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There is no evidence that vitamin D supplementation drives the progression of Alzheimer's disease

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If there is anything the last few decades have taught us, it is that researchers must properly conduct studies on vitamin supplements before they can make health claims. In a recent paper by Lai et al. (2022), the authors state, “vitamin D supplementation worsens Alzheimer's progression” without sufficient evidence to support these conclusions. While certain findings are scientifically interesting, readers must understand substantial limitations in the approach and methodology utilized in the paper limit conclusions one can make about the role of vitamin D in brain health and Alzheimer's disease (AD).

Before proceeding further, it is important for readers to understand that there are three different forms of vitamin D pertinent to this discussion. Cholecalciferol is the form of vitamin D₃ synthesized in the skin upon exposure to UVB rays that typically come from sunlight. It is also the form found in dietary supplements. The liver converts cholecalciferol to calcidiol (25-hydroxyvitamin D₃), the circulating form used by clinicians to determine vitamin D status. Certain cells in the body will then convert calcidiol to calcitriol (1,25-dihydroxyvitamin D₃), the “active” form of vitamin D in the body (Bikle, 2000).

Calcitriol is a high-affinity, potent ligand for the vitamin D receptor (VDR) and regulates most VDR-dependent gene transcription. The body only produces calcitriol under certain physiological conditions, including low serum calcium levels or immune activation, and tightly controls its synthesis and catabolism to limit its physiological effects. On the other hand, cholecalciferol and calcidiol are considered inactive forms of vitamin D₃, as they are low-affinity ligands for VDR (Bikle, 2000). Because these three forms are not functionally or physiologically equivalent, referring to them all as “vitamin D” creates a great deal of confusion, especially since cholecalciferol

is found in vitamin D supplements or fortified foods and beverages, but calcitriol is appropriately classified as a drug (Vieth, 2020).

The study by Lai et al. begins with data from neuronal cell culture. Here, the authors demonstrate that treatment with both calcidiol and calcitriol increases apoptosis and autophagy in undifferentiated SH-SY5Y cells upon exposure to A β 42. SH-SY5Y is a neuroblastoma cell line typically used in experiments after differentiation into a homogeneous, more mature neuron-like cell, making them useful for AD research (Agholme et al., 2019). Prior reports show calcitriol protects differentiated SH-SY5Y cells against A β (1–42) peptide cytotoxicity (Vieth, 2020), although others have reported protection of undifferentiated SH-SY5Y cells from A β (25–35) toxicity upon treatment with calcitriol (Lin, Chang, et al., 2020). While the study by Lai et al. reports contradictory findings, the authors do not discuss them in the context of the greater literature base, so it is unclear what could have explained these divergent responses.

Encouraged by their cell culture findings, the authors performed a vitamin D (cholecalciferol) feeding study in an APP/PS1 transgenic mouse model. This model, like most murine models for AD, recapitulates a rare form of AD that mirrors limited aspects of human AD pathology. It does not represent normal cognitive decline or even commonly seen forms of AD in humans. These animals also have difficulties maintaining vitamin D status, as evidenced by lower serum calcidiol levels compared to wild-type controls when maintained on a 600IU/kg cholecalciferol diet. Feeding the mice a high vitamin D diet containing 8044IU/kg cholecalciferol starting at the age of 4.5 months restored serum calcidiol levels. However, after 3 months of supplementation, the authors observed “more severe A β plaque deposits and reactive gliosis in the hippocampus compared to the controls,” an increased expression of pro-degenerative factors in the

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hippocampus, and worse cognitive functioning in the Morris water maze.

These findings are at odds with prior results in which vitamin D supplementation or treatment with calcitriol in several other mouse models of AD reduced amyloid burden and improved cognition (Durk et al., 2014; Lin, Lin, et al., 2020; Morello et al., 2018; Yu et al., 2011). In the 5XFAD mouse model, for example, female mice fed a high vitamin D (as cholecalciferol) diet (7500 IU/kg) had fewer plaques in the frontal cortex, hippocampus and neocortex, decreased astrogliosis, and cognitive defects as compared to the untreated mice (Landel et al., 2016). Researchers also observed similar effects of vitamin D supplementation in the A β PP (Durk et al., 2014) and the 3xTg-AD (Landel et al., 2016) transgenic mouse models. In Tg2576 and TgCRND8 mice, calcitriol administration decreased plaque burden and improved cognitive function (Lin, Lin, et al., 2020). Furthermore, intraperitoneal injection of calcitriol also protected Long-Evans rats from neuronal degeneration after intrahippocampal injection of aggregated A β (1–42); Pierucci et al., 2017). Again, the authors do not adequately discuss their findings in the context of the prior literature. The findings from this and prior studies underscore the importance of using multiple animal models to evaluate potential therapies and translate findings to humans (Drummond & Wisniewski, 2017).

The second half of the paper is a retrospective, population-based longitudinal study that attempts to quantify the risk for dementia and mortality in older adults taking vitamin D₃ supplements. According to the authors, their analysis indicates prolonged supplementation worsens the progression of AD by increasing dementia and mortality risk. However, this is a completely inaccurate interpretation of the data. While described as “taking vitamin D₃ supplements during the period 2000–2009”, the participant data comes from Taiwan's National Health Insurance Research Database that describes the use of calcitriol, a prescription medication—not a dietary supplement. Physicians prescribe calcitriol to increase calcium levels in patients whose kidneys or parathyroid glands are not functioning normally. A prescription for calcitriol is not indicative of good health, as the individuals taking calcitriol often have one or more comorbidities, such as osteoporosis, thyroid disorders, diabetes, hyperlipidemia, and hypertension. Each of these comorbidities indicates a predisposition toward dementia. Calcitriol is also often prescribed to patients with chronic kidney disease, who are already prone to cognitive decline and AD (Zhang et al., 2020). Considering the potent nature of calcitriol, it cannot be equated to taking vitamin D₃ as a dietary supplement.

Of note, calcitriol overuse is associated with an increased risk of hypercalcemia. Hypercalcemia has been associated with dementia and changes in cognition (de Oliveira Martins Duarte et al., 2019; Lourida et al., 2015; Walker & Silverberg, 2018). Prolonged elevation in serum calcium levels, even if not to the level of hypercalcemia, can predict cognitive decline and conversion from nondemented status to AD (Ma et al., 2021). Since Lai et al. found that only medium-to-long-term calcitriol use (but not short-term use) was associated with increased dementia or mortality risk, it is possible what the authors

reported were side effects of a prolonged drug regimen, not the physiological effects associated with vitamin supplementation.

In contrast to the authors' conclusions, the current body of evidence from human clinical studies supports the role of vitamin D in cognitive health. Observational research shows that a higher 25(OH)D₃ (calcidiol) status is associated with a lower risk for AD and all-cause dementia (DeLuca et al., 2013; Littlejohns et al., 2014; Mayne & Burne, 2019). Randomized controlled trials with vitamin D₃ (cholecalciferol) supplementation have reported improved AD bio-measures and cognitive function (Jia et al., 2019). In older adults, vitamin D₃ supplementation either improved or had no association with declines in cognitive function (Kang et al., 2021; Navale et al., 2022; Rossom et al., 2012; Tong et al., 2020).

While there are clearly opportunities for more research on the role of vitamin D supplementation in cognitive health, the authors' conclusions that “vitamin D supplementation worsens Alzheimer's progression” is not justified. Conflating the data from cell culture, a murine model system and a retrospective epidemiological observation using prescription calcitriol reaches this flawed conclusion and lies in stark contrast to the large body of evidence that vitamin D status and vitamin D supplementation support cognitive health. The findings of this paper should have been placed in the proper context before these inflammatory statements on AD were released for public view.

AUTHOR CONTRIBUTIONS

All authors designed the manuscript and read and approved the final manuscript.

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CONFLICT OF INTEREST

AFG has received research funding from Bayer Consumer Care and has acted as an advisor/consultant for and has received reimbursement for travel and/or speaking from Bayer Consumer Care, GSK, DSM, Kellogg's, and The Coca-Cola Company. AJM consults for dietary supplement companies. ME is president of the Gesellschaft für Angewandte Vitaminforschung (Germany), is a member of the scientific board of PM International, and consults for companies in the nutrition and supplement field.

DATA AVAILABILITY STATEMENT

None.

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REFERENCES

Agholme, L., Lindström, T., Kågedal, K., Marcusson, J., & Hallbeck, M. (2019). An in vitro model for neuroscience: Differentiation of SH-SY5Y cells into cells with morphological and biochemical



- characteristics of mature neurons. *Journal of Alzheimer's Disease*, 20(4), 1069–1082.
- Bikle, D. (2000). Vitamin D: Production, metabolism, and mechanisms of action. [Updated 2021 Dec 31]. In K. R. Feingold, B. Anawalt, A. Boyce, G. Chrousos, W. W. de Herder, K. Dhatariya, K. Dungan, J. M. Hershman, J. Hershman, S. Kalra, G. Kaltsas, C. Koch, P. Kopp, M. Korbonits, C. S. Kovacs, W. Kuohung, B. Laferrère, M. Levy, E. A. McGee, ... D. P. Wilson (Eds.), *Endotext [Internet]*. MDText.com, Inc.
- de Oliveira Martins Duarte, J., Pereira, P., Lopes, J. N. G., Goes, A. T. L., Duran, D. C., Sobral, A., Rita, H. J. B., & Costa, J. A. S. E. (2019). A reversible case of rapidly progressive dementia-hypercalcemia due to hyperparathyroidism. *Clinical Case Reports*, 7(12), 2571–2574.
- DeLuca, G. C., Kimball, S. M., Kolasinski, J., Ramagopalan, S. V., & Ebers, G. C. (2013). Review: The role of vitamin D in nervous system health and disease. *Neuropathology and Applied Neurobiology*, 39(5), 458–484.
- Drummond, E., & Wisniewski, T. (2017). Alzheimer's disease: Experimental models and reality. *Acta Neuropathologica*, 133(2), 155–175.
- Durk, M. R., Han, K., Chow, E. C., Ahrens, R., Henderson, J. T., Fraser, P. E., & Pang, K. S. (2014). 1 α ,25-Dihydroxyvitamin D₃ reduces cerebral amyloid-beta accumulation and improves cognition in mouse models of Alzheimer's disease. *The Journal of Neuroscience*, 34(21), 7091–7101.
- Jia, J., Hu, J., Huo, X., Miao, R., Zhang, Y., & Ma, F. (2019). Effects of vitamin D supplementation on cognitive function and blood A β -related biomarkers in older adults with Alzheimer's disease. *Journal of Neurology, Neurosurgery, and Psychiatry*, 90(12), 1347–1352.
- Kang, J. H., Vyas, C. M., Okereke, O. I., Ogata, S., Albert, M., Lee, I. M., D'Agostino, D., Buring, J. E., Cook, N. R., Grodstein, F., & Manson, J. A. E. (2021). Effect of vitamin D on cognitive decline: Results from two ancillary studies of the VITAL randomized trial. *Scientific Reports*, 11(1), 23253.
- Lai, R. H., Hsu, C. C., Yu, B. H., Lo, Y. R., Hsu, Y. Y., Chen, M. H., & Juang, J. L. (2022). Vitamin D supplementation worsens Alzheimer's progression: Animal model and human cohort studies. *Aging Cell*, 21(8), e13670.
- Landel, V., Millet, P., Baranger, K., Lloriod, B., & Feron, F. (2016). Vitamin D interacts with Esr1 and Igf1 to regulate molecular pathways relevant to Alzheimer's disease. *Molecular Neurodegeneration*, 11, 22.
- Lin, C. I., Chang, Y. C., Kao, N. J., Lee, W. J., Cross, T. W., & Lin, S. H. (2020). 1,25(OH)₂D₃ alleviates A β (25–35)-induced tau hyperphosphorylation, excessive reactive oxygen species, and apoptosis through interplay with glial cell line-derived neurotrophic factor signaling in SH-SY5Y cells. *International Journal of Molecular Sciences*, 21(12), 4215.
- Lin, F. Y., Lin, Y. F., Lin, Y. S., Yang, C. M., Wang, C. C., & Hsiao, Y. H. (2020). Relative D₃ vitamin deficiency and consequent cognitive impairment in an animal model of Alzheimer's disease: Potential involvement of collapsin response mediator protein-2. *Neuropharmacology*, 164, 107910.
- Littlejohns, T. J., Henley, W. E., Lang, I. A., Annweiler, C., Beauchet, O., Chaves, P. H. M., Fried, L., Kestenbaum, B. R., Kuller, L. H., Langa, K. M., Lopez, O. L., Kos, K., Soni, M., & Llewellyn, D. J. (2014). Vitamin D and the risk of dementia and Alzheimer disease. *Neurology*, 83(10), 920–928.
- Lourida, I., Thompson-Coon, J., Dickens, C. M., Soni, M., Kuzma, E., Kos, K., & Llewellyn, D. J. (2015). Parathyroid hormone, cognitive function and dementia: A systematic review. *PLoS One*, 10(5), e0127574.
- Ma, L. Z., Wang, Z. X., Wang, Z. T., Hou, X. H., Shen, X. N., Ou, Y. N., Dong, Q., Tan, L., & Yu, J. T. (2021). Serum calcium predicts cognitive decline and clinical progression of Alzheimer's disease. *Neurotoxicity Research*, 39(3), 609–617.
- Mayne, P., & Burne, T. H. J. (2019). Vitamin D in synaptic plasticity, cognitive function, and neuropsychiatric illness. *Trends in Neurosciences*, 42(4), 293–306.
- Morello, M., Landel, V., Lacassagne, E., Baranger, K., Annweiler, C., Feron, F., & Millet, P. (2018). Vitamin D improves neurogenesis and cognition in a mouse model of Alzheimer's disease. *Molecular Neurobiology*, 55(8), 6463–6479.
- Navale, S., Mulugeta, A., Zhou, A., Llewellyn, D. J., & Hyppönen, E. (2022). Vitamin D and brain health – An observational and Mendelian randomization study. *The American Journal of Clinical Nutrition*, 116, 531–540.
- Pierucci, F., Garcia-Gil, M., Frati, A., Bini, F., Martinesi, M., Vannini, E., Mainardi, M., Luzzati, F., Peretto, P., Caleo, M., & Meacci, E. (2017). Vitamin D₃ protects against A β peptide cytotoxicity in differentiated human neuroblastoma SH-SY5Y cells: A role for S1P1/p38MAPK/ATF4 axis. *Neuropharmacology*, 116, 328–342.
- Rossum, R. C., Espeland, M. A., Manson, J. E., Dysken, M. W., Johnson, K. C., Lane, D. S., LeBlanc, E. S., Lederle, F. A., Masaki, K. H., & Margolis, K. L. (2012). Calcium and vitamin D supplementation and cognitive impairment in the women's health initiative. *Journal of the American Geriatrics Society*, 60(12), 2197–2205.
- Tong, Y., Wang, H. W., Ying, X., Chen, C. C., Keran, D., Jingya, J., & Fei, M. (2020). Vitamin D supplementation improves cognitive function through reducing oxidative stress regulated by telomere length in older adults with mild cognitive impairment. *Journal of Alzheimer's Disease*, 78(4), 1509–1518.
- Vieth, R. (2020). Vitamin D supplementation: cholecalciferol, calcifediol, and calcitriol. *European Journal of Clinical Nutrition*, 74(11), 1493–1497.
- Walker, M. D., & Silverberg, S. J. (2018). Primary hyperparathyroidism. *Nature Reviews. Endocrinology*, 14(2), 115–125.
- Yu, J., Gattoni-Celli, M., Zhu, H., Bhat, N. R., Sambamurti, K., Gattoni-Celli, S., & Kindy, M. S. (2011). Vitamin D₃-enriched diet correlates with a decrease of amyloid plaques in the brain of A β PP transgenic mice. *Journal of Alzheimer's Disease*, 25(2), 295–307.
- Zhang, C. Y., He, F. F., Su, H., Zhang, C., & Meng, X. F. (2020). Association between chronic kidney disease and Alzheimer's disease: An update. *Metabolic Brain Disease*, 35(6), 883–894.

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