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Vitamin B_{12} Intake and Status and Cognitive Function in Elderly People

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Current recommendations on vitamin B_{12} intake vary from 1.4 to 3.0 μg per day and are based on the amount needed for maintenance of hematologic status or on the amount needed to compensate obligatory losses. This systematic review evaluates whether the relation between vitamin B_{12} intake and cognitive function should be considered for underpinning vitamin B_{12} recommendations in the future. The authors summarized dose-response evidence from randomized controlled trials and prospective cohort studies on the relation of vitamin B_{12} intake and status with cognitive function in adults and elderly people. Two randomized controlled trials and 6 cohort studies showed no association or inconsistent associations between vitamin B_{12} intake and cognitive function. Random-effects meta-analysis showed that serum/plasma vitamin B_{12} (50 pmol/L) was not associated with risk of dementia (4 cohort studies), global cognition *z* scores (4 cohort studies), or memory *z* scores (4 cohort studies). Although dose-response evidence on sensitive markers of vitamin B_{12} status (methylmalonic acid and holotranscobalamin) was scarce, 4 of 5 cohort studies reported significant associations with risk of dementia, Alzheimer's disease, or global cognition. Current evidence on the relation between vitamin B_{12} intake or status and cognitive function is not sufficient for consideration in the development of vitamin B_{12} recommendations. Further studies should consider the selection of sensitive markers of vitamin B_{12} status.

aged; cognition; dementia; nutritional requirements; recommended dietary allowances; review; vitamin B_{12}

Abbreviations: holo-TC, holotranscobalamin; MMA, methylmalonic acid; MMSE, Mini-Mental State Examination; RCT, randomized controlled trial; RR, relative risk.

INTRODUCTION

Dietary recommendations provide guidance on the nutrient intake levels that should be sufficient to fulfill requirements of nearly all apparently healthy people in a specified population. Traditionally, these recommendations were intended to prevent deficiency disorders, but today the focus is slowly changing toward promoting optimal health, including consideration of relations between diet and prevention of chronic diseases (1, 2). Current recommendations on vitamin B_{12} intake are similar for adults and elderly people and vary from 1.4 to 3.0 μg per day in Europe. They are based on the amount needed for the maintenance of hematologic status and on the amount needed to compensate obligatory losses (3–5). Relations between vitamin B_{12} intake and health-related outcomes, such as cardiovascular diseases, cognitive function, and osteoporosis, are not yet taken into account when vitamin B_{12} recommendations were developed. To support transparent decision-making on whether these relations should be considered in setting vitamin B_{12} recommendations in the future, systematic reviews and meta-analyses are needed to objectively evaluate and integrate the available evidence (6). Previously, 5 systematic reviews addressed the relation between vitamin B_{12} intake or status and cognitive function in a qualitative manner (7–11). The aim of the present review was to summarize dose-response evidence from randomized controlled trials (RCTs) and prospective cohort

studies on the relation of vitamin B_{12} intake and status with cognitive function in adults and elderly people and to identify research gaps relevant for developing vitamin B_{12} recommendations.

MATERIALS AND METHODS

This systematic review with dose-response meta-analyses was conducted according to standardized methodology as developed within the scope of the EURRECA (EURopean micronutrient RECommendations Aligned) Network of Excellence, which is described briefly below.

Search

We conducted a systematic literature search in the databases MEDLINE (US National Library of Medicine, Bethesda, Maryland), Embase (Elsevier, Amsterdam, the Netherlands), and Cochrane Library Central (John Wiley & Sons, Ltd., Chichester, United Kingdom) through February 17, 2009, using search terms on study designs in humans *and* vitamin B_{12} *and* (intake *or* status). The search terms included both Medical Subject Heading (MeSH) terms and words to be found in titles or abstracts. The strategy was adapted for each database to fit database-specific features. To be able to use the same search to identify publications on other health-related outcomes both in adults and elderly people and in younger population groups, no terms were added to limit the search to health outcome or study population. Moreover, by using a broad search, we expected a more complete retrieval of relevant publications. The search was not limited by language. Web Appendix 1 (available at http://aje.oxfordjournals.org/) shows the full MEDLINE search strategy. The initial search yielded 5,219 references after exclusion of duplicates via Endnote XII (Thomson Reuters, New York, New York). In addition, we reviewed the reference lists of 10 review articles reporting on the relation between vitamin B_{12} intake or status and cognitive function to identify potentially relevant references that had not yet been collected by the database search ($n = 134$). We updated the searches on February 11, 2010 ($n = 560$), and from February 2010 to January 2012 we checked database alerts.

Selection of studies

For the selection of relevant publications for our systematic review, we used predefined inclusion and exclusion criteria. In general, studies were eligible for inclusion if they were conducted in apparently healthy human subjects aged ≥18 years and if they addressed cognitive function as a health outcome. We defined 4 categories of cognitive function: incident dementia, incident Alzheimer's disease, global cognition, and domain-specific cognition. The specific domains of cognitive function used in this review were based on the classification of cognitive tests proposed by Wald et al. (12): memory, speed, language, and executive function. Global cognition comprised assessment methods addressing different domains of cognition—for example, a compound z score combining z scores of different cognitive performance tests or the Mini-Mental State Examination (MMSE) combining aspects of orientation, memory, and attention into one questionnaire (13). Domain-specific cognition includes cognitive performance tests assessing a single domain of cognitive function.

Observational studies were included if they 1) had a prospective cohort or nested case-control design and 2) addressed exposure by either validated dietary assessment methods or serum/plasma concentration of markers indicating vitamin B_{12} status (vitamin B_{12}, methylmalonic acid (MMA), or holotranscobalamin (holo-TC)). Serum/plasma vitamin B_{12} is most commonly used as a marker of vitamin B_{12} status, but the functional markers of vitamin B_{12}, holo-TC and MMA, have been suggested to be more sensitive and specific. Holo-TC represents the fraction of vitamin B_{12} that is delivered to body cells, and MMA is the substrate for the vitamin B_{12}-dependent enzyme methylmalonyl coenzyme A mutase, so in case of vitamin B_{12} deficiency MMA levels will increase (14–17).

Intervention studies were included if they 1) had an RCT design; 2) studied the effects of supplements, fortified foods, or micronutrient intake from natural food sources and included a placebo or untreated comparison group; and 3) had a minimum intervention duration of 2 weeks. Studies were excluded if they included only patients with preexisting disease because relations of vitamin B_{12} intake or status with cognitive function in such study populations might not be representative for the general, apparently healthy population.

First, 2 reviewers (E. L. D., Silvia Bell) screened titles and abstracts of all references identified with the searches according to the inclusion and exclusion criteria. Second, 4 reviewers (E. L. D., J. P. v. W., A. S., Maria Plada) evaluated full texts of the remaining references against the same criteria. For the purpose of alignment and quality control, each reviewer screened and evaluated 10% of the total number of references in duplicate with another reviewer. The rare discrepancies were resolved by group consultation among all reviewers until consensus was reached. During the selection process, all reasons for exclusion were registered; details are shown in Figure 1.

Data extraction

Data extraction was performed by a single reviewer (E. L. D., J. P. v. W., or A. S.) using standardized data extraction forms in a Microsoft Access (Microsoft Corporation, Redmond, Washington) database. A second reviewer verified the data. Disagreements were discussed and settled, if needed, in consultation with a third reviewer. Extracted data included general characteristics of the study design and study population; details on measures of intake, status, and cognitive function; and details on data analysis and results. In addition, we extracted information about the validity of studies, including sequence allocation (RCTs); blinding (RCTs); compliance (RCTs); reproducibility and between-population comparability of intake, status, and cognitive measures; and control for confounders (at least age, sex, education, vascular disease, and apolipoprotein E ε4) and other forms of bias. We assessed the overall risk of