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Editorial

Homocysteine and Dementia: An International Consensus Statement

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Abstract. Identification of modifiable risk factors provides a crucial approach to the prevention of dementia. Nutritional or nutrient-dependent risk factors are especially important because dietary modifications or use of dietary supplements may lower the risk factor level. One such risk factor is a raised concentration of the biomarker plasma total homocysteine, which reflects the functional status of three B vitamins (folate, vitamins B12, B6). A group of experts reviewed literature evidence from the last 20 years. We here present a Consensus Statement, based on the Bradford Hill criteria, and conclude that elevated plasma total homocysteine is a modifiable risk factor for development of cognitive decline, dementia, and Alzheimer's disease in older persons. In a variety of clinical studies, the relative risk of dementia in elderly people for moderately raised homocysteine (within the normal range) ranges from 1.15 to 2.5, and the Population Attributable risk ranges from 4.3 to 31%. Intervention trials in elderly with cognitive impairment show that homocysteine-lowering treatment with B vitamins markedly slows the rate of whole and regional brain atrophy and also slows cognitive decline. The findings are consistent with moderately raised plasma total homocysteine (>11 μmol/L), which is common in the elderly, being one of the causes of age-related cognitive decline and dementia. Thus, the public health significance of raised tHcy in the elderly should not be underestimated, since it is easy, inexpensive, and safe to treat with B vitamins. Further trials are needed to see whether B vitamin treatment will slow, or prevent, conversion to dementia in people at risk of cognitive decline or dementia.

Keywords: Homocysteine, folate, vitamin B12, cobalamin, vitamin B6, cognitive impairment, dementia, Alzheimer's disease, brain atrophy, risk-factor, causation

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INTRODUCTION

It is 20 years since two case-control studies found that raised plasma or serum total homocysteine (tHcy)

was associated with Alzheimer's disease (AD), as diagnosed by clinical [1] and histopathological [2] criteria. The histopathological study also found that vascular dementia was associated with raised tHcy [2]. The B-vitamins, folate and cobalamin (B12), are major determinants of tHcy [3], and it was found that low red blood cell folate [1, 2], low serum folate, and low serum B12 [2] were also associated with a diagnosis of AD. These reports prompted an editorial that posed the question: '*Hyperhomocysteinemia. A new risk factor for Alzheimer disease?*' [4].

This Consensus Statement is not a systematic review, but represents the conclusions of a panel of experts on the evidence concerning the causal role of raised tHcy in dementia, based upon recent reviews [5–9]. The Consensus Statement concludes that the question of causality of tHcy in dementia can be answered in the affirmative, with significant implications for public health.

Development of cognitive impairment is a multifactorial condition with raised tHcy being just one component of 'sufficient causes' of dementia. According to the causal theory introduced by Rothman [10], a sufficient cause of dementia would contain a variety of 'component causes' such as age, hyperhomocysteinemia, hypertension, smoking, low physical activity, ApoE4 genotype, other vascular risk factors, etc. Notably, there are usually many distinct sufficient causes, with different components in each, and where hyperhomocysteinemia may belong to several (Fig. 1). The strength of hyperhomocysteinemia as a risk factor for dementia does not arise from the strength of its role in the etiology of dementia alone, but also depends on the prevalence of the other causal components in the sufficient causes where hyperhomocysteinemia belongs. By eliminating hyperhomocysteinemia from the elderly population, the 'sufficient causes' that include raised tHcy as a component will then become insufficient for causing dementia.

A question often asked is: is raised tHcy a direct cause of cognitive impairment or could elevated tHcy simply be a marker of causes like poor lifestyle, and/or inadequate B vitamin status [3, 11]? We suggest that in fact both direct and indirect pathways may well occur, as illustrated in Fig. 2. Nevertheless, most prospective studies have found that raised tHcy remained associated with cognitive impairment even after adjusting for B vitamin status [8], consistent with tHcy being a risk factor for cognitive impairment independent of the B vitamins. Furthermore, in the VITACOG trial, it was shown by Bayesian analysis, using the directed acyclic graph procedure, that lowering of tHcy by B vitamin treatment mediated the slowing of regional brain atrophy, which, in turn, mediated the slowing of cognitive decline [12]. As we shall argue below, there is good evidence that raised tHcy is a risk factor for cognitive impairment but it may well act in parallel with some of the factors that themselves determine tHcy.

The potential causal role of tHcy in dementia was analyzed by McCaddon and Miller [7] according to Bradford Hill's criteria of causation [13]. Hill suggested nine features that are helpful in supporting the idea of causation: strength, consistency, specificity, temporality, biological gradient, plausibility, coherence, analogy, and experiment. We will adopt the same approach, bearing in mind that the use of these features has several limitations [14].

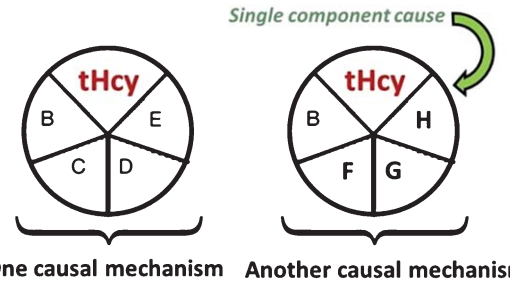

Fig. 1. Hypothetical 'sufficient causes' for dementia that involve raised plasma total homocysteine (tHcy) as one of the single component causes. For example, B might be age, C hypercholesterolemia, D hypertension, E smoking, F ApoE4, G low physical activity, H low education. Based on Rothman & Greenland [14].

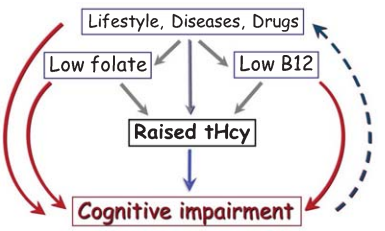

Fig. 2. Parallel pathways for causation of cognitive impairment involving homocysteine. Raised tHcy may directly cause cognitive impairment (blue arrow). Many modifiable factors determine tHcy [3, 11]. Some of these factors may directly cause cognitive impairment (red arrows) as well as causing cognitive impairment indirectly by raising tHcy (grey arrows). Reverse causality (dashed line) could also explain the association of Hcy with cognitive impairment.

STRENGTH OF THE ASSOCIATION BETWEEN RAISED tHcy AND DEMENTIA

To gain some idea of the risk of dementia associated with raised tHcy, we summarize in Table 1 the outcomes of prospective observational studies as reviewed in seven meta-analyses. All the meta-analyses revealed a significant association to dementia, with the pooled risk estimates varying from 1.15 to 2.5.

In one of the latest comprehensive meta-analyses, Xu et al. investigated the associations between 36 modifiable risk factors and AD [15]. The pooled relative risk of AD was 1.15 (1.02–1.27) for raised tHcy in 13 cohort studies on 6,310 subjects; this was classified as Grade 1 evidence. The variation of the risk estimates between these seven meta-analyses reflect in part that different cohorts were studied but also reflect the different definitions of high tHcy used. Nevertheless, the universal finding is of an increased risk of dementia in subjects with elevated tHcy.

A meta-analysis [16] based upon Mendelian randomization of the C677T polymorphism of *MTHFR*, which is associated with an increase in tHcy, avoids the potential biases of observational cohort studies. In 34 studies on a total of 9,397 subjects, there was an odds ratio of AD of 1.37 (1.15–1.63) for those with the TT alleles compared with those with the CC alleles. From the same meta-analysis, the authors also assessed tHcy and found a combined odds ratio of 3.37 (1.9–5.95) for each 1 SD increase in ln(tHcy); this association was stronger in Asian and mixed populations than in Caucasians.

The population attributable risk (PAR) of dementia for raised tHcy can be estimated from the prevalence of hyperhomocysteinemia and the relative risk of dementia. Table 1 shows PAR estimates based on independent relative risks and a prevalence of hyperhomocysteinemia of 25% or 30%, since most studies considered either the upper quartile or tertile of tHcy distribution as a cut-off for defining hyperhomocysteinemia. The PAR% is the proportion of dementia cases in the elderly population (i.e., exposed and non-exposed) that is due to hyperhomocysteinemia (the exposure in question) and so indicates the dementia incidence that would be prevented if hyperhomocysteinemia was eliminated. It is striking that, apart from one meta-analysis, the PAR estimates suggest that from 12% to 31% of cases of dementia or AD could be prevented by lowering tHcy.

CONSISTENCY OF THE ASSOCIATION BETWEEN RAISED tHcy AND COGNITIVE IMPAIRMENT

As shown in the above meta-analyses and in reviews [6, 17], there is a high degree of consistency between the large number of studies in all parts of the world that have examined cognitive impairment or dementia in relation to tHcy. Beydoun et al. [17] used multiple logistic regression to assess the consistency of risk factors and concluded their study of 8 different modifiable risk factors as follows: "Combining both criteria (strength of association in the case of incident AD and consistency overall), the strongest evidence thus far is an increased risk with elevated plasma Hcy levels or lower educational attainment and a lowered risk with increased physical activity." [17]

We conclude that the association between raised tHcy and cognitive impairment is both strong and consistent, but, as pointed out by Rothman and Greenland [14], 'a strong association is neither necessary nor sufficient for causality'.

SPECIFICITY OF THE ASSOCIATION BETWEEN RAISED tHcy AND COGNITIVE IMPAIRMENT

Besides dementia, raised tHcy has been associated with numerous clinical outcomes. For instance, diseases that involve damage to the vasculature, such as ischemic heart disease, stroke, and age-related macular degeneration, are also associated. It is likely that a significant component of cognitive impairment is directly caused by compromised cerebral vasculature and that vascular insufficiency also contributes to the damage to the nervous system that leads to cognitive impairment and dementia [8]. Thus, the association between tHcy and cognition is not specific. Nevertheless, the importance of the characteristic of 'specificity' must not be over-emphasized; indeed, it has been claimed 'the criterion is invalid as a general rule' [14].

TEMPORALITY OF THE ASSOCIATION BETWEEN RAISED tHcy AND COGNITIVE IMPAIRMENT

This characteristic is crucial to exclude reverse causality, for example that cognitive impairment leads to changes in diet, lifestyle factors, other diseases and drug use that in turn raise tHcy (Fig. 2).

Table 1
Meta-analyses since 2009 on the association between elevated plasma homocysteine and dementia or AD in prospective cohort studies

Meta-analysis	Studies/Subjects/Duration	Exposure threshold	Outcome	Pooled risk estimates (95%CI)	PAR% (95%CI) [Prev. 0.25]	PAR% (95%CI) [Prev. 0.30]
Van Dam, et al. [44]	3 prospective studies in 2,569 subjects (baseline free of AD)	tHcy >14.0, 15.0, or 15.6 μmol/L	Alzheimer's disease	RR: 2.5 (1.38–4.56)	27.3 (7.5–47.1)	31.0 (8.6–53.5)
Wald et al. [45]	8 cohorts of 8,669 subjects, median duration = 5 years. Cohort studies of individuals without cognitive impairment or dementia at the start of the study which reported serum homocysteine levels and the incidence or risk of dementia after at least 1 year of follow-up were included.	For a 5 μmol/L increase in tHcy (i.e., 10.0 ⟶ 15.0 μmol/L)	Dementia (the search criteria was mixed, memory, dementia, etc.)	Adjusted OR: 1.50 (1.13–2.0)	/	/
Beydoun et al. [17]	5 cohorts on 4,412 subjects	Elevated tHcy (variety of cut-offs: 14.0, 15.0, 15.6, 14.6 and 12.6 μmol/L)	Incident AD	RR: 1.93 (1.50–2.49)	18.9 (10.8–27.0)	21.8 (12.5–31.1)
Nie et al. [46]	14 cohorts on 15,908 subjects	Elevated tHcy (variety of cut-offs: 15.8, 15.0, 14.0, 27.5, 15.4, 15.0, 13.4, 13.0, 14.3, 21.0, 15.1, 14.5, 17.0 [?], 10.8 μmol/L)	Dementia, cognitive impairment	RR: 1.53 (1.23–1.9)	11.7 (3.8–19.6)	13.7 (6.3–21.2)
Shen et al. [47]	9 studies on 4,830 subjects (mixed study designs)	Elevated tHcy (variety of cut-offs: 14, 12.0, 13.1, 13.3, 27.4, 15.0, 13.0, 15.0 μmol/L)	AD	RR: 1.77 (1.37–2.16)	16.1 (9.1–23.1)	18.8 (10.7–26.9)
Xu et al. [15]	8 cohort studies on 5728 subjects	Elevated tHcy same as Shen et al. [47]	AD	RR: 1.15 (1.02–1.27)	3.6 (0.69–6.51)	4.3 (0.84–7.8)
Hu et al. [16]	34 cohort studies on 9,397 subjects	Mendelian randomisation of the *MTHFR* C677T as a cause for AD	AD	OR TT versus CC: 1.37 (1.15–1.63). OR CT versus CC 1.28 (1.14–1.44). OR (for each 1 SD increase in ln(tHcy)): 3.37 (1.9–5.95)		

AD, Alzheimer disease; CI, confidence intervals; tHcy, total homocysteine; MTHFR, methylentetrahydrofolate reductase; OR, odds ratio; PAR, Population Attributable Risk; Prev, prevalence of hyperhomocysteinemia (HHCY); RR, relative risk; SD, standard deviation. It should be noted that many of the meta-analyses included the same cohorts. PAR = 100 * [P(HHCY) * (RR–1)] / 1 + [P(HHCY) * (RR–1)]. 95% CI of PAR are according to Beydoun et al. [17] and the references cited there.

Although dementia may precede hyperhomocysteinemia at later stages (via feeding difficulties or micronutrient malabsorption), tHcy levels did not increase during 3 years as dementia worsened in the OPTIMA study [2]. In contrast, patients with higher tHcy at study entry showed a worse progression upon radiological re-examination of the brain [2]. A large number of prospective studies, in which blood samples were taken from subjects long before they showed signs of cognitive impairment, are consistent with a temporal relationship. The intervals between blood sampling to measure tHcy and diagnosis of cognitive impairment or dementia were up to 13 years in the Framingham study [18] and 35 years in the Gothenburg Women Study [19].

Thus, the criterion of temporality (hyperhomocysteinemia $\longrightarrow$ dementia) is fully satisfied.

BIOLOGICAL GRADIENT OF THE ASSOCIATION BETWEEN RAISED tHcy AND COGNITIVE IMPAIRMENT

A gradient relationship between tHcy and cognitive impairment or dementia is evident from many of the prospective studies reviewed. This gradient is often shown by a threshold concentration above which impairment occurs or by a concentration-response relationship, as can be seen from the exposure thresholds in the meta-analyses (Table 1). A notable example of the concentration-response relationship is a study from northern Italy in which an increasing incidence of dementia in normal elderly was observed as baseline tHcy increased; there was an almost 5-fold higher incidence in those with tHcy > 15.0 μmol/L compared with those with tHcy < 10.1 μmol/L [20]. In OPTIMA, patients with AD showed a marked concentration-dependent increase in the rate of cognitive decline over the range of 10.0 to 18.0 μmol/L of tHcy [21]. Threshold effects were found for the association of tHcy with the rate of atrophy of the medial temporal lobe in patients with AD, where the rate increased in patients with tHcy > 11.1 μmol/L compared with those with tHcy < 11.1 μmol/L [2] and in the Normative Aging Study an apparent threshold of 11 μmol/L tHcy was found for impairment in spatial copying ability [22]. We will return below to the matter of a threshold in relation to treatments that lower tHcy.

Thus the criterion of a biological gradient is fully satisfied in the relationship between raised tHcy and cognitive impairment.

PLAUSIBILITY OF THE ASSOCIATION BETWEEN RAISED tHcy AND COGNITIVE IMPAIRMENT

'Plausibility refers to the biological plausibility of the hypothesis, an important concern but one that is far from objective or absolute' [14]. The question whether raised tHcy itself causes dementia, or is a marker for other causes, such as B vitamin inadequacy, has been discussed above (Fig. 2) and in reviews [7, 8]. What can be said is that many different biological mechanisms are known that could link raised tHcy with cognitive impairment. These range from vascular mechanisms, to regional brain atrophy, neurofibrillary tangle and amyloid plaque formation, neuronal death, and epigenetic mechanisms; these are discussed in several reviews [7, 8, 23–27]. The mechanisms are not mutually exclusive and it is likely that several distinct pathways are involved—see Fig. 4 in the review by Smith and Refsum. [8]

We conclude that the association of tHcy with cognitive impairment is highly plausible.

COHERENCE OF THE ASSOCIATION BETWEEN RAISED tHcy AND COGNITIVE IMPAIRMENT

As stated by Rothman and Greenland [14], 'coherence implies that a cause-and-effect interpretation for an association does not conflict with what is known about the natural history and biology of the disease'.

Key biological aspects of cognitive impairment and of dementia are loss of neurons, leading to regional brain atrophy, and deposition of insoluble proteins such as amyloid-β in plaques and of phosphorylated tau (P-tau) in neurofibrillary tangles. In one of the early reports, raised tHcy was shown to be associated with the rate of atrophy of the medial temporal lobe in AD patients [2] and its association with regional brain atrophy has been extensively confirmed since then, most recently in the VITACOG trial. [12] In relation to P-tau, raised plasma tHcy and raised CSF S-adenosylhomocysteine are associated with increased levels of CSF P-tau [28] and, in a clinicopathological study, raised tHcy several years before death was associated with an increase in neurofibrillary tangle density in the cerebral cortex [29]. Animal studies have shown that hyperhomocysteinemia leads to epigenetic regulation of gene expression in the amyloid-β pathway, to increased amyloid deposition in the brain, to increased formation of P-tau

[30], to the death of hippocampal neurons in culture and *in vivo* [31], and to various cognitive deficits.

We conclude that the association of tHcy with impaired cognition and dementia is coherent across studies from isolated cells, through animals, and to human neuropathology.

ASSOCIATION BETWEEN RAISED tHcy AND COGNITIVE IMPAIRMENT BY ANALOGY

This criterion is not crucial for arguments about causation [14], but it should be noted that substances with a molecular similarity to homocysteine have toxic effects on the nervous system. Homocysteic acid is an excitatory amino acid that acts via NMDA receptors to cause cell death [32]. Homocysteine thiolactone is neurotoxic in animals and leads to the N-homocysteinylation of proteins on lysine residues [33, 34].

EXPERIMENTAL EVIDENCE OF THE ASSOCIATION BETWEEN RAISED tHcy AND COGNITIVE IMPAIRMENT

Hill considered that the strongest evidence of causality between a factor and an outcome was experimental intervention. Two questions arise: first, does deliberately increasing tHcy in the elderly lead to cognitive impairment; second, does lowering tHcy prevent cognitive impairment?

Several animal studies, summarized in the reviews, have shown that increasing tHcy, either by direct administration or by feeding the animals a B-vitamin deficient diet, is associated with cognitive impairment. It would not be ethical deliberately to increase tHcy in humans, but a common polymorphism (C677T in *MTHFR*) is associated with a modest increase in the concentration of tHcy and is associated with a significant increase in the risk of AD (Table 1) [16]. A person's level of tHcy may change over time, probably due to changes in lifestyle, and a Norwegian study in 1,670 elderly found that in those whose tHcy had increased over a 6-year period by up to 8 μmol/L, the mean memory test score was lower than in those whose tHcy did not change; in contrast, in those whose tHcy had decreased by up to 6 μmol/L over the 6-year period, the mean memory test score was higher [35].

Clinical trials

The question whether lowering tHcy slows cognitive decline or prevents cognitive impairment in humans has been the subject of several clinical trials in which B vitamins have been administered either to normal elderly, to elderly with mild cognitive impairment (MCI), or to patients with dementia. Critical reviews of these homocysteine-lowering trials and of the meta-analyses based upon them have been published [7, 8]. Both these reviews commented upon the futility of carrying out trials in which the placebo group showed no cognitive decline over the period of the trial; as one review stated " . . . you cannot prevent something that is not occurring" [7]. It is therefore unfortunate that 76% of 20,431 of the participants in the trials included in the largest meta-analysis did not have baseline measures of cognitive function, and so it was not possible to assess cognitive decline in the placebo group [36]. In two of the trials in the latter meta-analysis (on 2,825 participants), cognitive decline was shown in the placebo group and significant beneficial cognitive effects of treatment were observed in the B vitamin treated group who had high tHcy or poor B vitamins status at baseline. The authors of the meta-analysis considered that these latter findings were "due to chance" [36], despite the fact that these two trials were the only trials that could actually answer the question whether homocysteine-lowering with B vitamins slows cognitive decline.

We suggest that a meaningful clinical trial in this field should satisfy a set of criteria, listed in Table 2, in order to give a valid outcome.

Currently, there are three published trials in the elderly that fully satisfy the conditions listed in Table 2 and in which the active treatment was one or more of the B vitamins (folic acid, vitamins B6 and B12). We will briefly summarize the main findings from these trials.

FACIT trial [37]

This trial, the *Folic Acid and Carotid Intima-media Thickness* trial, recruited 818 normal elderly in The Netherlands whose baseline tHcy was in the range 13–26 μmol/L. Active treatment was daily 0.8 mg folic acid for 3 years, which led to a fall of 26% in tHcy compared with the placebo group. Three cognitive domains relating to speed (information processing, sensorimotor, complex) showed declining scores in the placebo group, whereas memory score improved in the placebo group (probably due

Table 2
Essential criteria for showing that lowering raised tHcy can influence the outcome

Risk factor: baseline tHcy or B-vitamins*	The exposure (risk factor) to be treated, elevated tHcy or sub-optimal B vitamin status, should be present at baseline so that treatment benefit may occur
Outcome measurement	Sensitive tests must be used for measuring the outcome of the trial such as individual cognitive domains, brain volumes by MRI
Absence of dementia at baseline	Participants should not be demented, but should be at risk of cognitive decline or dementia
Duration	Should be sufficient to measure a clinically relevant change in the placebo group, e.g., cognitive decline, loss of brain volume; probably at least 12–24 months, or longer if conversion to dementia is the endpoint
Vitamin dose and combinations	Simple dietary modification is inadequate; a combination of pharmacological doses (especially of B_{12}) of B vitamins is needed, sufficient to lower tHcy in the majority of participants
Sensitivity analysis	The protocol should pre-specify analysis according to baseline concentrations of tHcy and/or of B vitamins
Subgroup analyses	The protocol should pre-specify data analysis according to factors that may interact with the effect of B vitamin treatment, e.g., omega-3 fatty acids, other dementia risk factors and anti-platelet drug use

*In this table, the term 'B vitamins' means those that are directly required for homocysteine metabolism, i.e., folate, vitamin B_{12}, vitamin B_6. Vitamin B_2 may also influence homocysteine indirectly via its role as cofactor for MTHFR.

to learning effect). Folic acid treatment slowed the decline in information processing and the effect was greater in those participants with baseline tHcy above the median. The folic acid group showed a larger improvement in memory scores than the placebo group and also showed an improvement in a composite global cognitive function score. The authors estimated that folic acid treatment gave an individual a performance of someone 4.7 years younger for memory, 1.7 years younger for sensorimotor speed, 2.1 years younger for information processing speed, and 1.5 years younger for global cognitive function. These results show that lowering tHcy can slow some of the cognitive changes that occur in natural aging.

Alzheimer disease cooperative study trial [38]

This trial in the USA included 340 participants with a diagnosis of probable AD. Active treatment was daily 5 mg folic acid, 1 mg B12, and 25 mg B6 for 18 months, which lowered tHcy by 26% (from 9.2 to 6.78 μmol/L). There was no significant difference between the placebo and active treatment groups in several cognitive and clinical measures in the whole cohort, but a subgroup analysis showed an interaction between baseline Mini-Mental State Examination (MMSE) score and B vitamin treatment effect so that patients with a higher MMSE at baseline showed significant benefit from B vitamins. A similar effect was seen when patients with a baseline Clinical Dementia Rating (CDR) score of 0.5 were studied: B vitamin treatment slowed the rate of decline in MMSE over the 18 month period of the trial (see Fig. 7 in the review by Smith & Refsum [8]). These results suggest that B vitamin treatment may be effective in patients with mild AD but not in those in whom the disease has progressed to the moderate stage.

VITACOG Trial (reviewed [8, 9])

The '*Homocysteine and B Vitamins in Cognitive Impairment*' trial was designed to see whether lowering tHcy by daily treatment with B vitamins (0.8 mg folic acid, 0.5 mg B12, 20 mg B6) for 2 years would slow the accelerated rate of whole brain atrophy in people with MCI. Secondary outcomes were cognitive and clinical changes. In the 168 participants who underwent MRI scans, B vitamin treatment lowered tHcy by 30.2% and slowed the rate of brain atrophy by 29.6% compared with the placebo group. The effect of B vitamin treatment on brain atrophy was markedly influenced by the baseline tHcy concentration: Participants in the top quartile (>13 μmol/L tHcy) showed a 53% slowing of brain atrophy rate. A strong effect of baseline tHcy was also found for cognitive and clinical assessments: Only those with tHcy above the median (11.3 μmol/L) showed significant cognitive decline in the placebo group. B vitamin treatment slowed, or prevented, cognitive decline in those with tHcy above the median for episodic memory, semantic memory and global cognition (MMSE). B vitamin treatment also had a beneficial effect on two clinical measures (CDR and IQCODE) but only in partici-

pants with tHcy > 13 μmol/L. Further voxel-based analysis of the scan data from VITACOG showed that B vitamin treatment markedly slowed, by 88.5%, the rate of atrophy of those brain regions that are most severely affected in AD. Bayesian directed acyclic graph analysis demonstrated the following causal pathway:

B vitamins (mainly B12) ⟶ lower tHcy ⟶ slow brain atrophy ⟶ slow cognitive decline

These results are consistent with the view that lowering tHcy in those with MCI who have raised tHcy slows down progression of the disease [9].

It should be noted that a *post-hoc* analysis of blood samples from participants in the VITACOG trial showed that it was only those with a good omega-3 fatty acid status at baseline who benefitted from B vitamin treatment with a slowing of brain atrophy and of cognitive and clinical decline [39, 40]. This result suggests that in future trials of B vitamins, it will be important to maintain a good omega-3 fatty acid status in the participants, or to administer a combination of B vitamins and omega-3 fatty acids. The VITACOG trial also confirmed findings from the cardiovascular trials, i.e., that use of antiplatelet drugs may interact with the B vitamin treatment, with beneficial effects limited to those not taking the drugs. Interesting, in VITACOG, use of NSAIDs did not have the same effect as aspirin.

Overall, we conclude from this summary of the last of Hill's criteria that there is a great deal of 'experimental evidence' consistent with a causal role of raised tHcy in cognitive impairment. The many trials that have reported no effect of B vitamins have all suffered from flawed design, i.e., that the subjects were unlikely to respond, or that cognitive decline was not demonstrated in the placebo group.

CONCLUSIONS AND FUTURE DIRECTIONS

We conclude, from the analysis of published findings according to the principals proposed by Bradford Hill, that raised tHcy is a strong and modifiable risk factor for cognitive impairment and dementia.

Some potential public health implications follow from this conclusion. Screening for raised tHcy should be carried out in memory clinics and those with raised tHcy should be offered supplementary B vitamins. Such a procedure already occurs in Sweden [41]. Furthermore, a modelling study suggests that this policy would be highly cost-effective in the UK [42]. It will be important to identify a threshold tHcy concentration above which clinical actions are taken. In the latter modelling study, a value of > 13 μmol/L was used. This is the same cut-off value used for recruitment into the FACIT trial and the concentration at which B vitamin treatment in the VITACOG trial had clinical benefits; it thus has a sound basis. On the other hand, cognitive benefits were demonstrated in VITACOG at levels in the range 11–13 μmol/L and > 11 μmol/L was the cut-off at which significant atrophy of the medial temporal lobe was detected in the original OPTIMA study. Furthermore, a concentration of 11 μmol/L was the threshold for the association of tHcy with impaired spatial copying in the Normative Aging Study [22] and in an epidemiological study from Scotland, the incidence of dementia already increased at a tHcy level of 10.8 μmol/L [43]. Should these latter findings be confirmed, then a threshold of between 10 and 11 μmol/L may be more appropriate. Threshold concentrations of 10 to 13 μmol/L would be well within the normal range for tHcy found in the elderly [3].

There is clearly an urgent need for a large intervention trial in accordance with the criteria shown in Table 2 to see whether further cognitive decline or conversion to dementia is slowed or prevented in those with MCI who are given supplementary B vitamins (ideally together with omega-3 fatty acids). The results we have summarized suggest to us that such a trial would probably succeed if, but only if, the target group is likely to respond, i.e., have initial high tHcy and/or poor status of B vitamins involved in homocysteine metabolism, and if the trial has sufficient duration for those in the placebo group to show further cognitive decline or dementia. If further large, well-designed trials confirm that lowering tHcy slows the development of dementia, then screening of tHcy should be expanded to include all people over 65 years, i.e., the age that the rate of cognitive decline in the population starts to accelerate.

DISCLOSURE STATEMENT

Authors' disclosures available online (https://www.j-alz.com/manuscript-disclosures/17-1042r2).

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