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The Challenging Task of Addressing the Role of Vitamin D in Late-life Depression: considerations of measures, confounders, mediators and moderators

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The study by de Koning et al.(1) adds to a growing literature on the role of vitamin D in risk of depression among older adults(2). Specifically, with a large sample of nearly 2,000 well-characterized community-dwelling participants in the Longitudinal Aging Study Amsterdam, the study represents an important contribution to the body of observational research evidence. Depression was examined longitudinally – as an outcome of depressive mood symptoms – allowing for both cross-sectional and prospective analyses. While there were no cross-sectional relations of vitamin D level to depression after adjustment for confounders, there was a prospective relation among older women (but not among men or younger persons) of high vitamin D levels to lower depression scores over the follow-up. There was also modest evidence of mediation by physical functioning, but this was restricted to the significant vitamin D-depression association observed among older women.

Although traditional limitations in observational research were present in this study – such as non-randomized assignment to vitamin D status, unmeasured confounders, potential for residual confounding due to weaker measurement of some covariates (e.g., physical activity as a past-year variable, rather than as longer-term, habitual physical activity), and cohort generalizability issues – major strengths are also apparent. These strengths included use of biochemical vitamin D levels to determine vitamin D status, repeated measurement of the depression outcome, and characterization of physical functioning using subjective and objective metrics (Short Physical Performance Battery, SPPB)(3).

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DISCLOSURES

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Incorporating another important element in research on potential determinants of late-life depression, the study gave attention to plausible moderators and mediators. In particular, sex differences are known to be important in all aspects of depression research, given the universality of the nearly two-fold higher burden of depression among females compared to males. Specifically, it has been illustrated that sex differences in depression prevalence and incidence are not merely phenomena among younger persons; rather, these differences are present at all ages(4) and persist into late-life as 1.5-fold higher rates of incident and recurrent depression among women vs. men(5). Thus, the authors' work was strengthened by the specific approach of addressing sex as a biological variable and evaluating potential differences by sex in vitamin D-depression associations. In addition, the paper addressed physical functioning as a potential mediator of vitamin D-depression relations. Indeed, physical functioning has been consistently identified as a major determinant of late-life depression risk(6–10). Because of vitamin D's hypothesized influences on skeletal and extra-skeletal outcomes that determine physical function and performance(11, 12), it appears reasonable to explore the mediating role of physical function. Moreover, the current study attempted to address important methodologic concerns in epidemiologic research. It can be difficult to ascertain whether a variable is a mediator, measurement confounder or both. Furthermore, it can be difficult in this setting to parse whether there may be direct influences of both the exposure and outcome variables on a third variable(13, 14) – for example, of vitamin D and depression on physical functioning. The study used structural equation modeling (SEM) to address the relations of vitamin D to longitudinal depressive symptoms and to partition mediation by physical functioning. Ultimately, readers may vary in how convincing they consider the exploratory nature of the finding on mediation by physical functioning among older women, and the authors acknowledge this issue. Replication of the findings, particularly of differences that were observed by sex, would advance knowledge in this area.

Biochemical vitamin D levels were obtained for this study as serum 25-hydroxy vitamin D (25(OH)D), and participants could be characterized as having sufficient or deficient vitamin D status. Furthermore, the study addressed more refined tiers of vitamin D status by blood 25(OH)D level (although there remain some differences in opinion among experts regarding the precise nmol/L thresholds that should be used to defined frank deficiency, deficiency, sufficiency, etc.)(11, 15). It is important to address higher tiers of presumed "sufficient" vitamin D, especially as potential extra-skeletal effects such as mood outcomes may be more influenced by attained vitamin D levels in the higher ranges, particularly among older persons(11, 16). Thus, it is helpful that the study authors identified those who had sufficient 25(OH)D levels (≥ 50 nmol/L) as well as those with higher levels (>75 nmol/L). That said, recent evidence suggests that the practice of characterizing vitamin D status using total 25(OH)D may be more nuanced than initially thought(17). Blood concentration of total 25(OH)D remains the most commonly used biomarker of vitamin D status(18). However, newer data highlight the relevance of capturing bioavailable vitamin D (ie, the fraction that is unbound to vitamin D binding protein (DBP) and therefore available to exert intracellular, biologic effects) or free 25(OH)D; racial and/or genetic variations in DBP and DBP affinity may influence the extent to which total 25(OH)D is an indicator of "true" vitamin D status. It has not been resolved whether free vs. total 25(OH)D is a superior marker(18). Thus,

measurement of free vs. total vitamin D may be important in research investigations – in addition to considerations of known environmental and behavioral confounders such as physical activity, season, body mass index, diet, smoking and others. Studies of the role of vitamin D levels in late-life depression outcomes need to give careful attention to the issue of optimal measurement of biochemical vitamin D status.

Overall, de Koning and colleagues are to be commended for addressing challenging methodologic issues involved in evaluating physical activity and physical functioning with respect their roles as analytic variables in the vitamin D-late-life depression association. Although there were limitations in the approach regarding the precision with which physical activity was measured, and also the findings regarding mediation by physical functioning are ultimately exploratory at this time, the study suggests important future directions. Specifically, results from the paper inform how randomized trials might be designed to reduce bias, avoid confounding, assess moderators, and capture mediating effects with higher precision. For example, randomized allocation to long-term vitamin D treatment/supplementation would most effectively minimize bias and confounding in estimation of the effect of vitamin D on late-life depression outcomes, and repeated ascertainment of detailed subjective and objective measures of physical functioning would strengthen the ability to conduct tests of mediation. Furthermore, studies could be designed to ensure adequate power to address possible mediators as well as moderator variables such as biological sex. Currently, there are ongoing or planned larger-size trials of randomized vitamin D supplementation that feature older adults and in which depression/mood will be assessed(2, 19–21). Thus, the present study is relevant to collection and analysis of trial data such that greater understanding can ultimately be achieved regarding the relation of vitamin D to longitudinal depression outcomes in later-life.

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REFERENCES

1. de Koning E, Elstgeest L, Comijs H, et al.: Vitamin D status and depressive symptoms in older adults: a role for physical functioning? *Am J Geriatr Psychiatry* 2018; in press
2. Okereke OI, Singh A: The role of vitamin D in the prevention of late-life depression. *J Affect Disord* 2016; 198:1–14 [PubMed: 26998791]
3. Guralnik JM, Simonsick EM, Ferrucci L, et al.: A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. *J Gerontol* 1994; 49:M85–94 [PubMed: 8126356]
4. Kessler RC, Berglund P, Demler O, et al.: Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry* 2005; 62:593–602 [PubMed: 15939837]
5. Luijckendijk HJ, van den Berg JF, Dekker MJ, et al.: Incidence and recurrence of late-life depression. *Arch Gen Psychiatry* 2008; 65:1394–1401 [PubMed: 19047526]
6. Chang SC, Pan A, Kawachi I, et al.: Risk factors for late-life depression: A prospective cohort study among older women. *Prev Med* 2016; 91:144–151 [PubMed: 27514249]

7. Lyness JM, Yu Q, Tang W, et al.: Risks for depression onset in primary care elderly patients: potential targets for preventive interventions. *Am J Psychiatry* 2009; 166:1375–1383 [PubMed: 19833788]
8. Schoevers RA, Smit F, Deeg DJ, et al.: Prevention of late-life depression in primary care: do we know where to begin? *Am J Psychiatry* 2006; 163:1611–1621 [PubMed: 16946188]
9. Smits F, Smits N, Schoevers R, et al.: An epidemiological approach to depression prevention in old age. *Am J Geriatr Psychiatry* 2008; 16:444–453 [PubMed: 18515688]
10. Reynolds CF 3rd, Cuijpers P, Patel V, et al.: Early intervention to reduce the global health and economic burden of major depression in older adults. *Annu Rev Public Health* 2012; 33:123–135 [PubMed: 22429161]
11. Bischoff-Ferrari HA, Giovannucci E, Willett WC, et al.: Estimation of optimal serum concentrations of 25-hydroxyvitamin D for multiple health outcomes. *Am J Clin Nutr* 2006; 84:18–28 [PubMed: 16825677]
12. Wacker M, Holick MF: Vitamin D—Effects on Skeletal and Extraskeletal Health and the Need for Supplementation. *Nutrients* 2013; 5:111–148 [PubMed: 23306192]
13. Greenland S: Quantifying biases in causal models: classical confounding vs collider-stratification bias. *Epidemiology (Cambridge, Mass.)* 2003; 14:300–306
14. Hernan MA, Hernandez-Diaz S, Robins JM: A structural approach to selection bias. *Epidemiology (Cambridge, Mass.)* 2004; 15:615–625
15. Holick MF: Vitamin D deficiency. *N Engl J Med* 2007; 357:266–281 [PubMed: 17634462]
16. Aloia JF, Patel M, Dimaano R, et al.: Vitamin D intake to attain a desired serum 25-hydroxyvitamin D concentration. *Am J Clin Nutr* 2008; 87:1952–1958 [PubMed: 18541590]
17. Powe CE, Evans MK, Wenger J, et al.: Vitamin D-binding protein and vitamin D status of black Americans and white Americans. *N Engl J Med* 2013; 369:1991–2000 [PubMed: 24256378]
18. Bikle D, Bouillon R, Thadhani R, et al.: Vitamin D metabolites in captivity? Should we measure free or total 25(OH)D to assess vitamin D status? *J Steroid Biochem Mol Biol* 2017; 173:105–116 [PubMed: 28093353]
19. Okereke OI, Reynolds CF, Mischoulon D, et al.: The VITamin D and Omega-3 Trial—Depression Endpoint Prevention (VITAL-DEP): Rationale and design of a large-scale ancillary study evaluating vitamin D and marine omega-3 fatty acid supplements for prevention of late-life depression. *Contemp Clin Trials* 2018; 68:133–145 [PubMed: 29526608]
20. Burt LA, Gaudet S, Kan M, et al.: Methods and procedures for: A randomized double-blind study investigating dose-dependent longitudinal effects of vitamin D supplementation on bone health. *Contemp Clin Trials* 2018; 67:68–73 [PubMed: 29471124]
21. Rafiq R, Aleva FE, Schrumpf JA, et al.: Prevention of exacerbations in patients with COPD and vitamin D deficiency through vitamin D supplementation (PRECOVID): a study protocol. *BMC pulmonary medicine* 2015; 15:106 [PubMed: 26399451]