INPLASY PROTOCOL

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None declared.

Vitamin B12 levels and risk of all-cause, cardiovascular disease and cancer mortality: a systematic review and dose-response meta-analysis of cohort studies

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Review question / Objective: **To quantify the dose-response relationship between vitamin B12 levels and the risk of all-cause mortality, CVD mortality, and cancer mortality.**
Information sources: **We systematically searched the electronic databases of PubMed, Embase, and the Cochrane Library for all relevant studies published until May 2022 using the strings (fatal or death or mortality) and (vitamin B12 or cobalamin). The research was limited to studies conducted in humans with no other restrictions. We did not apply language restrictions and conducted a Google Scholar search using similar keywords for gray literature.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 21 May 2022 and was last updated on 21 May 2022 (registration number INPLASY202250129).

INTRODUCTION

Review question / Objective: **To quantify the dose-response relationship between vitamin B12 levels and the risk of all-cause mortality, CVD mortality, and cancer mortality.**

Condition being studied: **Cardiovascular disease (CVD) and cancer are two leading causes of death, contributing to 18.6 million deaths worldwide in 2019 and 10.0 million deaths worldwide in 2020. Vitamin B12 deficiency has been associated with increased risk of cardiovascular disease and cancer. As a coenzyme in two essential**

enzymatic reactions catalyzed by cytosolic methionine synthase and mitochondrial methylmalonyl-CoA mutase, vitamin B12 plays a vital role in cellular metabolism, especially DNA synthesis, methylation, and mitochondrial metabolism. Serum vitamin B12 level relies on dietary intake of meat, eggs, dairy products, and other animal products. Previous studies suggest that abnormal vitamin B12 levels may be associated with various physiological disorders or diseases. B12 deficiency can lead to reversible megaloblastic anemia, demyelinating neurologic disease, and chronic atrophic gastritis, caused by inadequate intake, malabsorption, chemical inactivation, or inherited B12 transport disruption or intracellular metabolism. The consequences of elevated vitamin B12 levels may be caused by immunological, inflammatory, infectious, hematologic, and oncologic diseases, which are associated with an increased risk of cardiovascular diseases and cancers.

METHODS

Participant or population: Adults (≥ 18 years).

Intervention: Vitamin B12 levels.

Comparator: Adults (≥ 18 years).

Study designs to be included: prospective or retrospective cohort

Eligibility criteria: serum vitamin B12 concentration was the exposure of interest; the outcome was all-cause mortality or CVD or cancer mortality; reported the vitamin B12 concentration in the exposure category; and reported the hazard ratio (HR) with a 95% confidence interval (95%CI) for two or more quantitative categories.

Information sources: We systematically searched the electronic databases of PubMed, Embase, and the Cochrane Library for all relevant studies published until May 2022 using the strings (fatal or death or mortality) and (vitamin B12 or cobalamin). The research was limited to studies conducted in humans with no other restrictions. We did not apply language restrictions and conducted a Google Scholar search using similar keywords for gray literature.

Main outcome(s): Vitamin B12 levels and the risk of all-cause mortality, CVD mortality, and cancer mortality.

Quality assessment / Risk of bias analysis: The quality of the cohort studies was evaluated according to the Newcastle-Ottawa Scale (NOS) for observational studies, and the quality of evidence for each outcome was assessed according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE).

Strategy of data synthesis: Stata version 15.0 (Stata Corp LP, College Station, TX, USA) was used to perform all statistical analyses.

Subgroup analysis: For each category of vitamin B12 concentration we used the median or mean if reported in the publication or otherwise estimated the midpoint of the upper and lower bound. When extreme categories were open ended, we used the width of the adjacent interval to calculate an upper or lower cut-off value. To examine a potential nonlinear relationship between vitamin B12 levels and the outcomes, a two-stage dose-response meta-analysis was performed using random-effects model considering heterogeneity in observational studies. Vitamin B12 levels were modeled using restricted cubic splines limited by four knots at fixed percentiles (5%, 35%, 65%, and 95%) of the distribution. In the first stage, considering the correlation within each set of published HR, a restricted cubic spline model with three spline transformations (four knots minus one) was fitted.

Sensitivity analysis: Sensitivity analysis was performed to exclude studies that did not report the number of subjects (total number of deaths and cohort size or total

number of person-years of follow-up and number of deaths) to avoid biases in estimated variances

Language: No restriction.

Country(ies) involved: China.

Keywords: vitamin B12; all-cause; CVD; cancer; mortality; dose-response meta-analysis.

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