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Low and high homocysteine are associated with mortality independent of B group vitamins but interactive with cognitive status in a free-living elderly cohort

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ABSTRACT

Hyperhomocysteinemia and cognitive impairment both predict mortality and partly because of dietary associations. We have hypothesized that for, nutritional reasons, homocysteine and cognition may act jointly to determine elder survival. In a Nutrition and Health Survey in Taiwan (1999-2000), some 1412 representative elderly were followed up for mortality up to 10 years. Cognition was assessed by the Short Portable Mental Status Questionnaire. Food and B vitamin intakes with their biomarkers, and plasma homocysteine, were measured at baseline. The possible effects of cognition on homocysteine-associated mortality were ascertained with Cox proportional-hazards models. Homocysteine was higher in those who were older, male, and single, consumed less fish and tea, and with alcohol and smoking. In models adjusted for these variables, when homocysteine exceeded 14.5 μmol/L, mortality was 1.80-fold more than when <9.3 μmol/L (hazard ratio [HR], 1.80; 95% confidence interval [95% CI], 1.20-2.71). *P* for trend was 0.002 and interactive with sex ($P < .002$). However, these homocysteine-mortality associations were dependent on cognition ($P = .03$); adjustment for food intake or nutrient status made little difference. Homocysteine did not predict cognitive impairment (adjusted OR, 1.40; 95% CI = 0.50-3.93). Vitamins B_1, B_2, and B_6 accounted somewhat for cognitive impairment. Cognition predicted mortality, fully adjusted for available covariates and also for homocysteine (HR, 3.66; 95% CI, 1.64-8.20) but interactively with homocysteine. Thus, the B-group vitamin insufficiency and cognitive impairment associations with premature

Abbreviations: BMI, body mass index; CI, confidence interval; DDS, Dietary Diversity Score; EGRAC, erythrocyte glutathione reductase activity coefficient; ETKAC, erythrocyte transketolase activation coefficient; HR, hazards ratio; NAHSIT, Nutrition and Health Survey in Taiwan; PLP, pyridoxal phosphate; SPMSQ, Short Portable Mental Status Questionnaire.

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mortality are confirmed. Yet cognition is inter-related with homocysteine in its association with survival in ways not detectably altered by foods or food-derived vitamins.

1. Introduction

Hyperhomocysteinemia is associated with increased risk of total, cardiovascular and non-cardiovascular mortalities [1-3]. While much of the non-cardiovascular mortality linkage is related to cancer, the strongest associations are with non-cardiovascular and non-cancer mortalities, especially accidental, violent or other heterogeneous deaths [1]. Death by injury may relate to impaired cognition as with falls in the aged [4]. Cognitive impairment has been shown to increase the risk of mortality [5,6], subject to dietary quality [7]. It is possible; therefore, that homocysteine and cognition-related mortalities are linked. Hyperhomocysteinemia is a risk factor for cognitive impairment [8-12], although the expression of this risk may be dependent on MTHFRC677T polymorphism [13,14].

Lower intakes of some B group vitamins, namely, vitamins, B_2 [15,16], folate [17], and B_{12} [18] and combinations of them are associated with hyperhomocysteinemia. The B-group vitamin profile responsible may vary by food cultures like the Taiwanese [19] where, with normal renal function, folate, vitamin B_2, B_6, and B_{12} status are lower in males with hyperhomocysteinemia, while only folate and vitamin B_{12} are lower in females with hyperhomocysteinemia; and in the United States, folate and B_{12}, but not B_6, are associated with it [20]. Since these vitamins (at least as supplements) may slow neurodegeneration [21,22], they may reduce cognitive decline via homocysteine. In vegetarians and more plant-based food cultures, folate status may be adequate, but B_{12} is not and the reasons for higher homocysteine concentrations are correspondingly different [23]. Homocysteine concentrations in Taiwan have increased over the period from 1999 to 2000 to 2005 to 2008 [24]. However, doubt remains about the interpretation and significance of these effects [25]. Even intervention studies with vitamin supplementation which purport to support a homocysteinemia pathway for B-group vitamin effects on cognition or brain atrophy may still have circumstantial findings [21,22]. Moreover, high folate intakes have actually been associated with more rapid cognitive decline [26]. In the case of vitamin B_1, its supplementation may affect mood without effect on memory [27], although its deficiency is associated with memory deficits and confabulation [28]. In any case, some of the reduction in mortality attributable to B-group vitamin status may act via pathways other than homocysteine or cognition [29].

There is little evidence that reduction of homocysteine with vitamin supplementation changes survival [3,25], which raises questions about their time-to-effect, if any; at which stage of life; and whether these micronutrients may not actually be surrogates for other diet-related factors. Diverse dietary patterns [30,31] like the traditional Mediterranean [32-34] are associated with better cognition. In a Taiwanese cohort, an association between cognition and survival was favorable with a more diversified diet [7]. Similarly, diets to which animal-derived foods (especially fish or n-3 fatty acids) [7,35-38] or ones providing choline [39] contribute are associated with lower plasma homocysteine concentrations. This understanding may both assist the management of risk for cognitive impairment with age and improve survival with food-based approaches. The case for B group vitamin approaches to the prevention of hyperhomocysteinemia, cognitive impairment, and improved survival is unresolved, unless these nutrients form part of a diverse diet [29,40].

When mortality is considered, Dangour et al showed that homocysteine predicts mortality in the United Kingdom, but not on account of folate or vitamin B_{12} status [2]. If the status of these vitamins is associated with homocysteine concentrations, then it may not be a way in which cognition is linked to mortality.

In addition to diet, whether foods [7,33,41-44] or nutrients [10,45-51], in an ageing population in which homocysteine increases with age [52], there is a broader context where cognitive decline may be partly avoidable through attention to social support [53] and personal behaviors like physical activity [54].

Hypothetically, both homocysteine and cognition status might be nutritionally-determined and act jointly to alter survival in elders (Fig. 1). We have undertaken a population-based cohort study to assess the relative contributions and interactions of cognition and homocysteine to mortality and how food-dependent B-group vitamin status (as opposed to supplements) might be involved.

2. Methods and materials

2.1. *Subjects*

The present study used data from the Elderly Nutrition and Health Survey in Taiwan (NAHSIT Elderly), a nationally representative sample of the free-living elderly 65 years and older, conducted in 1999 and 2000. Details of design and sampling for this survey can be found elsewhere [55]. The

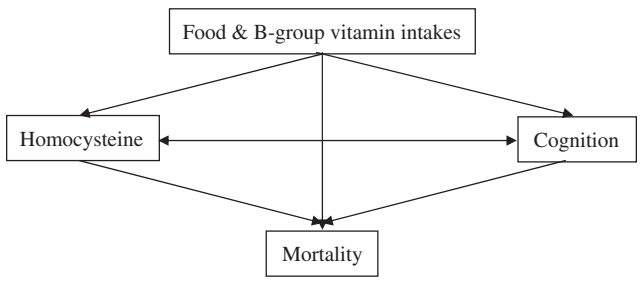

Fig. 1 – Hypothetical pathways linking homocysteine and cognition with mortality.