



## Review

# Efficacy and acceptability of vitamin D supplements for depressed patients: A systematic review and meta-analysis of randomized controlled trials



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## ABSTRACT

**Objectives:** This systematic review and meta-analysis synthesized the evidence from randomized controlled trials comparing vitamin D and placebo in reducing depressive symptoms and contributing to all-cause dropout rates.

**Methods:** Inclusion criteria were randomized controlled trials comparing reduced depression between depressed patients receiving vitamin D and those receiving placebo. We searched PubMed, Embase, Web of Science, and the Cochrane Central Register of Controlled Trials through January 2022.

**Results:** Eighteen trials (1980 participants, median age 39 y) were included in the meta-analysis. Vitamin D supplements were significantly superior to placebo in reducing depression (standardized mean difference =  $-0.49$ ; 95% confidence interval [CI],  $-0.75$  to  $-0.23$ ;  $I^2 = 81\%$ ). Depressed adults (standardized mean difference =  $-0.70$ ; 95% CI,  $-1.09$  to  $-0.31$ ) responded to vitamin D significantly better than children and adolescents (standardized mean difference =  $0.10$ ; 95% CI  $-0.27$  to  $0.47$ ). Vitamin D administered as bolus doses (oral intermittent high doses or intramuscular single high dose) appeared to be more effective than that taken daily by the oral route ( $P < 0.01$ ). Patients with more severe depression tended to respond better than those with less severity ( $P = 0.053$ ). We found no moderating effect of concurrent antidepressant use, presence of major depressive disorder diagnosis, physical comorbidity, sex, duration and doses of vitamin D supplement, serum 25-hydroxyvitamin D levels at baseline, and changes in serum 25-hydroxyvitamin D levels in the vitamin D group. Dropout rates were indifferent between the groups (17 trials; risk ratio =  $0.84$ ; 95% CI,  $0.6$ – $1.16$ ;  $I^2 = 0$ ).

**Conclusions:** Heterogeneous data suggested that vitamin D supplements are effective and safe for depressed patients.

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The protocol was registered in Prospero, titled "Efficacy and safety of vitamin D for depressed patients: a systematic review and meta-analysis of randomized controlled trials" (CRD42021264585) (Supplementary Method 1). The registered protocol is available at: [https://www.crd.york.ac.uk/prospero/display\\_record.php?RecordID=264585](https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=264585). Protocol amendments are described in Supplementary Method 2.

The data and the code are available at <https://osf.io/zn2ef/>.

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## Introduction

Depression is one of the leading causes of disability and does not respond well to current treatments. In 2017, ~264 million people suffered from depressive disorders, resulting in 4.3 million years of living with disability [1]. Disability-adjusted life-years due to depressive disorder increased by 61% in the past three decades, contributing to ~1.85% of total loss of disability-adjusted life-years in 2019 [2]. Although antidepressants, psychotherapy, and their combinations are widely used, these treatments still have high dropout rates and low remission rates [3].