Midlife homocysteine and late-life dementia in women. A prospective population study

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Abstract

Elevated serum total homocysteine (tHcy) is an established risk factor for cardiovascular disease. Its role in dementia is still controversial, and no study has examined the role of midlife tHcy, or reports longer than 8 years of follow-up. We examined the relation between midlife tHcy and late-life dementia in women followed for 35 years.

The Prospective Population Study of Women in Gothenburg began in 1968–1969, comprising a representative population of women aged 38–60 years. Four extensive follow-ups were conducted by 2003. Serum samples from 1968 to 1969 were analysed for tHcy in 1368 women. In total, 151 women developed dementia. The highest tHcy tertile was related to a hazard ratio of 1.7 (95% CI 1.1–2.6) for developing any dementia, 2.1 (95% CI 1.2–3.7, $n = 100$) for AD and 2.4 (95% CI 1.3–4.7, $n = 68$) for AD without cerebrovascular disease. Kaplan–Meier plots showed divergence with respect to dementia after 22 years of follow-up. In conclusion, high homocysteine in midlife is an independent risk factor for the development of late-life Alzheimer dementia in women.
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1. Introduction

The number of people with dementia is increasing dramatically with global aging (Ferri et al., 2005). Vascular risk factors and disorders have been associated with the development of Alzheimer's disease (AD) (Mielke et al., 2007), a neurodegenerative disease and the most common form of dementia. The second most common form of dementia, vascular dementia, is caused by cerebrovascular disease (CeVD) (Vicenzini et al., 2007), and is thus also associated with vascular risk factors. Hyperhomocysteinemia is a recognized risk factor for vascular disorders, such as myocardial infarction (Zylberstein et al., 2004), and stroke (Srikanth et al., 2006), and recently lacunar infarcts (Zylberstein et al., 2008). A relation between homocysteine (Hcy) and dementia has therefore been hypothesised (Hogervorst et al., 2002).

The literature on Hcy and dementia is mixed. Four prospective studies conducted in elderly populations and with follow-ups ranging from 4 to 8 years have reported associations between high tHcy (total Hcy) and AD (Haan et al., 2007; McCaddon et al., 1998; Ravaglia et al., 2005; Seshadri et al., 2002), while others did not find an association (Luchsinger et al., 2004). Further support for an association between tHcy and dementia comes from studies showing associations between high tHcy and lower cognitive function among non-demented individuals as well as with increased conversion rate from mild cognitive impairment to AD (Blasko et al., 2008). Hcy has also been suggested to be directly associated with the pathogenesis of AD (Hogervorst

et al., 2002). A recently published meta-analysis has confirmed the role of homocysteine as a risk factor for CVD (Humphrey et al., 2008). However, the role of tHcy in middle age for AD in late life has not been examined. Thus it is has not been easy to elucidate whether the association between homocysteine and dementia is a manifestation of early disease or a causal risk factor. The purpose of the present paper was to assess whether tHcy in blood samples drawn in 1968/1969 is associated to the development of dementia in a representative sample of 38–60 year old women who were followed 35 years.

2. Methods

2.1. Subjects

The study is part of the Prospective Population Study of Women in Gothenburg (Bengtsson et al., 1973; Lissner et al., 2003) which was initiated in 1968. Women born in 1908, 1914, 1918, 1922 and 1930 were systematically sampled from the census register based on specific birth dates in order to yield a representative sample at the ages studied. Among those sampled, 1462 women were examined (participation rate 90%). Baseline tHcy data are available for 1368 of those examined in 1968. The baseline examination included blood pressure in the sitting position, anthropometric measurements e.g. body mass index (BMI), 24-h dietary recall and questions on medical history and risk factors, e.g. smoking, conducted by a physician, as described previously (Bengtsson et al., 1973). Follow-ups were performed in 1974–1975, 1980–1981, 1992–1993 and 2000–2003, with participation rates (among survivors from baseline study at each examination) of 91%, 83%, 70% and 71%, respectively (Lissner et al., 2003). Psychiatric examinations were performed at every stage of the study. Dates of death were obtained from the Swedish Population Register. The Ethics Committee of Gothenburg University approved the study. All subjects gave informed consent to participate, in accordance with the provisions of the Helsinki Declaration.

2.2. Blood samples

The original survey (Bengtsson et al., 1973) included fasting blood sampling aimed both for immediate and future analyses. Approximately 120 ml blood was drawn from each study subject. A small part of the blood at the baseline examination was used for the initial analyses and the rest was allowed to clot in room temperature for 2–3 h. After centrifugation the serum was stored at $-20\,^{\circ}C$ in 2.5 ml covered polystyrene cups enclosed together in small batches, in firmly tied plastic bags. The original frozen samples in the present study were stored for 28 years at $-20\,^{\circ}C$, thawed once for other analyses and restored for 2 years at $-80\,^{\circ}C$. Stability of tHcy in long time stored samples has been previously reported by other investigators (Israelsson et al., 1993).

Total tHcy was determined in all the original serum samples by the Abbott IMX homocysteine assay (Abbot Laboratories, Abbot Park, IL, USA). We have reported close agreement between previously thawed vs. non-thawed samples regarding tHcy (Zylberstein et al., 2004). S-creatinine, s-triglycerides, s-cholesterol and vitamin B12 were among the blood tests originally performed at the baseline examination in 1968–1969.

2.3. Diagnoses of dementia

2.3.1. Psychiatric and medical examinations

Neuropsychiatric examinations were performed in 1968–1969, 1974–1975, 1980–1981 and 1992–1993 by psychiatrists, and in 2000–2003 by experienced psychiatric nurses. All examinations were semi-structured, thus allowing for clarifying questions, and included a comprehensive psychiatric interview and observation of mental symptoms during the interview. More detailed assessments of cognitive symptoms were included at the examinations in 1992–1993 and 2000–2003, as the population reached ages when dementia is common. These examinations used identical instruments and included ratings of common signs and symptoms of dementia, e.g. assessments of memory, orientation, general knowledge, apraxia, visuospatial function, understanding proverbs, following commands, naming ability and language. The neuropsychiatric batteries used in the examinations included the Comprehensive Psychopathological Rating Scale (Åsberg et al., 1978), Gottfries–Bråne–Steen Scale (Gottfries et al., 1982), the Mini Mental State Examination (Folstein et al., 1975), the Alzheimer's Disease Assessment Scale (ADAS-Cog) (Rosen et al., 1984), and the Clinical Dementia Rating (CDR) (Hughes et al., 1982).

The nurses who performed the examinations in 2000–2003 were supervised and trained by psychiatrists who were involved in the examinations in 1992–1993. In training sessions, nurses and psychiatrists rated symptoms and signed both on demented and non-demented persons. Inter-rater reliability between examiners was studied in 50 individuals. Kappa estimates for the presence vs. absence of signs and symptoms used in the dementia diagnoses (e.g. memory, language, visuospatial ability, apraxia) were between 0.74 and 1.00.

Close informant interviews were performed by psychiatrists and psychiatric research nurses in 1992–1993 and 2000–2003. The interviews were semi-structured and comprised questions about changes in behaviour and intellectual function, psychiatric symptoms, activities of daily living, and, when relevant, age of dementia onset and disease course, as well as the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) (Jorm and Korten, 1988). The interviews have been described in detail previously (Skoog et al., 1993).

Medical records on all women were collected from all inpatient and outpatient departments and general practitioners' offices in Gothenburg. *The Swedish Hospital Discharge*

Table 1
Baseline characteristics in 1968/69 of 1368 women born 1908, 1914, 1918, 1922 and 1930 and followed for 35 years.

	Total	Without dementia (n = 1217)	With dementia (n = 151[a])
Systolic BP mmHg mean (±SD)	135.5(22.7)	135.3(23.0)	137.4(19.6)
Diastolic BP mmHg mean (±SD)	84.9(11.4)	84.9(11.5)	85.5(10.7)
BMI mean (±SD)	24.0(3.8)	24.0(3.0)	24.5(3.7)
Cholesterol mmol l mean (±SD)	6.8 (1.1)	6.8(1.1)	7.1(1.0)
Triglycerides mmol l mean (±SD)	1.22(0.55)	1.22(0.56)	1.26(0.53)
B12 pmol l mean (±SD)	396.9(138.4)	396.5(137.9)	401.6(144.9)
Dietary folate μg-day mean (±SD)	170.2(90.2)	170.9(91.3)	161.5(74.8)
Creatinine μmol l mean (±SD)	76.7(22.7)	76.6(23.4)	78.7(11.3)
Smokers (%)	40	40	35
Education above mandatory (%)	30	31	26
Minimal physical activity (%)	18	18	19
Mean age in 1968/69 (years)	46.8	46.5	50.0
Mean tHcy 1968/69 μmol/l (+SD)	11.8(4.6)	11.8(4.6)	12.1(4.0)

[a] All dementia types.

Registry provided information on diagnoses of all individuals discharged from hospitals on a nationwide basis since 1978.

2.3.2. Diagnostic criteria

Final dementia diagnoses were made by geriatric psychiatrists based on the symptoms rated by the examiners during the neuropsychiatric examinations and close informant interviews, as described in detail elsewhere (Skoog et al., 1993). Diagnoses were made according to the Diagnostic and Statistical Manual of Mental Disorders (third edition, revised) (DSM-III-R) criteria (APA, 1987). Altogether 113 cases of dementia were diagnosed among participants in the examinations.

Dementia diagnoses for individuals lost to follow-up were based on information from medical records evaluated by geriatric psychiatrists in consensus conferences, and the Swedish Hospital Discharge Registry. The diagnoses had to be compatible with DSM-III-R criteria. This procedure yielded another 38 dementia cases (6 from medical records, 10 from the Hospital Discharge Register, 22 from both medical records and hospital discharge register). Among those diagnosed with dementia from the examinations, 45 (40%) were also detected by medical records and–or hospital discharge registry.

Subtypes of dementia were also diagnosed by geriatric psychiatrists. AD (probable or possible) was diagnosed according to the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA, 1985). The criteria for vascular dementia (VaD) were similar to the criteria proposed by the National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherce et l'Enseignement en Neurosciences (NINDS-AIREN) (Roman et al., 1993). Pure VaD was diagnosed when there was a temporal relationship (within 1 year) between a history of acute focal neurological symptoms and signs (hemiparesis or motor aphasia) and the first symptoms of dementia. Due to the difficulties to diagnose dementia subtypes because of the controversy regarding

the relative importance of cerebrovascular disease (CeVD), we explored various ways of defining dementia subtypes. The AD group was divided into AD with or without CeVD. We also created a group 'dementia with CeVD' which included individuals with dementia and stroke without considering the temporal relationship between the occurrence of dementia and stroke. Practically, this group includes pure VaD and AD with CeVD. Other dementias were diagnosed when other causes were likely to have caused the dementia.

2.4. Statistical methods

Cox regression models were used to study tHcy and relevant baseline covariates in 1968–1969 in relation to the incidence of dementia from 1968 to 2003. The hazard ratios (HR) are given for each tertile of tHcy, where the lowest tertile is the reference representing HR = 1. The hazard ratios were also calculated with tHcy as a continuous variable (per μmol/l). The basic model included age only. The full models were adjusted for age, education, BMI, cholesterol, triglycerides, systolic and diastolic blood pressure, smoking, creatinine and vitamin B12. Additional controlling for dietary folate and physical activity (not shown) did not modify the results, and were not included in the model.

For non-demented women, person-years at risk were calculated from the date of the baseline examination to (a) the date of the last follow-up examination for participants in 2000–2003; (b) the date of death for those who died during follow-up; or (c) December 31, 2003 for surviving dropouts. For women who developed dementia, person-years at risk were calculated from the date of the baseline examination to the estimated date of dementia onset. Information on dementia onset was obtained only from the close informant interview in 50 (33%) cases, only from medical records and–or hospital registry in 44 (29%) cases, and from both informant interview and medical records and–or hospital registry in 39 (26%) cases. For cases lacking information on dementia onset from these sources (n = 18), the date of dementia onset was estimated as the midpoint between the

Table 2
Hazard ratios (HR, 95% confidence intervals) for all dementia and for the subgroups.

	First tertile (range 3.1–9.8)	Second tertile (range 9.8–12.6)	Third tertile (range 12.6–78.9)
All dementia $n = 151$ mean tHcy 12.1 μmol/l (4.0)			
Adjusted for age only	1	1.70(0.77–1.78)	1.38(0.92–1.78)
Fully adjusted	1	1.30(0.84–2.0)	1.67(1.10–2.57)
All AD $n = 100$, mean tHcy 12.8 μmol/l (4.2)			
Adjusted for age only	1	1.47(0.85–2.56)	1.86(1.10–3.18)
Fully adjusted	1	1.59(0.91–2.79)	2.13(1.22–3.73)
AD without CeVD $n = 68$, mean tHcy 12.5 μmol/l (3.9)			
Adjusted for age only	1	1.40(0.72–2.74)	1.94(1.02–3.67)
Fully adjusted	1	1.54(0.78–3.05)	2.43(1.25–4.71)
AD with CeVD $n = 32$, mean tHcy 13.3 μmol/l (4.9)			
Adjusted for age only	1	1.72(0.65–6.61)	2.0(0.76–5.30)
Fully adjusted	1	1.56(0.57–4.26)	1.70(0.61–4.73)
VaD $n = 37$, mean tHcy 10.3 μmol/l (3.0)			
Adjusted for age only	1	0.75(0.36–1.71)	0.51(0.22–1.20)
Fully adjusted	1	0.76(0.35–1.64)	0.70(0.28–1.72)
Dementia with CeVD $n = 69$, mean tHcy 11.7 μmol/l (4.3)			
Adjusted for age only	1	1.01(0.57–2.54)	0.95(0.52–1.72)
Fully adjusted	1	0.99(0.55–1.80)	1.04(0.55–1.98)

Cox regression analyses. Fully adjusted model included creatinine, vitamin B12, education, and risk factors. First tertile is the reference with the hazard ratio set, per default, to 1. AD, Alzheimer's disease; CeVD, cerebrovascular disease; VaD, vascular dementia; tHcy, total homocysteine.

examination when dementia was first diagnosed and the previous examination.

The statistical software used was SAS version 8.02.

3. Results

The baseline characteristics of the sample in 1968 stratified by later development of dementia are shown in Table 1. In total, 151 individuals developed dementia, 100 any AD (68 pure AD, i.e. without known cerebrovascular disease (CeVD), and 32 AD with CeVD), 37 pure VaD, and 14 other types of dementia. None of the variables differ significantly between the stratified groups.

The hazard ratios for dementia and its subtypes in relation to tHcy in 1968 are shown in Table 2. The results are adjusted for age only and fully adjusted. Belonging to the highest tertile of tHcy in 1968 (compared to the lowest tertile) was associated with an increased risk for developing any dementia (HR = 1.67 (95% CI 1.10–2.57)), AD (HR = 2.13 (95% CI 1.22–3.73)) and AD without cerebrovascular disease (HR = 2.43 (95% CI 1.25–4.71)) in fully adjusted model. None of the covariates except age and Hcy was associated with dementia either analysed alone or in the full model.

The cumulative risk for dementia development is shown in Fig. 1.

The clear separation of strata arms cannot be observed until after approximately 22 years of follow-up. Additional analyses of the data including only those who developed dementia after 1992 ($N = 110$, 74 AD), showed similar point estimates for the associations between tHcy in 1968 and total dementia and AD, but the confidence intervals widened due
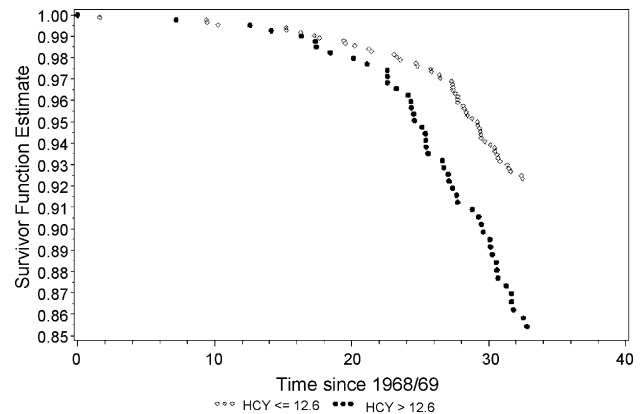

Fig. 1. Survival function estimate for Alzheimer's disease with CeVD (37 cases of vascular dementia and 14 cases of other type excluded) as a function of years since baseline examination, stratified according to the tertiles of homocysteine: open diamonds correspond to the two lowest tertiles pooled (homocysteine ≤ 12.6 μmol/l, 54 events, 876 individuals at risk) and filled dots give the result for the highest tertile (>12.6 μmol/l, 46 events, 441 individuals at risk).

to fewer demented cases (HR, fully adjusted, for all dementia 1.84 (95% CI 1.1–3.1) and for AD 2.3 (95% CI 1.2–4.5)).

4. Discussion

To the best of our knowledge, this is the first study to examine the association between tHcy in midlife and development of dementia in late life. We found that elevated tHcy levels in middle aged women followed for 35 years were related to an increased risk of dementia and AD in late life. The results

were consistent irrespective of whether analysing tertiles of tHcy or tHcy as a continuous variable, and the results were not attenuated by inclusion in the models of covariates otherwise associated with CeVD. Our findings are in line with those from four prospective studies (Haan et al., 2007; McCaddon et al., 1998; Ravaglia et al., 2005; Seshadri et al., 2002) showing that elevated tHcy is related to AD, and at odds with one which did not find associations between tHcy and dementia development (Luchsinger et al., 2004). Previous studies measured tHcy in populations with mean ages above 70 years, and had follow-ups of 4–8 years, while our study measured tHcy in midlife (mean age 47 years) and had a 35-year follow-up. In our study, the obvious separation of strata arms occurred after 22 years of follow-up, in parallel with our previous paper on Hcy and cardiovascular endpoints in the same population (Zylberstein et al., 2004). This probably reflects the age of our population at baseline in contrast to almost immediate separation of the strata arms in the Framingham study where individuals had a mean age of 76 years. Furthermore, in the present study higher tHcy remained a risk factor when only cases with onset at least 24 years after the blood sampling were included. It is remarkable that one measure of tHcy in blood sampled in 1968 is related to the development of dementia more than three decades later. In future studies, it would be preferable to have serial measurements of tHcy, to elucidate whether higher tHcy was a life-long trait in these women. To our knowledge there is no longitudinal study of tHcy levels over several decades. The question of whether midlife tHcy is more important for dementia than late-life tHcy cannot be answered with our data. However it might be a plausible assumption that individuals have similar ranking over decades, even if the population distribution shifts.

High tHcy has repeatedly been associated with increased risk for cerebrovascular disease and its pathogenic mechanisms (Hogervorst et al., 2002; Sachdev, 2004), and would therefore be expected to be associated with VaD, a hypothesis that we could not confirm. A similar pattern of associations between lower midlife respiratory function and dementia has previously been reported in this population (Guo et al., 2007). One reason for the lack of association with VaD may be selective survival. We have previously reported that tHcy is related to increased total morbidity and mortality from cardiovascular disease in this cohort. It may also be mentioned that 47% of subjects with lacunar infarcts in 1992–1993 (Zylberstein et al., 2008) were still alive 2000 as compared to 67% of the subjects without. Moreover, homocysteine is strongly associated with all cause mortality in our cohort. Thus women with high tHcy have an increased risk of dying before reaching older ages when dementia is likely to occur. Earlier mortality due to cardiovascular disease in individuals at risk of developing VaD may underestimate the relationship between tHcy and VaD during long follow-up.

It is also possible that higher tHcy is a predictor or marker for late-life dementia rather than a causal factor. Total homocysteine is related to present and past general health (Ueland and Refsum, 1989). Besides cardiovascular disorders, tHcy

is associated with socioeconomic status, nutritional status, and lifestyle factors such as smoking and physical activity (Dankner et al., 2004). However, our findings remained after adjustment for numerous baseline covariates, and remained also when only those who developed dementia after more than 24 years follow-up were included.

The results in the present study are mainly driven by AD. There are several possible explanations for this observation. As already mentioned, tHcy is associated with cardiovascular disorders and risk factors which have also been associated with AD (Mielke et al., 2007). Homocysteine may also be directly associated with pathogenic mechanisms of AD, such as stimulation of beta-amyloid production (Ho et al., 2001), downregulation of cholinesterases (Darvesh et al., 2007), activation of glutamate receptors (Boldyrev and Johnson, 2007), induction of tau phosphorylation (Mondragon-Rodriguez et al., 2008), upregulation of presenilin 1, BACE and amyloid-beta (Fuso et al., 2005), and oxidative stress (Ho et al., 2001).

The strengths of this study include a population based sample, which was representative for the female population in Gothenburg, the long follow-up with baseline measurement in midlife, above average participation rate as compared to similar studies, continuous monitoring of dementia incidence using multiple information sources, allowing for the diagnosis of dementia even in those lost to follow-up, and access to tHcy in samples obtained already in 1968, i.e. many years before the women were likely to be demented.

However, some methodological issues need to be considered. First, cumulative attrition is a problem in long-term follow-up studies. While this problem was, to some extent, alleviated by using medical records and the hospital registry data to diagnose dementia in those lost to follow-up, these sources probably underestimate the number of dementia cases. In fact, only 44% of those diagnosed in the examinations were also detected by medical records in our study (Guo et al., 2007). It should be noted, however, that almost all people in Sweden receive their hospital treatment within the public health system, and that the Swedish Hospital Discharge Register thus covers almost all hospitalizations in the entire country. Furthermore, the incidence of dementia in the present study is in agreement with other studies (Fratiglioni et al., 2000; Zhu et al., 2000) and the number of cases detected in the different age groups is what could be expected based on other incidence studies. Second, it is difficult to diagnose dementia subtypes on clinical grounds alone. Individuals with AD often have CeVD and individuals with VaD often have concomitant AD pathology; and CeVD may influence the presence and severity of clinical symptoms of AD (Mielke et al., 2007). It is thus often difficult to make a clear distinction between AD and VaD in patients with a history of stroke or CeVD, both on clinical grounds and at autopsy. As it is difficult to evaluate the relative importance of CeVD, we explored various ways of defining dementia subtypes (e.g. 'AD with and without CeVD', 'dementia with CeVD') and their relation to tHcy in 1968. Third, only women

were enrolled in this study, we can thus not comment on the relevance of these findings in men. The Framingham Study did not analyse men and women separately, however, including sex as a covariate did not attenuate their results. Fourth, the semi-structured examinations were performed by experienced psychiatrists in 1968–1969, 1974–1975, 1980–1981 and 1992–1993, and by experienced psychiatric nurses in 2000–2003. The instruments used were identical across examinations, and inter-rater reliability between psychiatrists and nurses regarding the symptoms assessed was satisfactory. It is therefore not likely that the use of different assessors could have influenced the main results of this study. Finally, serum samples were analysed for tHcy after 32 years of storage. Others have reported that long-term storage do not affect the reliability of the tHcy analyses (Israelsson et al., 1993).

Although our previous findings and those in this study suggest that high homocystein is a risk factor for cardiovascular disease and dementia, several recent trials do not support that Hcy lowering improve cardiovascular health and cognitive function (Bonaa et al., 2006; Ebbing et al., 2008; Lonn et al., 2006; McMahon et al., 2006). However, one of these studies (HOPE-2) demonstrated an effect for stroke in a sub analysis, and several others report protective effects against varying aspects of CVD with Hcy lowering therapy (Mashavi et al., 2008; Righetti et al., 2006; Björkegren and Svärdsudd, 2004). There may be several reasons for negative effects of Hcy lowering in trials. First, the present study, as well as our previous report (Zylberstein et al., 2004) show that strata arms separate after many years. Therefore, the trials performed so far might have had too short follow-up. Second, several studies started when participants already had vascular disease or cognitive impairment. It might then be too late to expect an effect of Hcy lowering. Third, there is an issue of a dosage of vitamins, and there may be interactions between the vitamins used, making it necessary to carefully consider proportions between the vitamins (Wang et al., 2006). Fourth, the risk for CVD is not linear in respect to tHcy concentrations. There seems to be a threshold in tHcy above which the vascular events are more likely to occur. We found such a threshold for dementia at $12.6\,\mu\text{mol/l}$ and for myocardial infarction at $14.2\,\mu\text{mol/l}$ (Zylberstein et al., 2004). Therefore, studies with low mean tHcy level at baseline might fail to show the effect of Hcy lowering. Finally, it has been suggested that folic acid treatment and not Hcy lowering is responsible for positive outcomes in intervention studies (Campbell et al., 2005). However, we did not find an interaction between tHcy and folate for the outcome of dementia in our study.

In conclusion, we found that higher tHcy in midlife is related to increased risk of AD in old age. We have previously found that high midlife tHcy is related to increased risk of cardiovascular disease (Zylberstein et al., 2004) and lacunar infarcts (Zylberstein et al., 2008). This emphasizes the potential importance of detecting high tHcy in middle aged women, as homocysteine lowering treatment, if shown promising in ongoing and future studies, is safe and not costly.

Conflict of interest statement

Acknowledgements

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