incluído abordagens metodológicas de análise de dados adequadas para cada objetivo. Fortaleceu-se o vínculo internacional para desenvolvimento de estudos bilaterais e disseminação do conhecimento adquirido ao longo da produção dos estudos.

As possíveis limitações a serem consideradas, envolvem a amostra reduzida para os estudos que utilizaram o nível sérico da vitamina D realizado na subamostra do EpiFloripa Idoso, entretanto para os estudos em que foi calculado o poder de amostra a posteriori, apresentaram um bom poder de amostra. Entretanto, esses idosos que

realizaram a coleta de exames podem ter melhores condições física e de saúde do que os não compareceram, pois houve a necessidade de deslocamento até a universidade, mesmo tendo sido fornecido transporte, mas que pode ter influenciado os resultados. Também pode ser considerada como limitação não ter a medida de vitamina D sérica na onda 3 para o estudo longitudinal, o que limitou a opções de modelagem estatística, e o número de participantes do acompanhamento ter reduzido na onda 3.

Todavia, o presente projeto possui pontos fortes que precisam ser elencados, como o rigor metodológico da coleta de dados, com entrevistadores treinados e supervisionados, estudo piloto, entrevistas face a face, e controle de qualidade da entrevista, e a aplicação de testes estatísticos robustos para a análise de dados. Além disso, é uma amostra somente com idosos, o que fortalece a literatura científica da área para essa população específica, pois a população é distinta, considerando as alterações metabólicas e aspectos do ciclo de vida. Outro ponto, é o uso da GDS-15 que é um dos instrumentos de rastreamento para sintomas depressivos mais utilizados em estudos semelhantes e foi validado para aplicação na população brasileira. Finalmente, o rigor estatístico e as parcerias com outras áreas do conhecimento nacionais e internacionais, com a realização do doutorado sanduíche, contribuindo para uma visão ampliada para a realização das análises estatísticas, apresentação dos resultados e discussão.

Sugestões de continuidade do estudo

Sugere-se para a continuidade da elucidação do tema, futuros estudos que possam investigar se a relação entre a adiposidade e os sintomas depressivos é mediada pela vitamina D, uma vez que a adiposidade se apresentou associada com ambos e possa haver plausibilidade nessa relação. Além disso, nos estudos desenvolvidos não foi possível realizar análises com medidas repetidas da vitamina D pela ausência do dado, o que é importante ser incluído em próximos estudos. A investigação da exposição solar, da dosagem da suplementação de vitamina D e da investigação através do consumo de alimentos por meio de questionário de frequência alimentar poderia ajudar no entendimento da alta prevalência de hipovitaminose D nessa população.

Estudos relacionado a vitamina D e sintomas depressivos com mortalidade também são importantes para mensurar o impacto de ambos no envelhecimento. A relação entre a atividade física, vitamina D, adiposidade e sintoma depressivo também é uma

sugestão futura, uma vez que apresentam relações individuais, entretanto ainda não foi explorado as interrelações em conjunto.

Por fim, é importante que os estudos com vitamina D utilizem medidas que sejam padronizadas, conforme o Programa de Certificação de Padronização de Vitamina D do Centro de Controle e Prevenção de Doenças, a fim de reduzir a variabilidade metodológica da medida da vitamina D entre os estudos, contribuindo para o desenvolvimento de metanálise com baixo risco de viés nesse sentido.

Conclusões sobre o percurso de formação

Ao longo de quatro anos e meio de realização de doutorado, foram adquiridas habilidades importantes para o amadurecimento e para a formação de um perfil de doutora. Pode-se citar a desenvoltura para tomada de decisões, autonomia no desenvolvimento e discussões das análises estatísticas, conhecimentos necessários para realização de análises estatísticas robustas, postura crítica e dinâmica acadêmica nas discussões temáticas, trabalho em equipe, realização de treinamentos e orientação de trabalhos, entre outros.

O treinamento teve início com a realização de disciplinas necessárias para a construção do projeto, de conhecimento e de pensamento crítico para o desenvolvimento da pesquisa, cursando disciplinas no PPGN e em outros programas de pós-graduação da UFSC e da UFMA. É importante também destacar a participação no grupo de pesquisa EpiFloripa Idoso, o engajamento em todas as etapas de planejamento, discussões, treinamentos e coleta de dados que propiciou amadurecimento, dinâmica de trabalho em grupo multiprofissional e tomadas de decisões. Ao longo de dois anos de pandemia, apesar de ser um período desafiador, foi um período importante de desenvolvimento de parcerias, desenvolvimento dos estudos e participação na construção e divulgação dos resultados do estudo EpiFloripa Idoso e dos estudos desta tese. Também se destaca a participação no grupo de estudos e pesquisa Nutrição e Neurociência Translacional que contribuiu para o desenvolvimento dos estudos da tese, postura dinâmica nas discussões de estudos e resultados dos estudos dos participantes.

Ao longo do período também foi possível formar uma parceria importante com o grupo de pesquisa *NeuroMood Lab*, de forma remota ao longo da pandemia e presencial em 2022, por meio do doutorado sanduíche na *Queen's University*. A experiência do estágio de doutorado sanduíche no exterior foi importante e impactou positivamente o

desenvolvimento da tese, formação pessoal, profissional, como propiciou uma parceria bilateral, contribuindo para o avanço científico do programa de pós-graduação e do país. A oportunidade de desenvolver pesquisa com profissionais de outros locais e nacionalidades em uma das mais conceituadas universidades do Canadá foi realizadora.

Por meio das parcerias formadas, participou-se da produção dos artigos para além da tese de doutorado, fortalecendo vínculo com pesquisadores de outros setores da UFSC, como da Saúde Coletiva, Educação Física e da Informática e Estatística e demais locais como Canadá, Portugal e Reino Unido (Figura 10).

Figura 10 - Parcerias acadêmicas realizadas ao longo do doutorado.

Fonte: elaborado pelos autores

Finalmente, é importante enaltecer a atuação de mulheres na ciência, que foram importantes para construção realização dessa tese, bem como auxiliaram no percurso do doutorado, a orientadora Prof. Dra. Júlia Dubois Moreira, Coorientadora Prof. Dra. Débora Kurrle Rieger Venske, Colaboradora Prof. Dra. Luciana Antunes, Coordenadora do EpiFloripa Idoso Prof. Dra. Eleonora d'Orsi, e supervisora do doutorado sanduíche Prof. Dra. Elisa Brietzke, dentre outros profissionais e pesquisadores pelo auxílio durante todo esse processo de construção de tese, bem como construção profissional e pessoal da formação de doutora.

REFERÊNCIAS

ABBAS, M. A. Physiological functions of Vitamin D in adipose tissue. **The Journal of Steroid Biochemistry and Molecular Biology**, v. 165, p. 369–381, 1 jan. 2017.

ALBOLUSHI, T.; BOUHAIMED, M.; SPENCER, J. Lower Blood Vitamin D Levels Are Associated with Depressive Symptoms in a Population of Older Adults in Kuwait: A Cross-Sectional Study. **Nutrient**s, v. 14, n. 8, p. 1548, jan. 2022.

ALEXOPOULOS, G. S. et al. The expert consensus guideline series. Pharmacotherapy of depressive disorders in older patients. Postgraduate Medicine, v. **Spec No Pharmacotherapy**, p. 1–86, out. 2001.

AL-HARBI, K. S. Treatment-resistant depression: therapeutic trends, challenges, and future directions. **Patient preference and adherence**, v. 6, p. 369–388, 1 maio 2012.

ALLALI, F. et al. High prevalence of hypovitaminosis D in Morocco: relationship to lifestyle, physical performance, bone markers, and bone mineral density. **Seminars in Arthritis and Rheumatism**, v. 38, n. 6, p. 444–451, jun. 2009.

ALMEIDA, O. P. et al. Vitamin D concentration and its association with past, current and future depression in older men: The Health In Men Study. **Maturitas**, v. 81, n. 1, p. 36–41, maio 2015.

ALMEIDA, O. P.; ALMEIDA, S. A. Short versions of the geriatric depression scale: a study of their validity for the diagnosis of a major depressive episode according to ICD-10 and DSM-IV. **International Journal of Geriatric Psychiatry**, v. 14, n. 10, p. 858–865, 1 out. 1999.

ALTIERI, B. et al. Vitamin D testing: advantages and limits of the current assays. **European Journal of Clinical Nutrition,** v. 74, n. 2, p. 231–247, fev. 2020.

AMERICAN PSYCHIATRIC ASSOCIATION. Diagnostic and Statistical Manual of Mental Disorders (DSM–5). 5. ed. Porto Alegre: Artmed, 2014.

AMERICAN PSYCHIATRIC ASSOCIATION. Guideline Development Panel for the Treatment of Depressive Disorders. Disponível em: <https://www.apa.org/depression-guideline/guideline.pdf>. Acesso em: 24 mar. 2020.

AMREIN, K. et al. Vitamin D deficiency 2.0: an update on the current status worldwide. **European Journal of Clinical Nutrition**, p. 1–16, 20 jan. 2020.

ANDRADE, F. C. D. et al. Life expectancy without depression increases among Brazilian older adults. **Revista de Saúde Pública**, v. 50, p. 12, 15 abr. 2016.

ANNWEILER, C. et al. Vitamin D and brain volumetric changes: Systematic review and meta-analysis. **Maturitas**, v. 78, n. 1, p. 30–39, 1 maio 2014.

ARABI, A.; EL RASSI, R.; EL-HAJJ FULEIHAN, G. Hypovitaminosis D in developing countries—prevalence, risk factors and outcomes. **Nature Reviews Endocrinology**, v. 6, n. 10, p. 550–561, out. 2010.

ASPELL, N. et al. The Prevalence and Determinants of Vitamin D Status in Community-Dwelling Older Adults: Results from the English Longitudinal Study of Ageing (ELSA). **Nutrients**, v. 11, n. 6, 1 jun. 2019.

AVASTHI, A.; GROVER, S. Clinical Practice Guidelines for Management of Depression in Elderly. **Indian Journal of Psychiatry**, v. 60, n. Suppl 3, p. S341–S362, fev. 2018.

BALLESTER, P. L. et al. Brain age in mood and psychotic disorders: a systematic review and meta-analysis. **Acta Psychiatrica Scandinavica**, v. 145, n. 1, p. 42–55, jan. 2022.

BARBOSA, F. B. M. et al. Transtorno depressivo no idoso: rastreamento, diagnóstico e aspectos epidemiológicos. **Geriatrics, Gerontology and Aging**, v. 7, n. 3, p. 228–233, 2013.

BARCELOS-FERREIRA, R. et al. Depressive morbidity and gender in community-dwelling Brazilian elderly: systematic review and meta-analysis. **International Psychogeriatrics**, v. 22, n. 5, p. 712–726, ago. 2010.

BERK, M. et al. So depression is an inflammatory disease, but where does the inflammation come from? **BMC Medicine**, v. 11, p. 200, 12 set. 2013.

BERRIDGE, M. J. Vitamin D cell signalling in health and disease. **Biochemical and Biophysical Research Communications**, v. 460, n. 1, p. 53–71, 24 abr. 2015.

BERRIDGE, M. J. Vitamin D and Depression: Cellular and Regulatory Mechanisms. **Pharmacological Reviews,** v. 69, n. 2, p. 80–92, 1 abr. 2017.

BEVILACQUA, G. et al. Determinants of circulating 25-hydroxyvitamin D concentration and its association with musculoskeletal health in midlife: Findings from the Hertfordshire Cohort Study. **Metabolism Open**, v. 12, p. 100143, 1 dez. 2021.

BIANCHI, S. et al. Preanalytical, analytical (DiaSorin LIAISON) and clinical variables potentially affecting the 25-OH Vitamin D estimation. **Clinical Biochemistry**, v. 45, n. 18, p. 1652–1657, 1 dez. 2012.

BIGMAN, G. Vitamin D metabolites, D3 and D2, and their independent associations with depression symptoms among adults in the United States. **Nutritional Neuroscience**, p. 1–9, 20 jul. 2020.

BIKLE, D.; CHRISTAKOS, S. New aspects of vitamin D metabolism and action — addressing the skin as source and target. **Nature Reviews Endocrinology**, v. 16, n. 4, p. 234–252, abr. 2020.

BIKLE, D. D. Vitamin D and the skin: Physiology and pathophysiology. **Reviews in endocrine & metabolic disorders**, v. 13, n. 1, p. 3–19, mar. 2012.

BIKLE, D. D.; PATZEK, S.; WANG, Y. Physiologic and pathophysiologic roles of extra renal CYP27b1: Case report and review. **Bone Reports**, v. 8, p. 255–267, jun. 2018.

BIVONA, G. et al. Non-Skeletal Activities of Vitamin D: From Physiology to Brain Pathology. **Medicina**, v. 55, n. 7, 5 jul. 2019.

BLACK, L. J. et al. In Pursuit of Vitamin D in Plants. **Nutrients**, v. 9, n. 2, 13 fev. 2017.

BONADIMAN, C. S. C. et al. Depressive disorders in Brazil: results from the Global Burden of Disease Study 2017. **Population Health Metrics**, v. 18, n. 1, p. 6, 30 set. 2020.

BORGES, L. J. et al. Fatores associados aos sintomas depressivos em idosos: estudo EpiFloripa. **Revista de Saúde Pública**, v. 47, n. 4, p. 701–710, ago. 2013.

BOUILLON, R. et al. Vitamin D and Human Health: Lessons from Vitamin D Receptor Null Mice. **Endocrine Reviews**, v. 29, n. 6, p. 726–776, out. 2008.

BOUILLON, R. et al. Vitamin D and energy homeostasis—of mice and men. Nature Reviews **Endocrinology**, v. 10, n. 2, p. 79–87, fev. 2014.

BOUILLON, R. Comparative analysis of nutritional guidelines for vitamin D. Nature Reviews **Endocrinology**, v. 13, n. 8, p. 466–479, ago. 2017.

BOUILLON, R. et al. Skeletal and Extraskeletal Actions of Vitamin D: Current Evidence and Outstanding Questions. **Endocrine Reviews**, v. 40, n. 4, p. 1109–1151, 1 ago. 2019.

BOYAN, B. D.; CHEN, J.; SCHWARTZ, Z. Mechanism of Pdia3-dependent 1α,25-dihydroxy vitamin D3 signaling in musculoskeletal cells. **Steroids**, v. 77, n. 10, p. 892–896, 1 ago. 2012.

BRANDÃO, D. J. et al. Depression and excess mortality in the elderly living in low- and middle-income countries: Systematic review and meta-analysis. **International Journal of Geriatric Psychiatry**, v. 34, n. 1, p. 22–30, 1 jan. 2019.

BRASIL. Quais são as indicações de dosagem e reposição de vitamina D em pacientes assintomáticos? – BVS Atenção Primária em Saúde. [s.l: s.n.]. Disponível em: <https://aps-repo.bvs.br/aps/quais-sao-as-indicacoes-de-dosagem-e-reposicao-de-vitamina-d-em-pacientes-assintomaticos/>. Acesso em: 9 nov. 2022.

BRASIL. CADERNOS DE ATENÇÃO BÁSICA 19 - Envelhecimento e saúde da pessoa idosa. DF: **Mnistério da Saúde**, 2006.

BRASIL. Vigitel Brasil 2021: vigilância de fatores de risco e proteção para doenças crônicas por inquérito telefônico: estimativas sobre frequência e distribuição sociodemográfica de fatores de risco e proteção para doenças crônicas nas capitais dos 26 estados brasileiros e no Distrito Federal em 2021. [s.l: s.n.]. Disponível em: <https://www.gov.br/saude/pt-br/centrais-de-conteudo/publicacoes/publicacoes-svs/vigitel/vigitel-brasil-2021-estimativas-sobre-frequencia-e-distribuicao-sociodemografica-de-fatores-de-risco-e-protecao-para-doencas-cronicas/view>. Acesso em: 27 set. 2022.

BRIGGS, R. et al. Vitamin D Deficiency Is Associated With an Increased Likelihood of Incident Depression in Community-Dwelling Older Adults. **Journal of the American Medical Directors Association**, v. 20, n. 5, p. 517–523, 1 maio 2019.

BROUWER-BROLSMA, E. M. et al. Low vitamin D status is associated with more depressive symptoms in Dutch older adults**. European Journal of Nutrition**, v. 55, p. 1525–1534, 2016.

BUCH, A. M.; LISTON, C. Dissecting diagnostic heterogeneity in depression by integrating neuroimaging and genetics. **Neuropsychopharmacology**, v. 46, n. 1, p. 156–175, jan. 2021.

BURCUSA, S. L.; IACONO, W. G. Risk for recurrence in depression. **Clinical Psychology Review**, v. 27, n. 8, p. 959–985, dez. 2007.

CALTON, E. K. et al. The Impact of Vitamin D Levels on Inflammatory Status: A Systematic Review of Immune Cell Studies. **PLoS ONE**, v. 10, n. 11, 3 nov. 2015.

CAMARGO, A. et al. Cholecalciferol counteracts depressive-like behavior and oxidative stress induced by repeated corticosterone treatment in mice**. European Journal of Pharmacology**, v. 833, p. 451–461, 15 ago. 2018.

CAPURON, L. et al. Association between immune activation and early depressive symptoms in cancer patients treated with interleukin-2-based therapy. **Psychoneuroendocrinology**, v. 26, n. 8, p. 797–808, 1 nov. 2001.

CAPURON, L. et al. Interferon-alpha–induced changes in tryptophan metabolism: relationship to depression and paroxetine treatment. **Biological Psychiatry**, v. 54, n. 9, p. 906–914, 1 nov. 2003.

CARRILLO-VEGA, M. F. et al. Vitamin D deficiency in older adults and its associated factors: a cross-sectional analysis of the Mexican Health and Aging Study. **Archives of Osteoporosis**, v. 12, n. 1, p. 8, dez. 2017.

CASTRO, L. C. G. DE. O sistema endocrinológico vitamina D. **Arquivos Brasileiros de Endocrinologia & Metabologia**, v. 55, n. 8, p. 566–575, nov. 2011.

CEOLIN, G. et al. Lower serum 25-hydroxycholecalciferol is associated with depressive symptoms in older adults in Southern Brazil. **Nutrition Journal**, v. 19, n. 1, p. 123, 14 nov. 2020.

CEOLIN, G. et al. Vitamin D and depression in older adults: Lessons learned from observational and clinical studies. **Nutrition Research Reviews**, p. 1–63, 13 jan. 2022a.

CEOLIN, G. et al. A Possible Antidepressive Effect of Dietary Interventions: Emergent Findings and Research Challenges. **Current Treatment Options in Psychiatry**, 23 abr. 2022b.

CESARI, M. et al. Vitamin D hormone: a multitude of actions potentially influencing the physical function decline in older persons. **Geriatrics & gerontology international**, v. 11, n. 2, p. 133–142, abr. 2011.

CHAN, R. et al. Association between serum 25-hydroxyvitamin D and psychological health in older Chinese men in a cohort study. **Journal of Affective Disorders**, v. 130, n. 1, p. 251–259, 1 abr. 2011.

CHEN, J. et al. Protein-disulfide Isomerase-associated 3 (Pdia3) Mediates the Membrane Response to 1,25-Dihydroxyvitamin D3 in Osteoblasts. **Journal of Biological Chemistry**, v. 285, n. 47, p. 37041–37050, 19 nov. 2010.

CHEN, J. et al. Plasma membrane Pdia3 and VDR interact to elicit rapid responses to 1α,25(OH)2D3. **Cellular Signalling**, v. 25, n. 12, p. 2362–2373, 1 dez. 2013.

CHEN, TAI. C. et al. Factors that Influence the Cutaneous Synthesis and Dietary Sources of Vitamin D. **Archives of biochemistry and biophysics**, v. 460, n. 2, p. 213–217, 15 abr. 2007.

CHENG, Q. et al. Factors associated to serum 25-hydroxyvitamin D levels among older adult populations in urban and suburban communities in Shanghai, China. **BMC Geriatrics**, v. 17, 24 out. 2017.

CHISHOLM, D. et al. Scaling-up treatment of depression and anxiety: a global return on investment analysis. **The Lancet Psychiatry**, v. 3, n. 5, p. 415–424, 1 maio 2016.

CHOURBAJI, S.; BRANDWEIN, C.; GASS, P. Altering BDNF expression by genetics and/or environment: Impact for emotional and depression-like behaviour in laboratory mice. **Neuroscience & Biobehavioral Reviews,** v. 35, n. 3, p. 599–611, 1 jan. 2011.

CLEMENS, T. L. et al. Increased skin pigment reduces the capacity of skin to synthesise vitamin D3. **Lancet,** v. 1, n. 8263, p. 74–76, 9 jan. 1982.

COLLIN, C. et al. Plasma vitamin D status and recurrent depressive symptoms in the French SU.VI.MAX cohort. **European Journal of Nutrition**, v. 56, n. 7, p. 2289–2298, out. 2017.

CONFORTIN, S. C. et al. Life and health conditions among elderly: results of the EpiFloripa Idoso cohort study. **Epidemiologia e Serviços de Saúde**, v. 26, n. 2, p. 305–317, jun. 2017.

CONFORTIN, S. C. et al. Estudo Longitudinal EpiFloripa Idoso – Rotinas de organização e protocolos referentes à coleta, análise e armazenamento de material biológico, exames de imagem e capacidade físico-funcional. **Cadernos Saúde Coletiva**, v. 27, n. 2, p. 210–224, jun. 2019.

CONFORTIN, S. C. et al. Estudo de Coorte EpiFloripa Idoso: abordagens metodológicas e reposição da amostra durante a Onda 3 (2017-19). **Estudos Interdisciplinares do Envelhecimento** n. no prelo, 2022.

COVID-19 MENTAL DISORDERS COLLABORATORS. Global prevalence and burden of depressive and anxiety disorders in 204 countries and territories in 2020 due to the COVID-19 pandemic. **Lancet**, v. 398, n. 10312, p. 1700–1712, 6 nov. 2021.

CROARKIN, P. E.; LEVINSON, A. J.; DASKALAKIS, Z. J. Evidence for GABAergic inhibitory deficits in major depressive disorder. **Neuroscience & Biobehavioral Reviews**, v. 35, n. 3, p. 818–825, 1 jan. 2011.

CUI, X. et al. The vitamin D receptor in dopamine neurons; its presence in human substantia nigra and its ontogenesis in rat midbrain. **Neuroscience**, v. 236, p. 77–87, 16 abr. 2013.

CUI, X. et al. Vitamin D regulates tyrosine hydroxylase expression: N-cadherin a possible mediator. **Neuroscience**, v. 304, p. 90–100, 24 set. 2015.

CUI, X. et al. Vitamin D and the brain: Genomic and non-genomic actions. **Molecular and Cellular Endocrinology**. v. 453, p. 131–143, 15 set. 2017.

CUIJPERS, P. et al. A network meta-analysis of the effects of psychotherapies, pharmacotherapies and their combination in the treatment of adult depression. **World Psychiatry**, v. 19, n. 1, p. 92–107, 2020.

CUNHA, R. V. DA; BASTOS, G. A. N.; DUCA, G. F. D. Prevalência de depressão e fatores associados em comunidade de baixa renda de Porto Alegre, Rio Grande do Sul. **Revista Brasileira de Epidemiologia**, v. 15, n. 2, p. 346–354, jun. 2012.

D'ORSI, E. et al. Manual do Entrevistador Epifloripa Idoso. 2017. Disponível em: < https://repositorio.ufsc.br/handle/123456789/219632?show=full>.

D'ORSI, E. et al. Relatório Epifloripa Idoso. Disponível em: <https://repositorio.ufsc.br/handle/123456789/219631>.

DAWSON-HUGHES, B. et al. IOF position statement: vitamin D recommendations for older adults. **Osteoporosis International**, v. 21, n. 7, p. 1151–1154, jul. 2010.

DE KONING, E. J. et al. Vitamin D Status and Depressive Symptoms in Older Adults: A Role for Physical Functioning? **The American Journal of Geriatric Psychiatry**, v. 26, n. 11, p. 1131–1143, 1 nov. 2018.

DE OLIVEIRA, C. et al. Vitamin D and inflammatory markers: cross-sectional analyses using data from the English Longitudinal Study of Ageing (ELSA). **Journal of Nutritional Science**, v. 6, p. e1, 2017.

DE OLIVEIRA, C.; HIRANI, V.; BIDDULPH, J. P. Associations Between Vitamin D Levels and Depressive Symptoms in Later Life: Evidence From the English Longitudinal Study of Ageing (ELSA). **The Journals of Gerontology: Series A**, v. 73, n. 10, p. 1377–1382, 11 set. 2018.

DEARBORN, P. J.; ROBBINS, M. A.; ELIAS, M. F. Challenging the "jolly fat" hypothesis among older adults: High body mass index predicts increases in depressive symptoms over a 5-year period. **Journal of Health Psychology**, v. 23, n. 1, p. 48–58, 1 jan. 2018.

DELUCA, G. C. et al. Review: The role of vitamin D in nervous system health and disease. **Neuropathology and Applied Neurobiology**, v. 39, n. 5, p. 458–484, 1 ago. 2013.

DI GESSA, G. et al. Changes in vitamin D levels and depressive symptoms in later life in England. **Scientific Reports**, v. 11, n. 1, p. 7724, 8 abr. 2021.

DILUCA, M.; OLESEN, J. The Cost of Brain Diseases: A Burden or a Challenge? **Neuron**, v. 82, n. 6, p. 1205–1208, 18 jun. 2014.

DIRKS, N. F. et al. The When, What & How of Measuring Vitamin D Metabolism in Clinical Medicine. **Nutrients**, v. 10, n. 4, 13 abr. 2018.

DIX, C. F.; BARCLAY, J. L.; WRIGHT, O. R. L. The role of vitamin D in adipogenesis. **Nutrition Reviews**, v. 76, n. 1, p. 47–59, 1 jan. 2018.

DOMÍNGUEZ-LÓPEZ, S.; HOWELL, R.; GOBBI, G. Characterization of serotonin neurotransmission in knockout mice: implications for major depression. **Reviews in the Neurosciences**, v. 23, n. 4, p. 429–443, 1 ago. 2012.

DUDENKOV, D. V. et al. Serum 25-Hydroxyvitamin D Values and Risk of All-Cause and Cause-Specific Mortality: A Population-Based Cohort Study. **Mayo Clinic Proceedings**, v. 93, n. 6, p. 721–730, jun. 2018.

DUMAN, R. S.; SANACORA, G.; KRYSTAL, J. H. Altered Connectivity in Depression: GABA and Glutamate Neurotransmitter Deficits and Reversal by Novel Treatments. **Neuron**, v. 102, n. 1, p. 75–90, 3 abr. 2019.

ELSTGEEST, L. E. M. et al. Change in serum 25-hydroxyvitamin D and parallel change in depressive symptoms in Dutch older adults. **European Journal of Endocrinology**, v. 179, n. 4, p. 239–249, 01 2018.

ERSFELD, D. L. et al. Analytical and clinical validation of the 25 OH vitamin D assay for the LIAISON® automated analyzer. **Clinical Biochemistry**, v. 37, n. 10, p. 867–874, 1 out. 2004.

EVANS-LACKO, S. et al. Socio-economic variations in the mental health treatment gap for people with anxiety, mood, and substance use disorders: Results from the WHO World Mental Health (WMH) Surveys. **Psychological medicine**, v. 48, n. 9, p. 1560–1571, jul. 2018.

EYLES, D. W. et al. Distribution of the Vitamin D receptor and 1α-hydroxylase in human brain. **Journal of Chemical Neuroanatomy**, v. 29, n. 1, p. 21–30, 1 jan. 2005.

EYLES, D. W. et al. Developmental vitamin D deficiency causes abnormal brain development. **Psychoneuroendocrinology**. v. 34, p. S247–S257, 1 dez. 2009.

FAKHOURY, M. Revisiting the Serotonin Hypothesis: Implications for Major Depressive Disorders. **Molecular Neurobiology**, v. 53, n. 5, p. 2778–2786, 1 jul. 2016.

FALCI, D. M. et al. Uso de psicofármacos prediz incapacidade funcional entre idosos. **Revista de Saúde Pública**, v. 53, p. 21, 31 jan. 2019.

FEDOTOVA, J. et al. Different effects of vitamin D hormone treatment on depression-like behavior in the adult ovariectomized female rats. **Biomedicine & Pharmacotherapy**, v. 84, p. 1865–1872, 1 dez. 2016.

FEIZABAD, E. et al. Impact of air pollution on vitamin D deficiency and bone health in adolescents. **Archives of Osteoporosis**, v. 12, n. 1, p. 34, dez. 2017.

FERREIRA, C. E. S. et al. Consensus - reference ranges of vitamin D [25(OH)D] from the Brazilian medical societies. Brazilian Society of Clinical Pathology/Laboratory Medicine (SBPC/ML) and Brazilian Society of Endocrinology and Metabolism (SBEM). **Jornal Brasileiro de Patologia e Medicina Laboratorial**, v. 53, n. 6, p. 377–381, nov. 2017.

FIRTH, J. et al. The Effects of Dietary Improvement on Symptoms of Depression and Anxiety: A Meta-Analysis of Randomized Controlled Trials. **Psychosomatic Medicine**, v. 81, n. 3, p. 265–280, abr. 2019.

FLINT, J.; KENDLER, K. S. The Genetics of Major Depression. **Neuron**, v. 81, n. 3, p. 484–503, 5 fev. 2014.

FOGAÇA, M. V.; DUMAN, R. S. Cortical GABAergic Dysfunction in Stress and Depression: New Insights for Therapeutic Interventions. **Frontiers in Cellular Neuroscience**, v. 13, 12 mar. 2019.

FOOD & DRUG ADMINISTRATION, U. D. OF H. AND H. S. 510(k) Substantial equivalence determination. Decision summary. Assay only template. Disponível em: <https://www.accessdata.fda.gov/cdrh_docs/reviews/K071480.pdf>. Acesso em: 7 abr. 2020.

FULEIHAN, G. E.-H. et al. Serum 25-Hydroxyvitamin D Levels: Variability, Knowledge Gaps, and the Concept of a Desirable Range. **Journal of Bone and Mineral Research**, v. 30, n. 7, p. 1119–1133, 2015.

GAO, S.-F. et al. Reduced GAD65/67 immunoreactivity in the hypothalamic paraventricular nucleus in depression: A postmortem study. **Journal of Affective Disorders**, v. 149, n. 1, p. 422–425, 1 jul. 2013.

GIL, Á.; PLAZA-DIAZ, J.; MESA, M. D. Vitamin D: Classic and Novel Actions. **Annals of Nutrition and Metabolism**, v. 72, n. 2, p. 87–95, 2018.

GIUSTINA, A. et al. Controversies in Vitamin D: Summary Statement From an International Conference. **The Journal of Clinical Endocrinology & Metabolism**, v. 104, n. 2, p. 234–240, 1 fev. 2019.

GIUSTINA, A. et al. Consensus statement from 2nd International Conference on Controversies in Vitamin D. **Reviews in Endocrine and Metabolic Disorders**, v. 21, n. 1, p. 89–116, 1 mar. 2020.

GIUSTINA, A. et al. Vitamin D in the older population: a consensus statement. **Endocrine**, p. 1–14, 26 out. 2022.

GLOBAL HEALTH METRICS. Depressive disorders — Level 3 cause. Disponível em: <http://www.healthdata.org/results/gbd_summaries/2019/depressive-disorders-level-3-cause>. Acesso em: 6 jan. 2021.

GOES, V. F. et al. Severe obesity increases the prevalence but not the incidence of depressive symptoms in the elderly-population-based cohort in Southern Brazil. **International Psychogeriatrics**, v. 29, n. 8, p. 1307–1316, ago. 2017.

GOSHEN, I. et al. Brain interleukin-1 mediates chronic stress-induced depression in mice via adrenocortical activation and hippocampal neurogenesis suppression. **Molecular Psychiatry**, v. 13, n. 7, p. 717–728, jul. 2008.

GOWDA, U. et al. Vitamin D supplementation to reduce depression in adults: Meta-analysis of randomized controlled trials. **Nutrition**, v. 31, n. 3, p. 421–429, 1 mar. 2015.

GRANLUND, L. E. et al. Vitamin D status was not associated with anxiety, depression, or health-related quality of life in Middle Eastern and African-born immigrants in Sweden. **Nutrition Research**, v. 75, p. 109–118, 1 mar. 2020.

GRÖBER, U.; KISTERS, K. Influence of drugs on vitamin D and calcium metabolism. **Dermato-endocrinology**, v. 4, n. 2, p. 158–166, 1 abr. 2012.

HARDINGHAM, G. E.; FUKUNAGA, Y.; BADING, H. Extrasynaptic NMDARs oppose synaptic NMDARs by triggering CREB shut-off and cell death pathways. **Nature Neuroscience**, v. 5, n. 5, p. 405–414, maio 2002.

HAUSSLER, M. R. et al. Vitamin D receptor (VDR)-mediated actions of 1α,25(OH)2vitamin D3: Genomic and non-genomic mechanisms. **Best Practice & Research Clinical Endocrinology & Metabolism**, v. 25, n. 4, p. 543–559, 1 ago. 2011.

HAYNES, B. M. H. et al. Selected physiologic variables are weakly to moderately associated with twenty-nine biomarkers of diet and nutrition, NHANES 2003–2006. **The Journal of nutrition**, v. 143, n. 6, p. 1001S-1010S, jun. 2013.

HE, Y. et al. The 25(OH)D/VDR signaling may play a role in major depression. **Biochemical and Biophysical Research Communications**, v. 523, n. 2, p. 405–410, 5 mar. 2020.

HILGER, J. et al. A systematic review of vitamin D status in populations worldwide. **British Journal of Nutrition**, v. 111, n. 1, p. 23–45, jan. 2014.

HOLICK, M. F. Sunlight and vitamin D for bone health and prevention of autoimmune diseases, cancers, and cardiovascular disease. **The American Journal of Clinical Nutrition**, v. 80, n. 6, p. 1678S-1688S, 1 dez. 2004.

HOLICK, M. F. High Prevalence of Vitamin D Inadequacy and Implications for Health. **Mayo Clinic Proceedings**, v. 81, n. 3, p. 353–373, 1 mar. 2006.

HOLICK, M. F. Vitamin D Deficiency. **New England Journal of Medicine**, v. 357, n. 3, p. 266–281, 19 jul. 2007.

HOLICK, M. F. et al. Evaluation, Treatment, and Prevention of Vitamin D Deficiency: an Endocrine Society Clinical Practice Guideline. **The Journal of Clinical Endocrinology & Metabolism**, v. 96, n. 7, p. 1911–1930, 1 jul. 2011.

HOLICK, M. F. The vitamin D deficiency pandemic: Approaches for diagnosis, treatment and prevention. **Reviews in Endocrine & Metabolic Disorders**, v. 18, n. 2, p. 153–165, jun. 2017.

HOLICK, M. F.; CHEN, T. C. Vitamin D deficiency: a worldwide problem with health consequences. **The American Journal of Clinical Nutrition**, v. 87, n. 4, p. 1080S–6S, abr. 2008.

HOOGENDIJK, W. J. G. et al. Depression Is Associated With Decreased 25-Hydroxyvitamin D and Increased Parathyroid Hormone Levels in Older Adults. **Archives of General Psychiatry**, v. 65, n. 5, p. 508–512, 1 maio 2008.

HUANG, Q. et al. Linking What We Eat to Our Mood: A Review of Diet, Dietary Antioxidants, and Depression. **Antioxidants**, v. 8, n. 9, 5 set. 2019.

HUSEMOEN, L. L. N. et al. Serum 25-hydroxyvitamin D and self-reported mental health status in adult Danes. **European Journal of Clinical Nutrition**, v. 70, n. 1, p. 78–84, jan. 2016.

IMAI, C. M. et al. Depression and serum 25-hydroxyvitamin D in older adults living at northern latitudes – AGES-Reykjavik Study. **Journal of Nutritional Science**, v. 4, 20 nov. 2015.

INSTITUTO BRASILEIRO DE GEOGRAFIA E ESTATÍSTICA. Censo Demográfico 2010. Características da população e dos domicílios. Rio de Janeiro: [s.n.]. Disponível em: <https://censo2010.ibge.gov.br/resultados.html>. Acesso em: 18 out. 2020.

INSTITUTO BRASILEIRO DE GEOGRAFIA E ESTATÍSTICA. Pesquisa Nacional de Saúde 2013: Percepção do estado de saúde, estilos de vida e doenças crônicas. Brasil, Grandes Regiões e Unidades da Federação. [s.l.] **Ministério da Saúde**, 2014.

INSTITUTO BRASILEIRO DE GEOGRAFIA E ESTATÍSTICA. Florianópolis (SC) | Cidades e Estados | IBGE. Disponível em: <https://www.ibge.gov.br/cidades-e-estados/sc/florianopolis.html>. Acesso em: 14 jan. 2021.

JÄÄSKELÄINEN, T. et al. Higher serum 25-hydroxyvitamin D concentrations are related to a reduced risk of depression. **British Journal of Nutrition**, v. 113, n. 9, p. 1418–1426, 2015.

JADDOU, H. Y. et al. Depression is associated with low levels of 25-hydroxyvitamin D among Jordanian adults: results from a national population survey. **European Archives of Psychiatry and Clinical Neurosc1/9/23 10:47:00 AMience**, v. 262, n. 4, p. 321–327, 1 jun. 2012.

JAFARINASABIAN, P. et al. Aging human body: changes in bone, muscle and body fat with consequent changes in nutrient intake. **Journal of Endocrinology**, v. 234, n. 1, p. R37–R51, 1 jul. 2017.

JAFFE, D. H.; RIVE, B.; DENEE, T. R. The humanistic and economic burden of treatment-resistant depression in Europe: a cross-sectional study. **BMC Psychiatry**, v. 19, n. 1, p. 247, 7 ago. 2019.

JAMES, S. L. et al. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. **The Lancet**, v. 392, n. 10159, p. 1789–1858, 10 nov. 2018.

JÄPELT, R. B. et al. Quantification of vitamin D3 and its hydroxylated metabolites in waxy leaf nightshade (Solanum glaucophyllum Desf.), tomato (Solanum lycopersicum L.) and bell pepper (Capsicum annuum L.). **Food Chemistry**, v. 138, n. 2–3, p. 1206–1211, 1 jun. 2013.

JÄPELT, R. B.; JAKOBSEN, J. Vitamin D in plants: a review of occurrence, analysis, and biosynthesis. **Frontiers in Plant Science**, v. 4, 2013.

JOHNSON, E. J.; MOHN, E. S. Fat-Soluble Vitamins. **Nutrition for the Primary Care Provider**, v. 111, p. 38–44, 2015.

JOHNSTON, K. M. et al. The burden of treatment-resistant depression: A systematic review of the economic and quality of life literature. **Journal of Affective Disorders**, v. 242, p. 195–210, 1 jan. 2019.

JONES, G. 100 YEARS OF VITAMIN D: Historical aspects of vitamin D. **Endocrine Connections**, v. 11, n. 4, p. e210594, 22 abr. 2022.

JONES, K. S. et al. 25(OH)D2 half-life is shorter than 25(OH)D3 half-life and is influenced by DBP concentration and genotype. **The Journal of Clinical Endocrinology and Metabolism**, v. 99, n. 9, p. 3373–3381, set. 2014.

JORDE, R. et al. Tracking of serum 25-hydroxyvitamin D levels during 14 years in a population-based study and during 12 months in an intervention study. **American Journal of Epidemiology**, v. 171, n. 8, p. 903–908, 15 abr. 2010.

JORDE, R.; KUBIAK, J. No improvement in depressive symptoms by vitamin D supplementation: results from a randomised controlled trial. **Journal of Nutritional Science**, v. 7, p. e30, 2018.

JOVANOVA, O. et al. Vitamin D serum levels are cross-sectionally but not prospectively associated with late-life depression. **Acta Psychiatrica Scandinavica**, v. 135, n. 3, p. 185–194, 2017.

JÓZEFOWICZ, O. et al. Analysis of vitamin D status in major depression. **Journal of Psychiatric Practice**, v. 20, n. 5, p. 329–337, set. 2014.

JU, S.-Y.; LEE, Y.-J.; JEONG, S.-N. Serum 25-hydroxyvitamin D levels and the risk of depression: A systematic review and meta-analysis. **The journal of nutrition, health & aging**, v. 17, n. 5, p. 447–455, 1 maio 2013.

KALTENBOECK, A.; HARMER, C. The neuroscience of depressive disorders: A brief review of the past and some considerations about the future. **Brain and Neuroscience Advances**, v. 2, p. 2398212818799269, 1 jan. 2018.

KANDEL, E. R. et al. Princípios de neurociências. 5. ed. Porto Alegre: **AMGH**, 2014.

KANEKO, I. et al. 1,25-Dihydroxyvitamin D regulates expression of the tryptophan hydroxylase 2 and leptin genes: implication for behavioral influences of vitamin D. **The FASEB Journal**, v. 29, n. 9, p. 4023–4035, 2015.

KARAKIS, I. et al. Association of Serum Vitamin D with the Risk of Incident Dementia and Subclinical Indices of Brain Aging: The Framingham Heart Study. **Journal of Alzheimer's Disease**, v. 51, n. 2, p. 451–461, 1 jan. 2016.

KAREGE, F. et al. Decreased serum brain-derived neurotrophic factor levels in major depressed patients. **Psychiatry Research**, v. 109, n. 2, p. 143–148, 15 mar. 2002.

KESBY, J. P. et al. The effects of vitamin D on brain development and adult brain function. Molecular and Cellular Endocrinology, Vitamin D Metabolism: **Implication for Biological Activities**. v. 347, n. 1, p. 121–127, 5 dez. 2011.

KIM, J.; PARISH, A. L. Polypharmacy and Medication Management in Older Adults. **Nursing Clinics of North America**, v. 52, n. 3, p. 457–468, 1 set. 2017.

KIM, K. Identifying the Factors That Affect Depressive Symptoms in Middle-Aged Menopausal Women: A Nationwide Study in Korea. **International journal of environmental research and public health**, v. 17, n. 22, 2020.

KIM, S. H. et al. The factors associated with Vitamin D deficiency in community dwelling elderly in Korea. **Nutrition Research and Practice**, v. 12, n. 5, p. 387–395, out. 2018.

KIM, T. J.; VON DEM KNESEBECK, O. Income and obesity: what is the direction of the relationship? A systematic review and meta-analysis. **BMJ Open**, v. 8, n. 1, p. e019862, 5 jan. 2018.

KIMBALL, S. M.; HOLICK, M. F. Official recommendations for vitamin D through the life stages in developed countries. **European Journal of Clinical Nutrition**, v. 74, n. 11, p. 1514–1518, nov. 2020.

KNAPP, M.; WONG, G. Economics and mental health: the current scenario. v. 19, p. 3–14, 10 jan. 2020.

KÖHLER, C. A. et al. Peripheral cytokine and chemokine alterations in depression: a meta-analysis of 82 studies. **Acta Psychiatrica Scandinavica**, v. 135, n. 5, p. 373–387, 2017.

KÖHLER, C. A. et al. Mapping risk factors for depression across the lifespan: An umbrella review of evidence from meta-analyses and Mendelian randomization studies. **Journal of Psychiatric Research**, v. 103, p. 189–207, 1 ago. 2018.

KÖHNKE, C.; HERRMANN, M.; BERGER, K. Associations of major depressive disorder and related clinical characteristics with 25-hydroxyvitamin D levels in middle-aged adults. **Nutritional Neuroscience**, v. 0, n. 0, p. 1–10, 9 dez. 2020.

KOO, J. W. et al. Nuclear factor-κB is a critical mediator of stress-impaired neurogenesis and depressive behavior. **Proceedings of the National Academy of Sciences**, v. 107, n. 6, p. 2669–2674, 9 fev. 2010.

KRISHNAMOORTHY, Y.; RAJAA, S.; REHMAN, T. Diagnostic accuracy of various forms of geriatric depression scale for screening of depression among older adults: Systematic review and meta-analysis. **Archives of Gerontology and Geriatrics**, v. 87, p. 104002, 1 mar. 2020.

LAI, J. S. et al. A systematic review and meta-analysis of dietary patterns and depression in community-dwelling adults. **The American Journal of Clinical Nutrition**, v. 99, n. 1, p. 181–197, 1 jan. 2014.

LAIRD, E. et al. The Prevalence of Vitamin D Deficiency and the Determinants of 25(OH)D Concentration in Older Irish Adults: Data From The Irish Longitudinal Study on Ageing (TILDA). **The Journals of Gerontology: Series A**, v. 73, n. 4, p. 519–525, 14 mar. 2018.

LANDEL, V. et al. Differential expression of vitamin D-associated enzymes and receptors in brain cell subtypes. **The Journal of Steroid Biochemistry and Molecular Biology**, v. 177, p. 129–134, 1 mar. 2018.

LAPID, M. I.; CHA, S. S.; TAKAHASHI, P. Y. Vitamin D and depression in geriatric primary care patients. **Clinical Interventions in Aging**, v. 8, p. 509–514, 2013.

LEE, C.-H.; GIULIANI, F. The Role of Inflammation in Depression and Fatigue. **Frontiers in Immunology**, v. 10, 19 jul. 2019.

LEE, D. M. et al. Lower vitamin D levels are associated with depression among community-dwelling European men. **Journal of Psychopharmacology**, v. 25, n. 10, p. 1320–1328, 1 out. 2011.

LEE, S.-H. et al. Association of serum 25-hydroxyvitamin D and serum total cholesterol with depressive symptoms in Korean adults: the Fifth Korean National Health and Nutrition Examination Survey (KNHANES V, 2010-2012). **Public Health Nutrition**, v. 20, n. 10, p. 1836–1843, jul. 2017.

LI, H. et al. Serum 25-Hydroxyvitamin D Levels and Depression in Older Adults: A Dose–Response Meta-Analysis of Prospective Cohort Studies. **The American Journal of Geriatric Psychiatry**, v. 27, n. 11, p. 1192–1202, 1 nov. 2019.

LI, M.; D'ARCY, C.; MENG, X. Maltreatment in childhood substantially increases the risk of adult depression and anxiety in prospective cohort studies: systematic review, meta-analysis, and proportional attributable fractions. **Psychological Medicine**, v. 46, n. 4, p. 717–730, mar. 2016.

LIMA-COSTA, M. F. et al. Nationwide vitamin D status in older Brazilian adults and its determinants: The Brazilian Longitudinal Study of Aging (ELSI). **Scientific Reports**, v. 10, n. 1, p. 13521, 11 ago. 2020.

LIN, L.-Y. et al. Distribution of vitamin D status in the UK: a cross-sectional analysis of UK Biobank. **BJM Open**, v. 11, n. 1, 2020.

LIPS, P. Relative value of 25(OH)D and 1,25(OH)2D measurements. **Journal of Bone and Mineral Research**, v. 22, n. 11, p. 1668–1671, nov. 2007.

LIPSITZ, O. et al. Early symptomatic improvements as a predictor of response to repeated-dose intravenous ketamine: Results from the Canadian Rapid Treatment Center of Excellence. **Progress in Neuro-Psychopharmacology and Biological Psychiatry**, v. 105, p. 110126, 8 mar. 2021.

LISSEMORE, J. I. et al. Reduced GABAergic cortical inhibition in aging and depression. **Neuropsychopharmacology**, v. 43, n. 11, p. 2277–2284, out. 2018.

LOHMANN, T. G.; ROCHE, A. F.; MARTORELL, R. Anthropometric Standardization Reference Manual. [s.l.] Human Kinetics Books, **Champaign**, Ill., 1988.

LOPES, C. S. et al. Inequities in access to depression treatment: results of the Brazilian National Health Survey – PNS. **International Journal for Equity in Health**, v. 15, n. 1, p. 154, dez. 2016.

LUO, J. et al. The association between blood concentration of 25- hydroxyvitamin D and sarcopenia: a meta-analysis. **Asia Pacific Journal of Clinical Nutrition**, v. 27, n. 6, p. 1258–1270, 2018.

LUPPINO, F. S. et al. Overweight, obesity, and depression: a systematic review and meta-analysis of longitudinal studies. **Archives of General Psychiatry**, v. 67, n. 3, p. 220–229, mar. 2010.

MACIEL, Á. C. C.; GUERRA, R. O. Prevalência e fatores associados à sintomatologia depressiva em idosos residentes no Nordeste do Brasil. **Jornal Brasileiro de Psiquiatria**, v. 55, n. 1, p. 26–33, 2006.

MACLAUGHLIN, J.; HOLICK, M. F. Aging decreases the capacity of human skin to produce vitamin D3. **Journal of Clinical Investigation**, v. 76, n. 4, p. 1536–1538, out. 1985.

MAEDA, S. S. et al. Recommendations of the Brazilian Society of Endocrinology and Metabology (SBEM) for the diagnosis and treatment of hypovitaminosis D. **Arquivos Brasileiros de Endocrinologia Metabologia**, v. 58, n. 5, p. 411–433, jul. 2014.

MAKI, P. M. et al. Guidelines for the evaluation and treatment of perimenopausal depression: summary and recommendations. **Menopause** , v. 25, n. 10, p. 1069–1085, out. 2018.

MANZANOS, I. et al. Vitamin D: Between the brightness of the sun and the darkness of depression. **Revista Colombiana de Psiquiatría** , v. 51, n. 3, p. 199–205, 1 jul. 2022.

MARCINOWSKA-SUCHOWIERSKA, E. et al. Vitamin D Toxicity-A Clinical Perspective. **Frontiers in Endocrinology**, v. 9, p. 550, 2018.

MARINO, R.; MISRA, M. Extra-Skeletal Effects of Vitamin D. **Nutrients**, v. 11, n. 7, p. 1460, jul. 2019.

MATIAS, A. G. C. et al. Indicators of depression in elderly and different screening methods. **Einstein,** v. 14, n. 1, p. 6–11, mar. 2016.

MAYNE, P. E.; BURNE, T. H. J. Vitamin D in Synaptic Plasticity, Cognitive Function, and Neuropsychiatric Illness. **Trends in Neurosciences**, v. 42, n. 4, p. 293–306, 1 abr. 2019.

MENDES, M. M. et al. Vitamin D status in the tropics: Is sunlight exposure the main determinant? **Nutrition Bulletin**, v. 43, n. 4, p. 428–434, 2018.

MENDES-CHILOFF, C. L. et al. Depressive symptoms among the elderly in São Paulo city, Brazil: prevalence and associated factors (SABE Study). **Revista Brasileira de Epidemiologia**, v. 21, 2018.

MENKE, A. Is the HPA Axis as Target for Depression Outdated, or Is There a New Hope? **Frontiers in Psychiatry**, v. 10, 28 fev. 2019.

MIGLIACCIO, S. et al. Obesity and hypovitaminosis D: causality or casualty? **International Journal of Obesity Supplements**, v. 9, n. 1, p. 20–31, abr. 2019.

MILANESCHI, Y. et al. Serum 25-hydroxyvitamin D and depressive symptoms in older women and men. **The Journal of clinical endocrinology and metabolism**, v. 95, n. 7, p. 3225–3233, jul. 2010.

MILANESCHI, Y. et al. The association between low vitamin D and depressive disorders. **Molecular Psychiatry**, v. 19, n. 4, p. 444–451, abr. 2014.

MINISOLA, S. et al. Screening for hypovitaminosis D: cost-effective or not? **European Journal of Endocrinology**, v. 180, n. 3, p. D1–D7, 1 mar. 2019.

MO, M. et al. A systematic review and meta-analysis of the response of serum 25-hydroxyvitamin D concentration to vitamin D supplementation from RCTs from around the globe. **European Journal of Clinical Nutrition**, v. 73, n. 6, p. 816–834, jun. 2019.

MOITRA, M. et al. The global gap in treatment coverage for major depressive disorder in 84 countries from 2000–2019: A systematic review and Bayesian meta-regression analysis. **PLOS Medicine**, v. 19, n. 2, p. e1003901, 15 fev. 2022.

MORIGUCHI, S. et al. Glutamatergic neurometabolite levels in major depressive disorder: a systematic review and meta-analysis of proton magnetic resonance spectroscopy studies. **Molecular Psychiatry**, v. 24, n. 7, p. 952–964, 2019.

MOUSSAVI, S. et al. Depression, chronic diseases, and decrements in health: results from the World Health Surveys. **The Lancet**, v. 370, n. 9590, p. 851–858, 8 set. 2007.

MUKAI, Y.; TAMPI, R. R. Treatment of depression in the elderly: A review of the recent literature on the efficacy of single- versus dual-action antidepressants. **Clinical Therapeutics**, v. 31, n. 5, p. 945–961, 1 maio 2009.

MULUGETA, A.; LUMSDEN, A.; HYPPÖNEN, E. Relationship between Serum 25(OH)D and Depression: Causal Evidence from a Bi-Directional Mendelian Randomization Study. **Nutrients**, v. 13, n. 1, p. 109, jan. 2021.

NANRI, A. et al. Association between serum 25-hydroxyvitamin D and depressive symptoms in Japanese: analysis by survey season. **European Journal of Clinical Nutrition**, v. 63, n. 12, p. 1444–1447, dez. 2009.

NETO, F. L. et al. Neurotrophins Role in Depression Neurobiology: A Review of Basic and Clinical Evidence. **Current Neuropharmacology**, v. 9, n. 4, p. 530–552, dez. 2011.

NEURAUTER, G. et al. Chronic Immune Stimulation Correlates with Reduced Phenylalanine Turnover. **Current Drug Metabolism**, v. 9, n. 7, p. 622–627, 1 set. 2008.

NORMAN, A. W. The History of the Discovery of Vitamin D and Its Daughter Steroid Hormone. **Annals of Nutrition and Metabolism**, v. 61, n. 3, p. 199–206, 2012.

OGAWA, S. et al. Plasma L-tryptophan concentration in major depressive disorder: new data and meta-analysis. **The Journal of Clinical Psychiatry**, v. 75, n. 9, p. e906-915, set. 2014.

OLESEN, J. et al. The economic cost of brain disorders in Europe. **European journal of neurology**, v. 19, n. 1, p. 155–162, jan. 2012.

OLIVERI, B. et al. Vitamin D3 seems more appropriate than D2 to sustain adequate levels of 25OHD: a pharmacokinetic approach. **European Journal of Clinical Nutrition**, v. 69, n. 6, p. 697–702, jun. 2015.

ORMEL, J. et al. What is needed to eradicate the depression epidemic, and why. **Mental Health & Prevention**, v. 17, p. 200177, 1 mar. 2020.

OTTE, C. et al. Major depressive disorder. Nature reviews. **Disease primers**, v. 2, p. 16065, 15 set. 2016.

PADOVANI, R. M. et al. Dietary reference intakes: aplicabilidade das tabelas em estudos nutricionais. **Revista de Nutrição**, v. 19, n. 6, p. 741–760, dez. 2006.

PALACIOS, C.; GONZALEZ, L. Is vitamin D deficiency a major global public health problem? **The Journal of steroid biochemistry and molecular biology**, v. 144 Pt A, p. 138–145, out. 2014.

PAN, A. et al. Association between depressive symptoms and 25-hydroxyvitamin D in middle-aged and elderly Chinese. **Journal of Affective Disorders**, v. 118, n. 1, p. 240–243, 1 nov. 2009.

PAN, A. et al. Bidirectional association between depression and obesity in middle-aged and older women**. International Journal of Obesity**, v. 36, n. 4, p. 595–602, abr. 2012.

PARDRIDGE, W. M.; SAKIYAMA, R.; COTY, W. A. Restricted Transport of Vitamin D and A Derivatives Through the Rat Blood-Brain Barrier. **Journal of Neurochemistry**, v. 44, n. 4, p. 1138–1141, 1985.

PARIANTE, C. M. Risk Factors for Development of Depression and Psychosis. **Annals of the New York Academy of Sciences**, v. 1179, p. 144–152, out. 2009.

PARKER, G. B.; BROTCHIE, H.; GRAHAM, R. K. Vitamin D and depression. **Journal of Affective Disorders**, v. 208, p. 56–61, 15 jan. 2017.

PASSERON, T. et al. Sunscreen photoprotection and vitamin D status. **The British Journal of Dermatology**, v. 181, n. 5, p. 916–931, nov. 2019.

PASSOS, V. M. DE A. et al. The burden of disease among Brazilian older adults and the challenge for health policies: results of the Global Burden of Disease Study 2017. **Population Health Metrics**, v. 18, n. 1, p. 14, 30 set. 2020.

PATEL, V. et al. Income inequality and depression: a systematic review and meta-analysis of the association and a scoping review of mechanisms. **World Psychiatry**, v. 17, n. 1, p. 76–89, fev. 2018.

PATRICK, R. P.; AMES, B. N. Vitamin D and the omega-3 fatty acids control serotonin synthesis and action, part 2: relevance for ADHD, bipolar disorder, schizophrenia, and impulsive behavior. **The FASEB Journal**, v. 29, n. 6, p. 2207–2222, 24 fev. 2015.

PEREIRA-SANTOS, M. et al. Epidemiology of vitamin D insufficiency and deficiency in a population in a sunny country: Geospatial meta-analysis in Brazil. **Critical Reviews in Food Science and Nutrition**, v. 59, n. 13, p. 2102–2109, 20 jul. 2019.

PETERSEN, B. et al. Sunscreen use and failures – on site observations on a sun-holiday. **Photochemical & Photobiological Sciences**, v. 12, n. 1, p. 190–196, 13 dez. 2012.

PLÓZER, E. et al. Intracranial volume inversely correlates with serum 25(OH)D level in healthy young women. **Nutritional Neuroscience**, v. 18, n. 1, p. 37–40, 1 jan. 2015.

PONTI, F. et al. Aging and Imaging Assessment of Body Composition: From Fat to Facts. **Frontiers in Endocrinology**, v. 10, 14 jan. 2020.

PRABHU, A. V. et al. DHCR7: A vital enzyme switch between cholesterol and vitamin D production. **Progress in Lipid Research**, v. 64, p. 138–151, 2016.

RABENBERG, M. et al. Association between vitamin D and depressive symptoms varies by season: Results from the German Health Interview and Examination Survey for Adults (DEGS1). **Journal of Affective Disorders**, v. 204, p. 92–98, 1 nov. 2016.

RAMOS, G. C. F. et al. Prevalência de sintomas depressivos e fatores associados em idosos no norte de Minas Gerais: um estudo de base populacional. **Jornal Brasileiro de Psiquiatria**, v. 64, n. 2, p. 122–131, jun. 2015.

READ, J. et al. The interpersonal adverse effects reported by 1008 users of antidepressants; and the incremental impact of polypharmacy. **Psychiatry Research**, v. 256, p. 423–427, 1 out. 2017.

REBOUL, E. Intestinal absorption of vitamin D: from the meal to the enterocyte. **Food & Function**, v. 6, n. 2, p. 356–362, 12 fev. 2015.

REPOUSI, N. et al. Depression and metabolic syndrome in the older population: A review of evidence. **Journal of Affective Disorders**, v. 237, p. 56–64, set. 2018.

REYNOLDS, S. L.; HALEY, W. E.; KOZLENKO, N. The impact of depressive symptoms and chronic diseases on active life expectancy in older Americans. **The American Journal of Geriatric Psychiatry**, v. 16, n. 5, p. 425–432, maio 2008.

RHEE, S. J.; LEE, H.; AHN, Y. M. Serum Vitamin D Concentrations Are Associated With Depressive Symptoms in Men: The Sixth Korea National Health and Nutrition Examination Survey 2014. **Frontiers in Psychiatry**, v. 11, 2020.

ROCHA-LIMA, M. T. et al. Depressive symptoms and level of 25-hydroxyvitamin D in free-living oldest old. **Practice Clinical & Research Aging**, v. 5, n.3, 2016.

ROLIZOLA, P. M. D. et al. Insuficiência de vitamina D e fatores associados: um estudo com idosos assistidos por serviços de atenção básica à saúde. **Ciência & Saúde Coletiva**, v. 27, p. 653–663, 2 fev. 2022.

RONALDSON, A. et al. Prospective associations between vitamin D and depression in middle-aged adults: findings from the UK Biobank cohort. **Psychological Medicine**, p. 1–9, 21 out. 2020.

ROSEN, C. J. et al. IOM Committee Members Respond to Endocrine Society Vitamin D Guideline. **The Journal of Clinical Endocrinology & Metabolism**, v. 97, n. 4, p. 1146–1152, 1 abr. 2012.

ROSENBLAT, J. D. et al. Inflamed moods: A review of the interactions between inflammation and mood disorders. **Progress in Neuro-Psychopharmacology and Biological Psychiatry**, v. 53, p. 23–34, 4 ago. 2014.

ROSS, A. C. et al. The 2011 Report on Dietary Reference Intakes for Calcium and Vitamin D from the Institute of Medicine: What Clinicians Need to Know. **The Journal of Clinical Endocrinology & Metabolism**, v. 96, n. 1, p. 53–58, 1 jan. 2011.

ROTH, D. E. et al. Global prevalence and disease burden of vitamin D deficiency: a roadmap for action in low- and middle-income countries. **Annals of the New York Academy of Sciences**, v. 1430, n. 1, p. 44–79, 2018.

RUTHERFORD, B. R. et al. Biological Aging and the Future of Geriatric Psychiatry. **The Journals of Gerontology Series A**, v. 72, n. 3, p. 343–352, mar. 2017.

SABIR, M. S. et al. Optimal vitamin D spurs serotonin: 1,25-dihydroxyvitamin D represses serotonin reuptake transport (SERT) and degradation (MAO-A) gene expression in cultured rat serotonergic neuronal cell lines. **Genes & Nutrition**, v. 13, 11 jul. 2018.

SACHS-ERICSSON, N. et al. Body Mass Index and Depressive Symptoms in Older Adults: The Moderating Roles of Race, Sex, and Socioeconomic Status. **The American Journal of Geriatric Psychiatry**, v. 15, n. 9, p. 815–825, 1 set. 2007.

SAHASRABUDHE, N. et al. Serum Vitamin D and Depressive Symptomatology among Boston-Area Puerto Ricans. **The Journal of Nutrition**, v. 150, n. 12, p. 3231–3240, 10 dez. 2020.

SALIM, S. Oxidative Stress and the Central Nervous System. **The Journal of Pharmacology and Experimental Therapeutics**, v. 360, n. 1, p. 201–205, jan. 2017.

SAVASTANO, S. et al. Low vitamin D status and obesity: Role of nutritionist. **Reviews in Endocrine and Metabolic Disorders**, v. 18, n. 2, p. 215–225, 1 jun. 2017.

SCHNEIDER, I. J. C. et al. EpiFloripa Aging cohort study: methods, operational aspects, and follow-up strategies. **Revista de Saúde Pública**, v. 51, 2017.

SEDAGHAT, K. et al. Mesolimbic dopamine system and its modulation by vitamin D in a chronic mild stress model of depression in the rat. **Behavioural Brain Research**, v. 356, p. 156–169, 1 jan. 2019.

SEMPOS, C. T. et al. Vitamin D assays and the definition of hypovitaminosis D: results from the First International Conference on Controversies in Vitamin D. **British Journal of Clinical Pharmacology**, v. 84, n. 10, p. 2194–2207, out. 2018.

SHADRINA, M.; BONDARENKO, E. A.; SLOMINSKY, P. A. Genetics Factors in Major Depression Disease. **Frontiers in Psychiatry**, v. 9, 23 jul. 2018.

SHEA, M. K. et al. Correlates and prevalence of insufficient 25-hydroxyvitamin D status in black and white older adults: The Health ABC Study. **Journal of the American Geriatrics Society**, v. 59, n. 7, p. 1165–1174, jul. 2011.

SHERCHAND, O. et al. Association between vitamin D deficiency and depression in Nepalese population. **Psychiatry Research**, v. 267, p. 266–271, 2018.

SHIN, Y.-C. et al. The associations among vitamin D deficiency, C-reactive protein, and depressive symptoms. **Journal of Psychosomatic Research**, v. 90, p. 98–104, nov. 2016.

SIVERTSEN, H. et al. Depression and Quality of Life in Older Persons: A Review. **Dementia and Geriatric Cognitive Disorders**, v. 40, n. 5–6, p. 311–339, 2015.

SKVERSKY, A. L. et al. Association of Glucocorticoid Use and Low 25-Hydroxyvitamin D Levels: Results from the National Health and Nutrition Examination Survey (NHANES): 2001–2006. **The Journal of Clinical Endocrinology and Metabolism**, v. 96, n. 12, p. 3838–3845, dez. 2011.

SMAGA, I. et al. Oxidative stress as an etiological factor and a potential treatment target of psychiatric disorders. Part 2. Depression, anxiety, schizophrenia and autism. **Pharmacological reports**, v. 67, n. 3, p. 569–580, jun. 2015.

SMITH, K. J. et al. The association between C-reactive protein, Interleukin-6 and depression among older adults in the community: A systematic review and meta-analysis. **Experimental Gerontology**, v. 102, p. 109–132, fev. 2018.

SONG, B. M. et al. Association between serum 25-hydroxyvitamin D concentrations and depressive symptoms in an older Korean population: A cross-sectional study. **Journal of Affective Disorders**, v. 189, p. 357–364, 1 jan. 2016.

SPEDDING, S. Vitamin D and Depression: A Systematic Review and Meta-Analysis Comparing Studies with and without Biological Flaws. **Nutrients**, v. 6, n. 4, p. 1501–1518, abr. 2014.

STETLER, C.; MILLER, G. E. Depression and hypothalamic-pituitary-adrenal activation: a quantitative summary of four decades of research. **Psychosomatic Medicine**, v. 73, n. 2, p. 114–126, mar. 2011.

STEWART, R.; HIRANI, V. Relationship Between Vitamin D Levels and Depressive Symptoms in Older Residents From a National Survey Population. **Psychosomatic Medicine**, v. 72, n. 7, p. 608, set. 2010.

STUMPF, W. E. et al. Brain target sites for 1,25-dihydroxyvitamin D3. **Science**, v. 215, n. 4538, p. 1403–1405, 12 mar. 1982.

SWARDFAGER, W. et al. Mapping inflammation onto mood: Inflammatory mediators of anhedonia. **Neuroscience & Biobehavioral Reviews**, v. 64, p. 148–166, 1 maio 2016.

TAKEUCHI, H. et al. Tumor Necrosis Factor-α Induces Neurotoxicity via Glutamate Release from Hemichannels of Activated Microglia in an Autocrine Manner. **Journal of Biological Chemistry**, v. 281, n. 30, p. 21362–21368, 28 jul. 2006.

THOMPSON, S. M. et al. An excitatory synapse hypothesis of depression. **Trends in neurosciences**, v. 38, n. 5, p. 279–294, maio 2015.

TIAN, X. Q.; HOLICK, M. F. Catalyzed thermal isomerization between previtamin D3 and vitamin D3 via beta-cyclodextrin complexation. **The Journal of Biological Chemistry**, v. 270, n. 15, p. 8706–8711, 14 abr. 1995.

TICINESI, A. et al. Nutrition and Inflammation in Older Individuals: Focus on Vitamin D, n-3 Polyunsaturated Fatty Acids and Whey Proteins. **Nutrients**, v. 8, n. 4, 29 mar. 2016.

TOFFANELLO, E. D. et al. Serum 25-hydroxyvitamin d and the onset of late-life depressive mood in older men and women: the Pro.V.A. study. **The Journals of Gerontology: Series A**, v. 69, n. 12, p. 1554–1561, dez. 2014.

TRIPKOVIC, L. et al. Comparison of vitamin D2 and vitamin D3 supplementation in raising serum 25-hydroxyvitamin D status: a systematic review and meta-analysis123. **The American Journal of Clinical Nutrition**, v. 95, n. 6, p. 1357–1364, jun. 2012.

TSIARAS, W. G.; WEINSTOCK, M. A. Factors influencing vitamin D status. **Acta Dermato-Venereologica**, v. 91, n. 2, p. 115–124, mar. 2011.

UMAR, M.; SASTRY, K. S.; CHOUCHANE, A. I. Role of Vitamin D Beyond the Skeletal Function: A Review of the Molecular and Clinical Studies. **International Journal of Molecular Sciences**, v. 19, n. 6, 30 maio 2018.

USDA, National Nutrient Database for Standard Reference Release. Nutrients: Vitamin D. Disponível em: <https://ods.od.nih.gov/pubs/usdandb/VitaminD-Content.pdf>.

VAN DEN BERG, K. S. et al. Vitamin D deficiency, depression course and mortality: Longitudinal results from the Netherlands Study on Depression in Older persons (NESDO). **Journal of Psychosomatic Research**, v. 83, p. 50–56, abr. 2016.

VAN DEN BERG, K. S. et al. A prospective study into change of vitamin D levels, depression and frailty among depressed older persons**. International Journal of Geriatric Psychiatry**, 8 fev. 2021.

VAN DEN BOSCH, M.; MEYER-LINDENBERG, A. Environmental Exposures and Depression: Biological Mechanisms and Epidemiological Evidence. **Annual Review of Public Health**, v. 40, n. 1, p. 239–259, 2019.

VIDGREN, M. et al. Serum Concentrations of 25-Hydroxyvitamin D and Depression in a General Middle-Aged to Elderly Population in Finland. **The journal of nutrition, health & aging**, v. 22, n. 1, p. 159–164, 1 jan. 2018.

VOEDISCH, A. J.; DUNSMOOR-SU, R.; KASIRSKY, J. Menopause: A Global Perspective and Clinical Guide for Practice. **Clinical Obstetrics and Gynecology**, v. 64, n. 3, p. 528–554, 1 set. 2021.

WACKER, M.; HOLICK, M. F. Sunlight and Vitamin D: A global perspective for health. **Dermato-Endocrinology**, v. 5, n. 1, p. 51–108, 1 jan. 2013a.

WACKER, M.; HOLICK, M. F. Vitamin D—Effects on Skeletal and Extraskeletal Health and the Need for Supplementation. **Nutrients**, v. 5, n. 1, p. 111–148, 10 jan. 2013b.

WANG, P. S. et al. Worldwide Use of Mental Health Services for Anxiety, Mood, and Substance Disorders: Results from 17 Countries in the WHO World Mental Health (WMH) Surveys. **Lancet**, v. 370, n. 9590, p. 841–850, 8 set. 2007.

WARSH, J. J.; ANDREOPOULOS, S.; LI, P. P. Role of intracellular calcium signaling in the pathophysiology and pharmacotherapy of bipolar disorder: current status. **Clinical Neuroscience Research**, v. 4, n. 3, p. 201–213, 1 dez. 2004.

WHITEFORD, H. A. et al. The global burden of mental, neurological and substance use disorders: an analysis from the Global Burden of Disease Study 2010. **PloS one**, v. 10, n. 2, p. e0116820–e0116820, 6 fev. 2015.

WILKINS, C. H. et al. Vitamin D deficiency is associated with low mood and worse cognitive performance in older adults. **The American Journal of Geriatric Psychiatry**, v. 14, n. 12, p. 1032–1040, dez. 2006.

WILLIAMS, J. A. et al. Low 25-Hydroxyvitamin D Concentrations Predict Incident Depression in Well-Functioning Older Adults: The Health, Aging, and Body Composition Study. **The Journals of Gerontology Series A**, v. 70, n. 6, p. 757–763, jun. 2015.

WIMALAWANSA, S. J. Vitamin D Deficiency: Effects on Oxidative Stress, Epigenetics, Gene Regulation, and Aging. **Biology**, v. 8, n. 2, 11 maio 2019.

WONG, S. K.; IMA-NIRWANA, K.-Y. C. AND S. Vitamin D and Depression: The Evidence from an Indirect Clue to Treatment Strategy. **Current Drug Targets**, v.19, n. 8, 2018.

WORLD HEALTH ORGANIZATION. Comprehensive Mental Health Action Plan 2013-2030. [s.l: s.n.]. 2021 Disponível em: < https://www.who.int/publications/i/item/9789240031029>.

WORLD HEALTH ORGANIZATION. ICD-11 - Mortality and Morbidity Statistics. Disponível em: <https://icd.who.int/browse11/l-m/en>. Acesso em: 2 mar. 2020.

WORLD HEALTH ORGANIZATION. Depression. Disponível em: <https://www.who.int/news-room/fact-sheets/detail/depression>. Acesso em: 13 fev. 2020.

WORLD HEALTH ORGANIZATION. Depression and Other Common Mental Disorders: Global Health Estimates. Geneva: World Health Organization, 2017. Disponível em: <http://www.who.int/mental_health/management/depression/prevalence_global_health_estimates/en/>.

WORLD HEALTH ORGANIZATION. Mental health atlas 2017. Geneva, Switzerland: World Health Organization, 2018.

WORLD HEALTH ORGANIZATION. WHO | Mental health action plan 2013 - 2020. 2013. Disponível em: <http://www.who.int/entity/mental_health/publications/action_plan/en/index.html>.

WORTSMAN, J. et al. Decreased bioavailability of vitamin D in obesity. **The American Journal of Clinical Nutrition**, v. 72, n. 3, p. 690–693, set. 2000.

YAO, Y. et al. The prevalence of depressive symptoms in Chinese longevous persons and its correlation with vitamin D status. **BMC Geriatrics**, v. 18, n. 1, p. 198, 29 ago. 2018.

YESAVAGE, J. A. et al. Development and validation of a geriatric depression screening scale: A preliminary report. **Journal of Psychiatric Research**, v. 17, n. 1, p. 37–49, 1982.

YUAN, J. P. et al. Homer binds TRPC family channels and is required for gating of TRPC1 by IP3 receptors. **Cell**, v. 114, n. 6, p. 777–789, 19 set. 2003.

ZHANG, J. et al. Peripheral interleukin-6 administration increases extracellular concentrations of serotonin and the evoked release of serotonin in the rat striatum. **Neurochemistry International**, v. 38, n. 4, p. 303–308, 1 abr. 2001.

ZHU, D. et al. The Relationship Between Serum Concentration of Vitamin D, Total Intracranial Volume, and Severity of Depressive Symptoms in Patients With Major Depressive Disorder. **Frontiers in Psychiatry**, v. 10, 2019.

ZHU, D. et al. The Relationship Between Vitamin D, Clinical Manifestations, and Functional Network Connectivity in Female Patients With Major Depressive Disorder. **Frontiers in Aging Neuroscience**, v. 14, 2022.

ZMIJEWSKI, M. A.; CARLBERG, C. Vitamin D receptor(s): In the nucleus but also at membranes? **Experimental Dermatology**, v. 29, n. 9, p. 876–884, 2020.

APÊNDICE A – NOTA DE IMPRENSA

Pesquisa realizada na Universidade Federal de Santa Catarina mostra que ter maior adiposidade e a falta da prática de atividade física estão entre os fatores de risco para o baixo nível sérico de vitamina D e que isso está associado ao risco de ter sintomas depressivos em idosos.

A vitamina D é conhecida por suas ações na saúde óssea, mas também tem ações na saúde muscular, mental, imunidade, entre outras. É produzida principalmente na pele, através da luz solar, mas também obtida através de alimentos como peixes gordurosos (salmão, peixes gordurosos (salmão, sardinha, cavala, atum), cogumelos, alimentos fortificados com vitamina D, e por suplementação.

Durante o envelhecimento, os idosos frequentemente tem sua dosagem de vitamina D sanguínea indicando insuficiência (21–29 ng/ml) ou em casos mais graves, deficiência (≤ 20 ng/ml). Isso tem sido implicado em várias condições, como risco de fratura óssea, fraqueza muscular e queda, e nos últimos anos tem despertado interesse em estudos com depressão, por apresentar alguns caminhos de atuação nas mesmas vias que desencadeiam a depressão.

Os dados desses estudo são provenientes do estudo EpiFloripa Idoso, coordenado pela Prof. Eleonora d'Orsi, que no ano de 2009-2010 entrevistou a primeira onda de idosos de Florianópolis-SC, e entrevistou novamente nos anos de 2013-2014 e 2017-2019. O objetivo da tese de doutorado foi investigar os determinantes do nível sérico de vitamina D e sua associação com sintomas depressivos. 574 idosos que participaram da pesquisa, também tiveram amostra de sangue coletada para análise da vitamina D em 2014-2015.

Como resultados, foi encontrado que 67,2% dos idosos tinham hipovitaminose D: 43,7% de insuficiência (21–29 ng/ml) e 23,5% com deficiência (≤ 20 ng/ml); os fatores de risco para o baixo nível sérico foram ser do sexo feminino, ter uma maior adiposidade (obesidade pelo percentual de gordura corporal: homens ≥ 31% e mulheres ≥43%; e índice de massa corporal, IMC ≥30 kg/m^2), ter maior dependência para atividades da vida diária (≥4 atividades), maior nível de colesterol LDL; como fator protetor foi a prática de atividade física de lazer (≥150 minutos/semana). É importante verificar com frequência o nível sérico de vitamina D no sangue e suplementar sempre que estiver baixo (sob

supervisão do médico ou nutricionista). Assim como a baixa vitamina D, a suplementação sem supervisão pode chegar a níveis muito altos, com consequências graves.

Foi identificado que 15.8% dos idosos em 2013/14, e 17,6% em 2017/19 tiveram rastreamento positivo para sintomas depressivos. Existem escalas específicas que são ferramentas práticas para identificação de sintomas depressivos, mas que que precisam de confirmação por meio de entrevista diagnóstica de depressão. Os idosos com níveis mais baixos de vitamina D (≤ 20 ng/ml) tiveram maior risco de 2,27 vezes maior de apresentar sintomas depressivos em 2013/14 e 2,90 vezes maior de manter ou desenvolver sintomas depressivos ao longo de 2 a 5 anos. Além disso, feito um levantamento bibliográfico sobre essa relação entre a vitamina D e depressão e a vitamina D adequada parece ter um papel preventivo, entretanto, mais estudos com apenas idosos precisam ser desenvolvidos.

Também, foi verificado que 28,4% dos idosos em 2017/19, acompanhados ao longo de 10 anos, tinham obesidade pelo índice IMC (≥30 kg/m^2) e que 59,1% tinham a circunferência da cintura elevada (homens: ≥102 mulheres: ≥88 cm), e que os idosos com obesidade tiveram um risco relativo de 76% de aumentar o score de sintomas depressivos ao longo de 10 anos.

Os estudos foram desenvolvidos no Programa de Pós-Graduação em Nutrição (PPGN/UFSC) que gerou a tese de doutorado “Determinantes das concentrações séricas da vitamina D e a sua associação com sintomas depressivos em idosos de Florianópolis-SC", de Gilciane Ceolin, PhD, defendida em dezembro de 2022, sob orientação da Prof. Júlia Dubois Moreira, PhD, e coorientação da Prof. Débora Kurrle Rieger Venske, PhD. Teve uma parte desenvolvida em estágio de doutorado sanduíche sob supervisão da Prof. Elisa Brietzke, PhD, no *Centre for Neuroscience Studies* da *Queen’s University* (Canadá). O estudo recebeu o apoio financeiro da Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), por meio de concessão de bolsa de estudo de doutorado e de doutorado sanduíche no exterior.

Para mais informações, entrar em contato com:

Gilciane Ceolin, *nutrigil@live.com*

Júlia Dubois Moreira, *juliamoreira@gmail.com*

Site do estudo EpiFloripa Idoso: https://epifloripaidoso.paginas.ufsc.br/

APÊNDICE B – CARTA AOS PARTICIPANTES DO EPIFLORIPA IDOSO

Prezado participante do Estudo EpiFloripa Idoso,

Queremos agradecer a sua participação na pesquisa, bem como compartilhar alguns resultados de estudos que só foram possíveis de serem realizados através da sua participação!

O estudo EpiFloripa Idoso, desenvolvido na cidade de Florianópolis-SC pela Universidade Federal de Santa Catarina (UFSC), tem acompanhado as condições de saúde e hábitos de vida de 1702 idosos por meio de entrevistas realizadas nos anos de 2009/10, 2013/14, exames clínicos em 2014/15, e 2017/2019.

A sua participação tornou possível a realização da tese de doutorado: "Determinantes das concentrações séricas da vitamina D e a sua associação com sintomas depressivos em idosos de Florianópolis-SC"! Assim, os principais resultados encontrados foram:

67,2% dos idosos Tinham em 2014/15 o nível de vitamina D no sangue, abaixo do recomendado (<30 ng/ml)

Os idosos são um dos grupos de risco para nível baixo de vitamina D. Ela é importante principalmente para a saúde óssea, mas também para saúde muscular, mental, imunidade, entre outras.

Idosos que praticavam atividade física de lazer de 150 minutos ou mais por semana, tiveram menor risco de ter nível baixo de vitamina D

Mulheres, pessoas com obesidade, com maior dependência em atividades da vida diária e maior nível de colesterol LDL, tiveram maior risco para ter nível baixo de vitamina D

A principal fonte de **vitamina D** é o sol, que produz a vitamina D na pele. Mas também pode ser obtida por alimentos como peixes gordurosos (salmão, sardinha, cavala, atum), cogumelos, alimentos fortificados com vitamina D, e por suplementação.

É importante verificar o nível sérico de vitamina D no sangue e suplementar sempre que estiver baixo (sob supervisão do médico ou nutricionista)

Mas, assim como a baixa vitamina D, a suplementação sem supervisão pode chegar a níveis muito altos, com consequências graves

Também identificamos que:

15.8% dos idosos em 2013/14, e **17,6%** em 2017/19

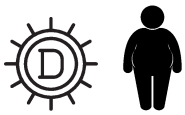
Tiveram rastreamento positivo para sintomas depressivos

A depressão pode ser rastreada através de uma lista de sintomas depressivos, mas precisa ser confirmada por um médico. A depressão causa sofrimento não somente ao idoso, mas também aos seus familiares e cuidadores.

28,4% dos idosos em 2017/19 tinham obesidade (IMC ≥30 kg/m2)

59,1% dos idosos em 2017/19 tinham a circunferência da cintura elevada (H: ≥102 M: ≥88 cm)

A obesidade e a circunferência da cintura elevada são risco para várias doenças crônicas, incluindo doenças cardiovasculares, diabetes mellitus, hipertensão arterial, etc.



Tanto a baixa vitamina D, quanto a obesidade se associaram aos sintomas depressivos, ou seja:

- os idosos com níveis mais baixos de vitamina D (≤ 20 ng/ml) tiveram maior risco de apresentar sintomas depressivos em 2013/14 e ao longo de 2 a 5 anos
- os idosos com obesidade (IMC≥ 30 kg/m2) tiveram maior risco de apresentar sintomas depressivos ao longo de 10 anos

Resumindo..

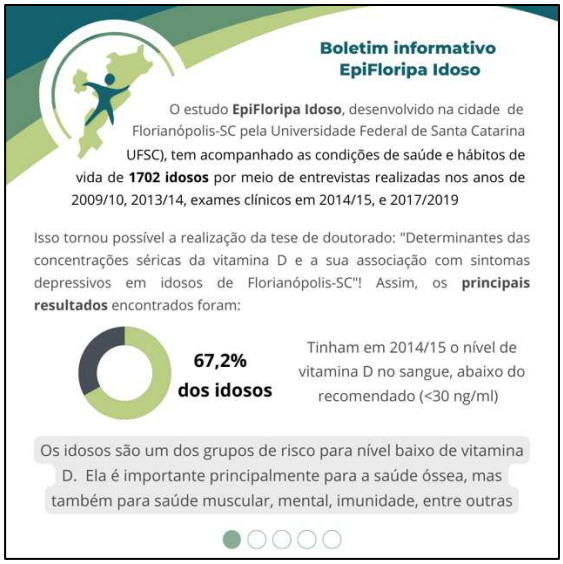
* A redução da obesidade e a prática de atividade física podem auxiliar na manutenção do nível sérico da vitamina D no sangue, e também são importantes para a manutenção da saúde em geral e mental;

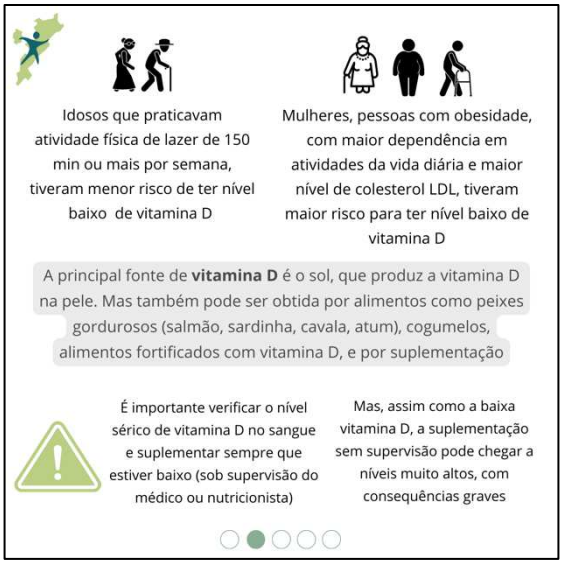
* é importante verificar a vitamina D no sangue com frequência para prevenir e tratar o baixo nível sérico.

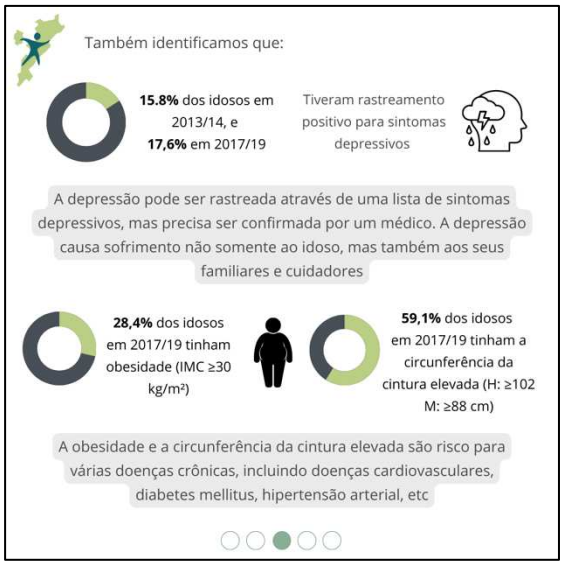
Este estudo foi desenvolvido no Programa de Pós-Graduação em Nutrição (UFSC), que gerou a tese de doutorado de Gilciane Ceolin, PhD, sob orientação da Prof. Júlia Dubois Moreira, PhD, e coorientação da Prof. Débora Kurrle Rieger Venske, PhD. Teve uma parte desenvolvida em estágio de doutorado sanduíche sob supervisão da Prof. Elisa Brietzke, PhD, no *Centre for Neuroscience Studies*, na *Queen's University* (Canadá). O estudo recebeu o apoio financeiro da Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES).

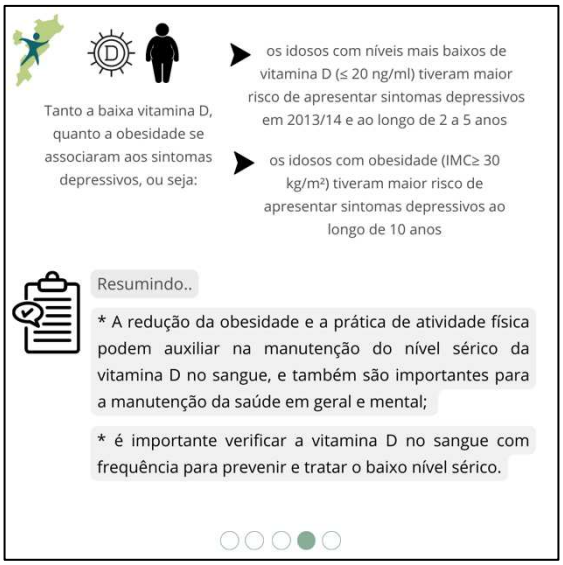
Para mais informações, entrar em contato com:
Gilciane Ceolin, nutrigil@live.com
Júlia Dubois Moreira, juliamoreira@gmail.com
Site do estudo EpiFloripa Idoso: https://epifloripaidoso.paginas.ufsc.br/

APÊNDICE C – POST PARA MÍDIAS SOCIAIS










Este estudo foi desenvolvido no **Programa de Pós-Graduação em Nutrição** (UFSC), que gerou a tese de doutorado de **Gilciane Ceolin**, PhD, sob orientação da Prof. **Júlia Dubois Moreira**, PhD, e coorientação da Prof. **Débora Kurrle Rieger Venske**, PhD.
Teve uma parte desenvolvida em estágio de doutorado sanduíche sob supervisão da Prof. **Elisa Brietzke**, PhD, no *Centre for Neuroscience Studies* da *Queen's University* (Canadá)
O estudo recebeu o apoio financeiro da **Coordenação de Aperfeiçoamento de Pessoal de Nível Superior** (CAPES)
Para mais informações, entrar em contato com:
Gilciane Ceolin, nutrigil@live.com
Júlia Dubois Moreira, juliamoreira@gmail.com
Site do estudo EpiFloripa Idoso: https://epifloripaidoso.paginas.ufsc.br/

ANEXO 1 – APROVAÇÃO DO COMITÊ DE ÉTICA EM PESQUISA DO ESTUDO EPIFLORIPA IDOSO

UNIVERSIDADE FEDERAL DE SANTA CATARINA
Pró- Reitoria de Pesquisa e Extensão
Comitê de Ética na Pesquisa em Seres Humanos

CERTIFICADO Nº 318

O Comitê de Ética na Pesquisa em Seres Humanos (CEPSH) da Pró-Reitoria de Pesquisa e Extensão da Universidade Federal de Santa Catarina, instituído pela PORTARIA N.º0584/GR/99 de 04 de novembro de 1999, com base nas normas para a constituição e funcionamento do CEPSH, considerando o contido no Regimento Interno do CEPSH, **CERTIFICA** que os procedimentos que envolvem seres humanos no projeto de pesquisa abaixo especificado estão de acordo com os princípios éticos estabelecidos pela Comissão Nacional de Ética em Pesquisa - CONEP

APROVADO

PROCESSO: 352/08 FR- 229650

TÍTULO: Condições de saúde da população idosa do município de Florianópolis, Santa Catarina: estudo de base populacional. 2008.

AUTOR: Eleonora d'Orsi.

DPTO.: Saúde Pública/CCS/UFSC

FLORIANÓPOLIS, 15 de dezembro de 2008.

Coordenador do CEPSH/UFSC - Prof.º Washington Portela de Souza

ANEXO 2 - TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO-TCLE DO ESTUDO EPIFLORIPA IDOSO

Termo de Consentimento Livre e Esclarecido

UNIVERSIDADE FEDERAL DE SANTA CATARINA
CENTRO DE CIÊNCIAS DA SAÚDE
DEPARTAMENTO DE SAÚDE PÚBLICA
TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO - TCLE

O Sr(a) está sendo convidado a participar da pesquisa **"Condições gerais de saúde e hábitos de vida em idosos: estudo longitudinal de base populacional em Florianópolis, SC, *EpiFloripa 2013"***. Sua colaboração neste estudo é MUITO IMPORTANTE, mas a decisão de participar é VOLUNTÁRIA, o que significa que o(a) Senhor(a) terá o direito de decidir se quer ou não participar, bem como de desistir de fazê-lo a qualquer momento.

Esta pesquisa tem como objetivo acompanhar a situação de saúde dos participantes do ***Estudo Epifloripa*** entrevistados em 2009/2010 e estabelecer sua relação com condições socioeconômicas, demográficas e de saúde.

Garantimos que será mantida a CONFIDENCIALIDADE das informações e o ANONIMATO. Ou seja, o seu nome não será mencionado em qualquer hipótese ou circunstância, mesmo em publicações científicas. NÃO HÁ RISCOS quanto à sua participação e o BENEFÍCIO será conhecer a realidade da saúde dos moradores de Florianópolis, a qual poderá melhorar os serviços de saúde em sua comunidade.

Será realizada uma entrevista e também serão verificadas as seguintes medidas: pressão arterial (duas vezes), peso, altura e cintura que não causarão problemas à sua saúde. Para isso será necessário aproximadamente uma hora. Os seus dados coletados anteriormente na entrevista realizada em 2009/2010 serão novamente utilizados para fins comparativos.

Em caso de dúvida o(a) senhor(a) poderá entrar em contato com Professora Eleonora d'Orsi, coordenadora deste projeto de pesquisa, no endereço abaixo:

DADOS DO PESQUISADOR RESPONSÁVEL PELO PROJETO DE PESQUISA:

Nome completo: Professora Eleonora d'Orsi,

Doc. de Identificação: 6271033 SSP/SC

Endereço completo: Universidade Federal de Santa Catarina - UFSC

Departamento de Saúde Pública - Trindade / Florianópolis/SC - 88040-900

Fone: (+55 48) 3721-9388 ramal 206

Endereço de email: eleonora@ccs.ufsc.br

IDENTIFICAÇÃO E CONSENTIMENTO DO VOLUNTÁRIO:

Nome completo _____

Doc. de Identificação _____

IDENTIFICAÇÃO E ASSENTIMENTO/ANUÊNCIA DE PARTICIPANTE VULNERÁVEL: (Quando se tratar de população vulnerável)

Nome completo _____

Doc. de Identificação_____

IDENTIFICAÇÃO E AUTORIZAÇÃO DO RESPONSÁVEL LEGAL:

(Quando se tratar de população vulnerável)

Nome completo _____

Doc. de Identificação _____

Tipo de representação: _____

CONSENTIMENTO PÓS-INFORMADO:

"Declaro que, em ____/____/____, concordei em participar, na qualidade de participante do projeto de pesquisa intitulado**"Condições gerais de saúde e hábitos de vida em idosos: estudo longitudinal de base populacional em Florianópolis, SC, *EpiFloripa 2013"***, assim como autorizo o acesso aos meus dados previamente coletados, após estar devidamente informado sobre os objetivos, as finalidades do estudo e os termos de minha participação. Assino o presente Termo de Consentimento Livre e Esclarecido em duas vias, que serão assinadas também pelo pesquisador responsável pelo projeto, sendo que uma cópia se destina a mim (participante) e a outra ao pesquisador."

"As informações fornecidas aos pesquisadores serão utilizadas na exata medida dos objetivos e finalidades do projeto de pesquisa, sendo que minha identificação será mantida em sigilo e sobre a responsabilidade dos proponentes do projeto."

"Não receberei nenhuma remuneração e não terei qualquer ônus financeiro (despesas) em função do meu consentimento espontâneo em participar do presente projeto de pesquisa. Independentemente deste consentimento, fica assegurado meu direito a retirar-me da pesquisa em qualquer momento e por qualquer motivo, sendo que para isso comunicarei minha decisão a um dos proponentes do projeto acima citados."

_____, _____ de _____, de _____

(local e data)

_____

(Assinatura do voluntário ou representante legal acima identificado)

ANEXO 3 - APROVAÇÃO DE BOLSA DE DOUTORADO SANDUÍCHE – CAPES PDSE

Ministry of Education - MEC
Brazilian Federal Foundation for Support and Evaluation of Graduate Education - CAPES
Setor Bancário Norte, Quadra 2, Bloco L, Lote 06
CEP 70.040-031 - Brasília, BRAZIL

Dear Mr.(s),
GILCIANE CEOLIN

Endereço pessoal omitido por confidencialidade

12/01/2022

Processo: PDSE - 88881.622860/2021-01

TO WHOM IT MAY CONCERN

We hereby certify that Mr./Mrs. **GILCIANE CEOLIN** has been awarded a scholarship from the CAPES Foundation, an agency under the Ministry of Education of Brazil, in order to conduct part of his doctoral research as a Visiting Student at **QUEEN'S UNIVERSITY**.

The scholarship includes:

Grant	Unit Value	Parcels (up to)	Total
Health insurance allowance	CAN 100.00	6	CAN 600.00
High cost city stipend	CAN 452.00	6	CAN 2,712.00
Monthly stipends	CAN 1,470.00	6	CAN 8,820.00
Settling-in allowance	CAN 1,470.00	1	CAN 1,470.00
Travel allowance - Single installment	CAN 1,680.00	1	CAN 1,680.00

*The parcels depend on the period of the scholarship stated below.

. The scholarship is valid from**02/2022** to **07/2022**.

. Travel allowance towards the cost of travel for the itinerary:**Brasil/Canadá/Brasil**

. The benefits granted are linked to the period spent abroad, within the approved period.

. Capes will not be responsible for costs related to academic and research fees.

Sincerely,

Emerson Antonio Maccari
General Coordinator for International Scholarships and Projects
This document is public and does not need signature recognition
- Article 19, interpolated proposition II, Federal Constitution of Brazil.

In order to validate the authentication of this document, please visit the website ***http://validadocumentos.capes.gov.br/*** *and enter the following code:* ***2FjjtvTGdReA=***

SOBRE A AUTORA

Apresentação da Autora

Gilciane Ceolin é graduada em nutrição pela Universidade de Passo Fundo (UPF), em parte por bolsa de complementação de estudos da própria universidade e em parte com bolsa Prouni (Passo Fundo-RS, 2012). Realizou especialização em Saúde do Idoso na modalidade Residência Multiprofissional Integrada pela UPF (Passo Fundo-RS, 2016). Obteve o título de mestre em Nutrição pelo Programa de Pós-Graduação em Nutrição, Universidade Federal de Santa Catarina, com bolsa Capes-DS (PPGN/UFSC, Florianópolis-SC), com a dissertação intitulada "Associação entre o consumo de peixes ricos em ômega 3 e sintomas depressivos em idosos de Florianópolis-SC (Florianópolis-SC, 2018)". Em 2018 iniciou doutorado em Nutrição no PPGN/UFSC com bolsa Capes-DS, em 2021 recebeu bolsa de doutorado sanduíche Capes-PDSE para um período de seis meses (fevereiro a julho de 2022) no *Centre for Neuroscience Studies* da *Queen's University* (Kingston, ON, Canadá), sob supervisão da Prof. Dra. Elisa Brietzke. Durante o período de 4 anos e meio conduziu os estudos da presente tese.

Durante uma parte do mestrado e uma parte do doutorado participou de todas as etapas, desde o planejamento até a execução da coleta de dados da terceira onda de pesquisa do Projeto EpiFloripa Idoso, e produção e divulgação dos resultados, e o qual deu origem aos estudos da presente Tese. Participou dos estudos e discussões sobre pesquisa nos grupos de pesquisa e estudo EpiFloripa Idoso, *Translational Nutritional Neuroscience* (UFSC) e *NeuroMood Lab (Queen's University)*. Também no doutorado, foi orientadora de trabalhos de conclusão no "Curso de Especialização em Atenção à Saúde das Pessoas com Sobrepeso e Obesidade" do Ministério da Saúde, oferecido pelo Una-SUS/UFSC.

Produções no período do doutorado

Artigos

GRIGOLON, R.B. et al. Effects of nutritional interventions on the severity of depressive and anxiety symptoms of women in menopausal transition and menopause: a systematic review, meta-analysis, and meta-regression. **Menopause - The Journal Of The North American Menopause Society**, no prelo, 2023.

CEOLIN, G. et al. Association between the consumption of omega-3-rich fish and depressive symptoms in older adults living in a middle-income country: EpiFloripa Aging Study. **Cad. Saúde Coletiva**, 27 nov. 2022.

CONFORTIN, S. C. et al. Estudo de Coorte EpiFloripa Idoso: abordagens metodológicas e reposição da amostra durante a Onda 3 (2017-19). **Estudos Interdisciplinares do Envelhecimento**, no prelo, 2022.

BREDA, V. et al. Is there a place for dietetic interventions in adult ADHD? **Progress in Neuro-Psychopharmacology and Biological Psychiatry**, 12 ago. 2022.

CEOLIN, G. et al. A Possible Antidepressive Effect of Dietary Interventions: Emergent Findings and Research Challenges. **Current Treatment Options in Psychiatry**, 23 abr. 2022.

CEOLIN, G. et al. VITAMIN D AND DEPRESSION IN OLDER ADULTS: LESSONS LEARNED FROM OBSERVATIONAL AND CLINICAL STUDIES. **Nutrition Research Reviews**, p. 1–63, 13 jan. 2022.

CEOLIN, G. et al. Association Between Physical Activity and Vitamin D is Partially Mediated by Adiposity in Older Adults: EpiFloripa Aging Cohort Study. **Nutrition Research**, 14 mar. 2022.

MATSUO, L. H. et al. Association between lower serum vitamin D (25-hydroxy-cholecalciferol) concentrations and cognitive impairment in older adults - Data from a populational-based cohort study in a middle income-country. **Public Health Nutrition**, p. 1–25, 25 out. 2021.

CEOLIN, G. et al. Vitamin D, Depressive Symptoms, and Covid-19 Pandemic. **Frontiers in Neuroscience**, v. 15, 2021.

CEOLIN, G. et al. Nutritional challenges in older adults during the COVID-19 pandemic. **Revista de Nutrição**, v. 33, 4 set. 2020.

CEOLIN, G. et al. Lower serum 25-hydroxycholecalciferol is associated with depressive symptoms in older adults in Southern Brazil. **Nutrition Journal**, v. 19, n. 1, p. 123, 14 nov. 2020.

CONFORTIN, S. C. et al. Sarcopenia, bone mineral density, and vitamin D: EpiFloripa aging study 2013/2014. **Geriatrics, Gerontology and Aging**, v. 14, n. 4, p. 282–289, 2020.

CONFORTIN, S. C. et al. Osteopenia/Osteoporosis and Its Association with Sarcopenia: EpiFloripa Aging Study 2013/2014. **Portuguese Journal of Public Health**, p. 1–8, 26 jun. 2020.

Apresentações de Trabalho

CEOLIN, G. et al. Oral presentation: Role of Vitamin D in Depression in older adults. 2022. Nutrition 2022: 3rd Edition of International Nutrition Research Conference.

CEOLIN, G. Utilização de Gráficos Acíclicos Direcionados em pesquisa, 2021. Apresentação nos grupos de pesquisa *Translational Nutritional Neuroscience* e Grupo de Estudos e Pesquisa em Ambiente Urbano & Saúde.

CEOLIN, G. et al. Determinants of serum concentrations of vitamin D and its association with depressive symptoms: a cross-sectional and longitudinal analysis of the Epifloripa Idoso. 2021. DOP Conference, Queen's University.

Resumos publicados em anais de congressos

GOMES, F. A. et al. Nutritional approaches and their impact on depressive symptoms in midlife women: a systematic review. In: The North America Menopause Society (NAMS) 2021 Annual Meeting, 2021, Washington, DC. Annual Meeting abstracts, 2021.

CEOLIN, G. et al., O Índice de Massa Gorda está associada a sintomas depressivos em idosos - Estudo EpiFloripa Idoso. In: CBNE 2019 - III Congresso Brasileiro de Nutrição e Envelhecimento, III Encontro Brasileiro de Fragilidade, 2019, São Paulo - SP. CBNE 2019, 2019.

CEOLIN, G. et al. Associação entre o percentual de gordura corporal e hipovitaminose D - Estudo EpiFloripa Idoso. In: CBNE 2019 - III Congresso Brasileiro de Nutrição e Envelhecimento, III Encontro Brasileiro de Fragilidade, 2019, São Paulo - SP. CBNE 2019, 2019.

CEOLIN, G. et al. Associação entre o percentual de gordura corporal e sintomas depressivos - Estudo EpiFloripa Idoso. In: CBNE 2019 - III Congresso Brasileiro de

Nutrição e Envelhecimento, III Encontro Brasileiro de Fragilidade, 2019, São Paulo- SP. CBNE 2019, 2019.

MATSUO, L. H. et al. Associação entre o consumo diário de frutas e déficit cognitivo em idosos - Estudo EpiFloripa. In: CBNE 2019 - III Congresso Brasileiro de Nutrição e Envelhecimento, III Encontro Brasileiro de Fragilidade, 2019, São Paulo- SP. CBNE 2019 (trabalho com premiação de melhor tema livre).

CEOLIN, G. et al. Consumo de Peixes Ricos em ômega 3 de idosos residentes em Florianópolis, SC - Estudo EpiFloripa Idoso. In: Congresso Brasileiro de Nutrição - CONBRAN, 2018, Brasília. ANAIS 2018 - CONBRAN. Pinheiros - SP: Revista da Associação Brasileira de Nutrição - RASBRAN, 2018. v. 9.

CEOLIN, G. et al. Associação entre o nível sérico de vitamina D e sintomas depressivos em idosos? Estudo EpiFloripa. In: VI Congresso Internacional de Estudos do Envelhecimento Humano 2018, 2018, Passo Fundo. ANAIS CIEEH 2018. Passo Fundo: Universidade de Passo Fundo, 2018. v. 4.

MATSUO, L. H. et al. Associação entre níveis séricos de vitamina D e déficit cognitivo em idosos de Florianópolis - SC. In: VI Congresso Internacional de Estudos do Envelhecimento Humano 2018, 2018, Passo Fundo. ANAIS CIEEH 2018. Passo Fundo: Universidade de Passo Fundo, 2018. v. 4.

CONFORTIN, S. C. et al. Qualidade de vida associada à força de preensão manual: Estudo EpiFloripa Idoso. In: VI Congresso Internacional de Estudos do Envelhecimento Humano 2018, 2018, Passo Fundo. ANAIS CIEEH 2018. Passo Fundo: Universidade de Passo Fundo, 2018. v. 4.

VENSKE, D. K. R. et al. Association of Serum vitamin D and risk of depression in elderly? EpiFloripa cohort study. In: 1thFENS Forum of Neuroscience, 2018, Berlin. 1thFENS Forum of Neuroscience, 2018.

Resumos expandidos publicados em anais de congressos

CEOLIN, G. et al. Associação entre sintomas depressivos e excesso de peso em idosos? Estudo EpiFloripa Idoso. In: I Congresso Nacional de Envelhecimento Humano, 2018, Curitiba-PR. Anais II CNEH. Curitiba-PR, 2018. v. 1.

Revisão de artigos em Periódicos

2021 - Biomed Research International

2022 - Revista de Nutrição

2022 - BMC Psychiatry

Produções Técnicas

D'ORSI, E. et al. Manual do Entrevistador EpiFloripa Idoso. Disponível em: <https://repositorio.ufsc.br/handle/123456789/219632>.

D'ORSI, E. et al. Relatório EpiFloripa Idoso. Disponível em: <https://repositorio.ufsc.br/handle/123456789/219631>.

FLORENTINO, C. S. et al. Conheça o PPGN UFSC. 2020. (Desenvolvimento de material didático ou instrucional - Vídeo de divulgação do Programa de Pós-Graduação em Nutrição).

Capítulo de livro

CEOLIN, G. et al. Atenção nutricional na equipe multiprofissional das ILPIS *in* Capacita ILPI Santa Catarina (ebook), no prelo, 2023.

Curso de curta duração ministrado

DORSI, E. et al. Curso de capacitação para atuar como entrevistador(a) do projeto Epifloripa Idoso. 2018.

Entrevistas, lives e comentários na mídia

BRIETZKE, E. ; CEOLIN, G. . Live: Relação entre a vitamina D e depressão. 2022.

FERNANDES, A. C. ; CEOLIN, G. ; FILIPINI, R. E. . Live Café com Cientista: Vitamina D e Saúde Mental, realizado no Canal do Youtube Café com Ciência da UFSC. 2021.

CEOLIN, G. et al. What are the main nutritional challenges in older adults during the COVID-19 pandemic? **Scielo Press release**, 2020. Disponível em: <Chamada *press-release*: https://pressreleases.scielo.org/en/2020/12/14/whats-are-the-main-nutritional-challenges-in-older-adults-during-the-covid-19-pandemic/>.

CEOLIN, G. Quais são os principais desafios nutricionais na saúde de idosos em tempos de pandemia da COVID-19?. **Scielo Press release,** 2020. Disponível em: <https://www.youtube.com/watch?v=v8NwPNrkY70&t=9s>.

Website

DORSI, E. et al. EpiFloripa Idoso. 2018; Tema: "Condições de Saúde dos Idosos de Florianópolis-SC- EpiFloripa Idoso".

Participação em bancas de trabalhos de conclusão de curso de graduação

CEOLIN, G. Participação em banca de Miriam Regina Alves Zanella. Efeito da dieta cetogênica sobre a densidade mineral óssea em pacientes adultos com epilepsia farmacorresistente: uma revisão narrativa da literatura. 2022. Trabalho de Conclusão de Curso (Graduação em Nutrição) – UFSC.

CEOLIN, G. Participação em banca de Giulia Pipolo Rodrigues Mano. Desenvolvimento de um aplicativo para smartphone para gerenciamento e manutenção da dieta cetogênica em pacientes adultos com epilepsia farmacorresistente. 2022. Trabalho de Conclusão de Curso (Graduação em Nutrição) - UFSC.

CEOLIN, G. Participação em banca de Natália Schmitt Hames. Desenvolvimento de um aplicativo para smartphone para gerenciamento e manutenção da dieta cetogênica em pacientes adultos com epilepsia farmacorresistente. 2022. Trabalho de Conclusão de Curso (Graduação em Nutrição) - UFSC

CEOLIN, G. Participação em banca de Camila Eduarda Carvalho Schultz. Desenvolvimento De Livro De Receitas Culinárias Cetogênicas Para Pacientes Com Epilepsia Refratária Atendidos No Ambulatório De Dieta Cetogênica Do Hospital Universitário/UFSC. 2019. Trabalho de Conclusão de Curso (Graduação em Nutrição) - UFSC.

Monografia de conclusão de curso de especialização - Especialização em atenção à saúde das pessoas com sobrepeso e obesidade (UNASUS-UFSC)

Alisson Luiz Gonçalves de Oliveira. Programa Academia da Saúde: Ferramenta para uma vida saudável. 2022.

Isabel Cristina Moura Brandão. Projeto de Intervenção para deter o avanço da obesidade infantil em alunos da Escola de Ensino Infantil Alaíde Ramos de Vasconcelos do município de Cruz (CE). 2022.

José Eliomar de Almeida Junior. Conscientizar e intervir para tratamento e controle da obesidade. 2022.

José Maria Gomes Filho. Plano de intervenção para qualificação da introdução alimentar em crianças de 6 meses a 1 ano de vida, em uma Unidade Básica de Saúde na cidade de Croatá-CE. 2022.

Mariella Cássia de Araújo. Plano de Ação para Prevenção e Controle do Sobrepeso e Obesidade em Gestantes em uma Cidade do Interior do Ceará. 2022.

Merlin Esmeraldo Lopes. Cuidados com a Saúde de Pessoas com Sobrepeso e Obesidade na Estratégia Saúde da Família. 2022.

Michelly de Castro Almeida. Plano de intervenção para redução do sobrepeso e obesidade dos moradores da área de abrangência da Unidade Básica De Saúde José Cavalcante Aragão no município de São Gonçalo do Amarante-Ceará. 2022.

Mirela Alexandre Virginio. SAÚDE NA COMUNIDADE: estratégias para o controle de sobrepeso e obesidade em adultos. 2022.

Marêssa Barbosa Martins. Educação permanente em alimentação e nutrição na Estratégia Saúde da Família no município de Ibaretama/Ceará. 2022.

Rita de Cássia Valentim de Jesus Encarnacao. Educação em saúde para a redução do sedentarismo e da obesidade na Unidade de Saúde da Família Estrada da Cosica em Salvador. 2022.

Roberta Lima da Silva. Prevenção e controle do sobrepeso e obesidade em adultos atendidos em Unidades de Saúde do município de Belém do Pará. 2022.

Thaissy Fernanda de Oliveira. Educação em saúde para mulheres no período gravídico. 2022.

Vanessa Neves de Lima. Benefícios da alimentação saudável e atividade física no controle do Diabetes Mellitus em pessoas com sobrepeso e obesidade. 2022.

Victor Buratto dos Santos Queiroz. Intervenção em saúde em mulheres com sobrepeso e obesidade em Unidade De Saúde Da Família De Três Lagoas -MS. 2022.

Wendi Cristina Silva de Oliveira. Ações para controle de Diabetes Mellitus associado a obesidade em uma unidade básica de saúde de São Paulo-SP. 2022.

Luciana Moura Morais. Projeto de intervenção para combater o sedentarismo e contribuir para o controle de peso de adultos numa comunidade litorânea do nordeste brasileiro. 2022.