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Elevated Blood Homocysteine and Risk of Alzheimer's Dementia: An Updated Systematic Review and Meta-Analysis Based on Prospective Studies

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Abstract

OBJECTIVE: To investigate whether high serum homocysteine (Hcy) levels is associated with the risk of developing Alzheimer's disease (AD) by performing a meta-analysis based on updated published data.

METHODS: We conducted a comprehensive research using Medline (Pubmed), Scopus, Web of Science and EMBASE databases to identify all prospective studies published any time to July 7, 2020 evaluating the association between elevated Hcy levels and AD risk.

RESULTS: From an initial screening of 269 published papers, 9 prospective investigations conducted on a total of 7474 subjects with mean follow-up of 9.5 years (range: 3.7-10) were included in the meta-analysis. Eight seventy-five of these subjects converted to AD. Hcy was significantly higher in these individuals (HRadjusted:1.48, 95% CI:1.23-1.76, I2=65.6%, p<0.0001) compared with who did not convert to AD. There was a significant publication bias (Egger's test, t=6.39, p=0.0003) and this was overcome by the trim and fill method, which allowed to calculate a bias-corrected imputed risk estimate of HRadjusted:1.20, 95% CI:1.01-1.44, Q value=41.92.

CONCLUSIONS: The present meta-analysis found that having higher Hcy increases the risk of AD in the elderly and this finding is consistent with the widely suggested role of this non-proteinogenic α-amino acid in AD neurodegeneration.

Key words: Alzheimer's disease, homocysteine, meta-analysis, prospective studies.

Introduction

Mounting epidemiological and clinical evidences have demonstrated a considerable overlap between Vascular dementia (VaD) and Alzheimer's disease (AD) (1, 2). The emerging scenario highlights that cardiovascular disease (CVD), atherosclerosis, and cerebral microvasculature abnormalities mutually interact promoting neurodegeneration since the earliest stage of AD, and influencing the disease progression (3, 4). In support of this view, several studies have demonstrated the presence of an association between cardiometabolic risk factors and development AD, besides VAD (5–9).

In this regard, hyperhomocysteinemia (H-Hcy), which represents a well-established cardiovascular risk factor (10), represents an emblematic example in this frame. The first solid demonstration showing that increased H-Hcy is an independent risk factor for the development of AD, and more in general dementia, was presented in 2002 (11). Since then, several epidemiological studies have been consistent with this finding, (12, 13), suggesting Hcy as a potential target for both non- and pharmacological treatments (14). Unfortunately, the causality of H-Hcy in AD has not yet been definitely confirmed, although experimental evidence clearly suggests its implication in pathogenic mechanism of the neurodegenerative disease (15, 16). One of the most intriguing hypotheses linking H-Hcy and AD onset, is inspired by the role of Hcy in the metabolism of methionine, and the importance of the latter in phosphatidylcholine synthesis. Indeed, Hcy is a product of methionine catabolism, but it can also be recycled back to the essential amino acid by the vitamin-B12 dependent methionine synthase, as well as via a folate-independent pathway (17, 18). Owing the crucial role of these two vitamins in methionine synthesis, a deficiency of either of them can result in H-Hcy and low bioavailability of methionine (19). In turn, a decrease in methionine may cause a lower synthesis of phosphatidylcholine (methionine is a precursor of this phospholipid), which serves as important carrier for docosahexaenoic acid (DHA) through the blood-brain barrier. Importantly, DHA is the most abundant fatty acid in the brain and its deficiency is associated with AD (20).

The clinical relevance of the topic, prompted us to provide an updated systematic review and meta-analysis based on published prospective studies evaluating the role of H-Hcy and the risk of AD.

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Methods

Search strategy

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline (Supplementary file 1) (21). Data were obtained searching MEDLINE, Scopus and Web of Science and EMBASE for all prospective studies in English language and without age restrictions, published any time to July 7, 2020 evaluating the association between H-Hcy and the risk of AD in the elderly. The risk of AD due to H-Hcy was chosen as the primary outcome of the study.

Study selection

The selection of studies to be included in our analysis was independently conducted by 2 authors (MZ, GZ) in a blinded fashion. Any discrepancies in study selection was resolved consulting a third author (CC). The following MeSH terms were used for the search: "Homocysteine" OR "Hyperhomocisteinemia" AND "Alzheimer's disease" OR "Dementia". Moreover, we searched the bibliographies of target studies for additional references. Case reports, review articles, abstracts, editorials/letters, and case series with less than 10 participants were excluded. Data extraction was independently conducted by 2 authors (AT, MZ). Any disagreements were resolved by consensus after discussion. Studies were included in the present analysis if they were prospective investigations or prospective nested case-control studies assessing the relationship between H-Hcy and AD and the results expressed as hazard ratio (HR) and relative 95% confidence interval (CI).

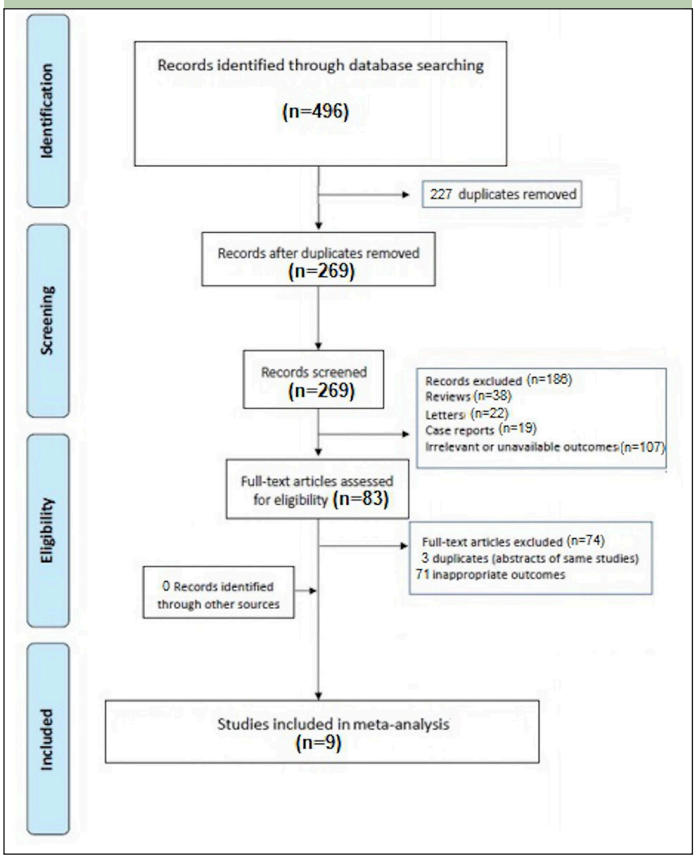
Data extraction

For each investigation included into the final analysis, the following items were extracted: year of publication, country, sample size, male gender, mean follow-up duration, diagnostic criteria for AD, method used for the assessment of blood Hcy concentration and covariates used in the multivariate analyses of each manuscript. The quality of included studies was graded using the Newcastle-Ottawa quality assessment scale (22).

Statistical analysis

Continues variables were expressed as mean ± standard deviation (SD) or range while categorical variables were presented as numbers and relative percentages. From each study, the adjusted hazard ratio (aHR) and 95% confidence interval (CI) for the higher versus the lower Hcy category comparison was pooled using a random-effects model, while a traditional forest plot was adopted to visually evaluate the results. Statistical heterogeneity between groups was measured using the Higgins I2 statistic. Specifically, a I2=0 indicated no heterogeneity while we considered low, moderate, and high degrees of heterogeneity the values of I2 as <25%, 25–75% and above 75%, respectively. Moreover, tau-squared (τ2) was also calculated to see the extent of variation among the effects observed in different studies. To evaluate potential bias, both the Egger's test and funnel plots were computed. In case of significant Egger's test, the Begg's rank correlation test was also carried out and the trim-fill method was used to re-calculate the pooled risk estimates. A p-value < 0.05 was considered statistically significant. All meta-analyses were conducted using Comprehensive Meta-Analysis software, version 3 (Biostat, USA).

Figure 1. PRISMA flow chart



Results

A total of 269 articles were retrieved after excluding duplicates. The initial screening excluded 186 articles because they did not meet inclusion criteria, leaving 83 articles to assess for eligibility. After evaluation of the full-text articles, 74 were excluded and 9 prospective investigations met the inclusion criteria (Figure 1) (11, 23–29).

Overall, 7474 community-dwelling adults (mean age 71 years, 53% male), with a mean follow-up of 9.5 years

Table 1. General characteristics of the studies included in the meat-analysis

Author	Country	Sample size, n	AD conversion, n	Age (years)§	Males(%)	Follow-up (years)	Diagnostic criteria	Hcy deetction method	NOS
Seshadri et al., 2002	USA	1092	83	76 ± 6	39	8	NINCDS	HPLC	7
Luchsinger et al., 2004	USA	679	237	76 ± 6	29	4.7	NINCDS	HPLC	6
Ravaglia et al., 2005	Italy	816	70	74 ± 6	47	3.8	NINCDS-ADRDA	IMx assay	8
Ravaglia et al., 2007	Italy	804	68	74 ± 6	47	3.7	NINCDS-ADRDA	IMx assay	8
Kivipelto et al., 2009	Sweden	213	61	81 ± 5	25	6.7	DSM-III-R	IMx assay	7
Hooshmand et al., 2010	Finland/Sweden	271	17	71 ± 4	38	7	NINCDS-ADRDA	Chemio-luminesceny assay	7
Zylberstein et al., 2011	Sweden	1368	68	47	0 (all females)	35	DSM-III-R	IMx assay	6
Miwa et al., 2016	Japan	643	24	67 ± 8	59	7.3	DSM-IV	HPLC	7
Chen et al., 2020	Japan	1588	247	71 ± 8	42	10	NINCDSADRDA NINDS-AIREN	Chromatography	8

§ age is expressed as mean ± standard (SD) deviation far all study sample, with the exception of Zylberstein et al. 2010, which did not report the value of SD; Hcy: Homocysteine; NOS: Newcastle-Ottawa quality assessment scale

Table 2. Confounders considered in each study for the estimation of Hazard risk

	Seshadri et al., 2002	Luchsinger et al., 2004	Ravaglia et al., 2005	Ravaglia et al., 2007	Kivipelto et al., 2009	Hooshmand et al., 2010	Zylberstein et al., 2011	Miwa et al., 2016	Chen et al., 2020
Age	X	X	X	X	X	X	X	X	X
Sex	X	X	X	X	X	X		X	X
Education	X	X	X	X	X	X	X	X	X
Apo-E4	X	X	X	X	X	X		X	
CVD				X					
Stroke	X	X	X	X		X			X
Smoking	X					X	X		X
Alcohol intake	X								X
T2D	X								
SBP	X					X and DBP	X and DBP		
BMI	X			X	X	X	X	X	
Physical activity				X					X
Serum creatinine			X	X	X		X		
Serum folate			X	X	X				X
Serum Vitamin B12			X	X	X		X		X
Other					Albumin; Hb; MMSE; holo-TC	Follow-up duration; MMSE	Cholesterol; Triglycerides	MMSE	HT; eGFR; albumin

CVD: Cardiovascular disease; Hb, Haemoglobin; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; BMI: Body mass index; MMSE: Mini-mental state; holo-TC: Holotranscobalamin; HT: Arterial hypertension; eGFR: Estimated glomerular filtration rate

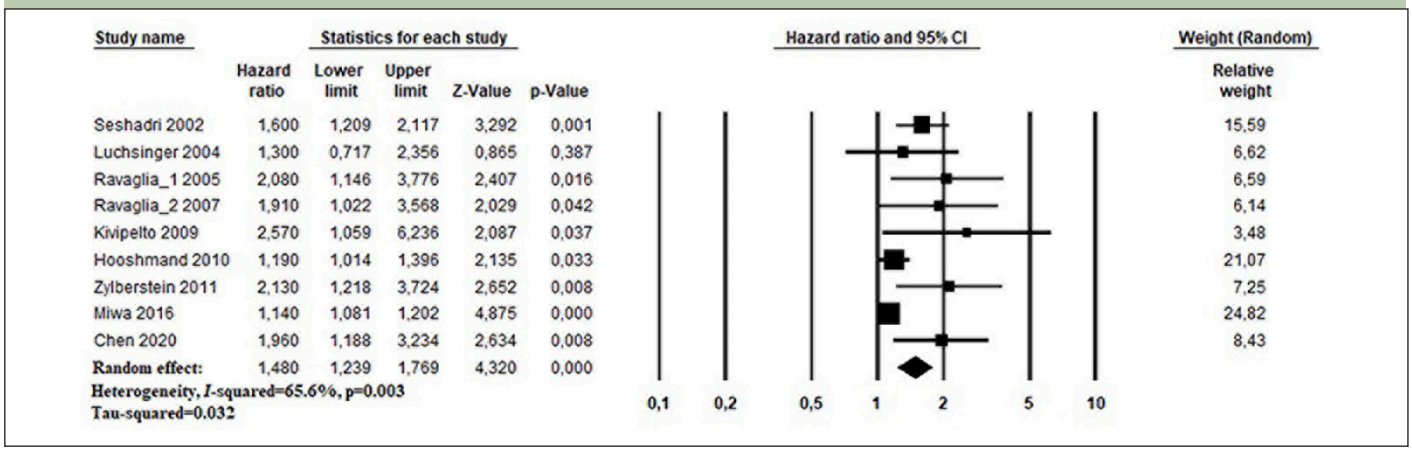
were analysed (Table 1). Eight seventy-five of these subjects (11.7%) converted to AD.

The diagnostic criteria used in the studies were: the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) (11, 25), the National Institute of Neurological and Communicative Disorders and Stroke of the United States and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) (23, 24, 26, 27), the revised Diagnostic and Statistical Manual of Mental Disorders criteria (DSM-III-R) (29, 30), DSM IV (28) and the National Institute of Neurological Disorders and Stroke (NINDS) Association Internationale pour la Recherche et l'Enseignement en Neurosciences (AIREN) criteria (NINDS-AIREN) (23).

The different confounders considered for the estimation of Hazard Risk in each analysis are shown in Table 2. Age (n=9 studies), sex (n=8), Apo E4 (n=7), education (n=9) and body mass index (n=7) were the most considered covariates; surprisingly, the most important determinants of Hcy, folate and vitamin B12, in less than 50% of the investigations. The studies included into the meta-analysis resulted of moderate-high quality according to the NOS.

The pooled analysis, based on a random effect model, revealed that subjects with higher vs. lower levels of blood Hcy had an increased risk of AD (Figure 2,

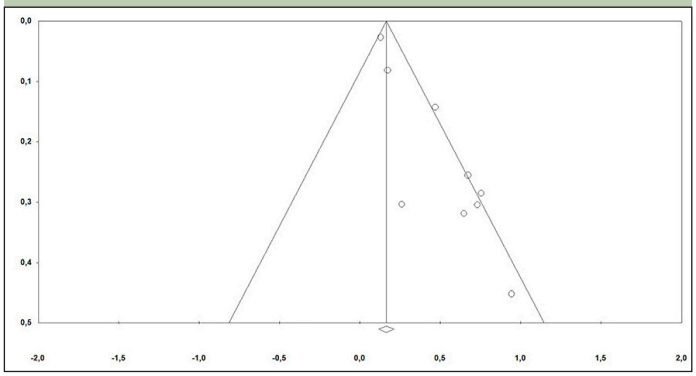
Figure 2. Forest plots investigating the risk of AD in patients with hyperhomocysteinemia



HRadjusted:1.48, 95% CI:1.23-1.76, p<0.0001), with a moderate heterogeneity in effects size between the studies (I2=65.6%).

However, as displayed by the Funnel Plot (Figure 3), there was a significant publication bias confirmed also by the Egger's test (t=6.39, p=0.0003). To overcome this limitation, the trim and fill method calculated a bias-corrected imputed risk estimate of HRadjusted:1.20, 95% CI:1.01-1.44, Q value=41.92.

Figure 3. : Funnel plot for the risk of AD in patients with hyperhomocysteinemia



Discussion

The result of the present meta-analysis confirms that higher concentration of blood Hcy increases the risk of developing AD in older individuals. The clinical value of Hcy is beyond its mere use as static biomarker; indeed, this cysteine homologue represents a well-known modifiable risk factor, especially in the field of cardiovascular prevention, as well as a potential therapeutic target.

H-Hcy has been found to be related with cognitive decline, global and regional brain atrophy (including hippocampus volumes), white matter damage, formation and/or accumulation of the major AD-neuropathological hallmarks, neurofibrillary tangles and neuritic plaques (31). Notably, some authors found that a nutritional model of B vitamin deficiency with Hcy cycle alteration could lead to increased amyloid β (Aβ) deposition, due to over-expression in presenilin 1 and β-secretase 1 activity (32). Similarly, Li and co-workers reported a dietary approach that leads to an increase in Hcy levels resulting in a typical AD phenotype where Aβ and tau neuropathology were accompanied by memory deficit (33). More recently, it has been shown that supraphysiological concentrations of Hcy (>0.5 μM) caused a decrease in synaptic proteins in AD animal model, with the concomitant increase in oxidative stress and excitatory transmission hyperactivity, which are all considered to be neurotoxic effects (34). Furthermore, it has been reported that H-Hcy plays a causal role in stroke (35), a frequent co-existing pathology and potent risk factor of AD (36, 37), and has deleterious effects on the cerebral vasculature, including blood brain barrier disruption (38), a well-recognized early event in AD pathogenesis (39).

A meta-analysis on studies published until June 2018 showed increase of 1 μmol/L in Hcy in the blood is linearly associated with a 15% increase in the relative risk of AD (40). Our work adds to those performed to Zhou et al, since we have considered around one thousand and six hundred more patients. Moreover, the cited authors performed a dose-response meta-analysis on the risk all-cause dementia (AD and vascular dementia), while our study aimed to confirm whether patients of general population with H-Hcy, were at higher risk of AD. Indeed, evaluating the risk of AD in terms of fixed increase of blood Hcy, as every 5 μmol/L results directly correlated with the baseline values. Conversely, it could be more useful for clinicians to establish a direct relationship between H-Hcy and AD in the evaluation of patients with dementia. Furthermore, whether the risk between H-Hcy and AD follow a linear or exponential growth, has not yet been defined.

H-Hcy remains a major and yet underrecognized risk factor for cognitive impairment and dementia in daily clinical practice (41). This is mostly due to the contrasting results of the clinical trials that failed to show a clear

beneficial effect of Hcy-lowering B vitamins (B-6, B-12 and folic acid) supplementation on cognitive decline. However, some studies found that baseline Hcy levels could be predictive of the response with beneficial effects of B vitamins administration only in subjects with high baseline Hcy (42, 43). The effectiveness of B vitamins supplementation could depend on other endogen and exogen factors; therefore, it could be helpful to identify subgroups that are likely to benefit of such supplementation in clinical trials. Of particular relevance to this context, two studies reported a beneficial effect of B vitamins supplementation on brain atrophy and cognitive decline only on those subjects which had high baseline levels of plasma omega (ω)-3 fatty acids (FA) (44, 45). Interestingly, the recent findings of Jerenlen et al. clearly suggest that B vitamins, Hcy and ω-3 FA influence each other. In fact, FAs supplementation seems to be effective on cognitive and clinical outcomes performance only on those AD patients with low baseline levels of Hcy (46).

Our findings confirm that the assessment of Hcy level in serum is a promising tool for the evaluation of AD risk in general population. However, it is undeniable that any case of h-Hcy should be adequately interpreted in a multidimensional evaluation because it could be expression of an underlying causal condition (e.g. chronic renal failure, alcohol consumption, smoke, use of some medications) or a consequence of cognitive decline itself (e.g. malnutrition in demented patients). Our analysis has some limitations. Firstly, being based on observational studies, the possibility of remaining residual confounding items, due either to unmeasured or underestimated risk factors in the reviewed studies cannot be excluded, representing a potential source of biases. At the same manner, we cannot exclude that patients enrolled in the reviewed cohort might be treated with vitamin B supplementation. However, potential bias resulted mitigated by the fact that some of the reviewed studies demonstrated that H-Hcy remained associated with AD, after adjustment for vitamin B levels (24, 30). However, the relative long follow-up period of the studies considered, our findings are less prone to be biased due to potential reversed causalities over the time. Finally, the lack of standardized cut-offs for H-Hcy represents another important limitation in our findings and analysis.

Conclusions

Our meta-analysis found that H-Hcy increases the risk of AD in the elderly and this finding is consistent with the potential role of Hcy in promoting neurodegeneration. Although interventional studies analysing B vitamins supplementation in terms of prevention of Hcy-related cognitive decline have shown scant results, promotion of healthy lifestyle, screening of high-risk subjects and earlier therapeutic approaches, before neurological damages have occurred, could get better results.

Key points

1. Homocysteine might play an important role in Alzheimer's disease-related neurodegeneration
2. In elderly, higher blood levels of homocysteine are associated with a greater risk of developing Alzheimer's disease

Conflicts of interest: All authors declare that they have no conflicts of interest.

Data availability statement: Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Funfing information: The research reported did not receive any specific grant from funding agencies in the public, commercial, or not- for- profit sectors.

Approval by ethical committee: Not necessary (systematic review)

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