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Homocysteine and Cognition:

A Systematic Review of 111 studies.

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HIGHLIGHTS

- There is a positive trend between cognitive decline and increased Hcy plasma concentrations.
- Vitamin supplementation fails to reduce the cognitive impairments once they appear.
- Earlier detection of elevated Hcy levels may prevent cognitive impairment and dementia.

ABSTRACT

Background: Elevated plasma homocysteine (Hcy) levels have been associated with cognitive dysfunction in a wide range of conditions. The aim of this review is to establish which cognitive domains and populations are the most affected.

Methods: We systematically review the literature and consider all articles that showed any relationship between plasma Hcy levels and scores achieved on cognitive performance tests in both, the general population and patients suffering from central nervous system disorders and other diseases. When effect sizes were available and combinable, several meta-analyses were performed.

Results: We found 111 pertinent articles. There were 24 cohort studies, 18 randomized trials, 21 case-control studies, and 48 cross-sectional studies. This review reveals a positive trend between cognitive decline and increased plasma Hcy concentrations in general population and in patients with cognitive impairments. Results from the meta-analyses also confirm this trend. Treatment with vitamin supplementation fails to show a reduction in cognitive decline.

Discussion: Further investigations are warranted to clarify this relationship. Earlier detection of the elevated Hcy levels may be an effective intervention to prevent cognitive impairment and dementia.

Keywords: Plasma Hcy, Hyperhomocisteinemia, Cognition, Cognitive Impairment, Cognitive Domains.

1. INTRODUCTION

Homocysteine (Hcy) is a non-protein, neurotoxic, sulfur-containing amino acid that originates from methionine metabolism. Methionine is an amino acid precursor of peptides and proteins that plays an important role in the metabolism and transfer of methyl groups (1, 2). There is a close relationship between plasma Hcy and folate, B6 and B12 vitamin levels, which act as coenzymes of methionine and Hcy metabolism. Deficiencies in folate, and B6 and B12 are potential factors that contribute to increase the plasma concentrations of Hcy (3).

The reference values for plasma Hcy range from 5 to 15 µmol/L (4). Hyperhomocysteinemia (HHcy) occurs at concentrations over 15 µmol/L in fasting serum. Moreover, HHcy has been classified as moderate (plasma total Hcy concentrations of 15-30 µmol/L), intermediate (plasma total Hcy concentrations of 31-100 µmol/L), or severe (plasma total Hcy concentrations 100 µmol/L) (5).

The total concentration of Hcy in plasma is the result of a complex interaction between multiple genetic and environmental factors. Physiological determinants, such as age, gender, ethnicity, menopause and pregnancy, are also involved. Thus, Hcy levels show a progressive increase with age. Moreover, higher total Hcy levels have been found in males and postmenopausal women. Additionally, the plasma Hcy levels are generally lower in the black and Asian population (6). Some genetic factors that predispose an individual to HHcy are

mutations in methionine synthase, cystathionine b synthase (CBS) and variants of the methylene tetrahydrofolate reductase (MTHFR) gene (7). Lifestyle determinants, such as smoking, alcohol and coffee consumption, and a lack of physical exercise or poor nutrition, may also contribute to the Hcy plasma levels (8, 9). Finally, it is worth knowing that some other variability sources differents than the indivudual facors, such as determinants related to sample collection and storage, may also alter the Hcy measurements (10).

There is growing evidence that higher Hcy levels are involved in age-related cognitive deficits and various types of central nervous system (CNS) disorders (11), including Alzheimer´s disease (AD) (12), Parkinson disease (PD) (13), multiple sclerosis (MS) (14), cerebrovascular diseases and strokes (15). The relationship between HHcy and age-related neurodegeneration has also been highlighted (16). Furthermore, elevated Hcy levels may influence the cognitive impairment that is commonly observed among patients with psychiatric disorders (17), such as affective disorders (18) or schizophrenia (SCZ) (19). In most of these cases, the associations remain strong, even after adjusting for vitamin status or renal function.

The CNS disorders related to HHcy may be explained by three possible mechanisms (20, 21). First, by promoting oxidative stress, Hcy may produce direct neurotoxicity, alter neurotransmission and induce neuronal excitotoxicity, apoptosis, β- amyloid accumulation and hyperactivation of the NMDA receptors (22, 23). Second, it has also been noted that a metabolic disruption in Hcy and the one-carbon metabolism may alter neurotransmitter synthesis. Finally, the association of homocysteinemia with occlusive vascular disease may be mediated through damage to the blood vessel wall or impaired blood coagulation.

By combining these results with the hypothesis that HHcy is a modifiable risk factor for cognitive dysfunctions, the aim of the present review is to identify which cognitive domains, if any, and populations are related to the increased Hcy levels in plasma.

2. MATERIALS AND METHODS

2.1. Comprehensive search of the literature

A systematic review of the literature was conducted through an electronic search of scientific journals in English and Spanish from the Medline database, via PubMed and Embase. The following key terms were used for the search: "homocysteine" and "cognition". We found 474 articles, and 373 articles were published between January 2005 and the end of December 2015. In addition, the references from these articles that met the established inclusion criteria were also included.

2.2. Eligibility and study selection

The full text of each potentially eligible article was read by two researchers (one medical doctor and one psychologist) before a final decision was reached about its inclusion in the present review. For inclusion, we considered all of the original articles that addressed the influence of the plasma Hcy levels on cognitive functions in healthy subjects and patients suffering for any disease or condition. The studies could report their results quantitatively or qualitatively. Non-original articles, such as reviews, meta-analyses, case series, letters to the editor, comments and case reports, were also excluded. We also rejected those studies where Hcy levels were measured in different fluids, such as cerebrospinal fluid. Finally, animal research articles were not included, as our purpose was to identify a relationship between HHcy and the cognitive domains in humans. Disagreements were resolved by consensus.

2.3. Data extraction

Data extraction was classified according the design of the selected studies. The articles were divided into four blocks based on their design: case-control studies, cohort studies, randomized clinical trials (RCTs) and cross sectional studies. A database was created and the common variables of each article were extracted: sample size (N) of the reference population in the study, Hcy levels in plasma, and the neurocognitive tests used to measure the cognitive functions and their scores, when available, among others. The time of follow-up was also

specified for the cohort study block. For the randomized controlled trials, the treatment received in each branch was also noted.

2.4. Data analysis

In regard to the qualitative approach, the studies were compared and grouped into categories regarding each clinical condition: Alzheimer's and other cognitive impairments, Parkinson´s disease, schizophrenia, bipolar disorder, geriatric depression, eating disorders, cardiovascular diseases, cerebrovascular diseases, multiple sclerosis, kidney diseases, other diseases (epilepsy, comorbidies in geriatric population, obstructive apnea sleep syndrome and multiple system atrophy), and the general population.

A quantitative approach was performed when average effect sizes and their corresponding standard errors were reported or could be calculated through confident intervals or *p* values. The quantitative assessments were presented as different meta-analyses for each study design (cohort, case-control, RCT and cross-sectional design), with subgroups analyses based on clinical conditions. All the analyses were performed using Stata 12 (StataCorp, College Station, Tex., USA). The calculated effect sizes (ES) were: standardized mean differences (Cohen´s *d*), for group comparisons (i.e. comparison of cognitive scores between the treatment and placebo groups, and Hcy concentration difference between cases and controls), and linear regression coefficient, to show the influence of Hcy variations in cognitive scores (i.e. cohort studies, cross sectional studies and case control studies).

Fixed and random effects were used to combine effect sizes, but only random effects are presented in the manuscript since they were deemed more suitable given the important differences between studies. This policy was followed for all the analyses despite low values of heterogeneity tests in several cases. Fixed effect results are available upon request. These results were pooled using the inverse variance method for fixed-effects analysis and

DerSimonian and Laird method for random-effects analysis (24). Overall and subgroup meta-analyses (by population) were performed when the possible.

Heterogeneity was assessed using Cochran's Q and I^2 statistics (25-27). An influence analysis was performed across individual studies by successively subtracting each study in order to know the effect size variation, considering the largest studies or studies which could contribute to the heterogeneity because of their special conditions or conducted in specific populations. Publication bias was assessed using the funnel plot method by a visual inspection (28).

3. RESULTS

Of the 373 articles that were selected based on the search criteria, 127 items were chosen as potentially relevant after reading the abstracts. Among them, seven studies were excluded because they did not identify a direct relationship between the blood Hcy levels and cognitive functions. From these 120 articles, 11 were excluded because they overlapped with other included studies in the place and time of performance (16, 29-38). Finally, two additional articles were added from the references as they met the established selection criteria (Figure I).

A total of 111 articles were included in the systematic review. Tables I to IV show the distribution of the articles according to their design: 24 cohort studies, 18 randomized double-blind trials, 21 case-control studies and 48 cross-sectional studies (Tables I-IV).

3.1. Alzheimer´s and cognitive impairment

The eight case-control studies showed significant associations between the plasma Hcy levels and cognitive functions in population with AD and/or cognitive impairment. In four studies, this association was determined using the Mini Mental State Examination (MMSE) test. Overall, an inverse correlation was found between the MMSE scores and the plasma Hcy levels in cases (39-42). Similarly, Kim and colleagues showed a significant negative relationship

between the plasma Hcy levels and the scores of the Word List Memory and Constructional Recall (WLMCR) test in the AD group, after adjusting for several covariates. However, this association did not remain significant in either the mild cognitive impairment (MCI) group or in the control group (43). Additionally, Faux and colleagues found a negative trend between the cognitive scores and plasma Hcy levels; a negative correlation between the plasma Hcy levels and different types of memory was also found (44). Irizarry and colleagues demonstrated a significant relationship between the plasma Hcy levels and cognitive function only in the group of patients with PD without dementia, while no correlations were shown in the dementia group (45). Finally, in the population over 75, Ford and colleagues observed that a two-fold increase in the plasma Hcy concentrations resulted in a 36% increase in cognitive impairment (46).

Eight case studies with cross sectional analyses of cases included people suffering from AD or cognitive impairment. Four of them, showed an inverse association between the plasma Hcy levels and the MMSE scores (47-50). Similarly, two other studies stated that high plasma Hcy levels are a risk factor for MCI (51, 52). Nevertheless, Manders and colleagues have found contradictory results in institutionalized patients, and did not find any relationship between the plasma Hcy levels and cognitive function (53). Finally, one study found several significant negative associations between the plasma Hcy levels and scores measuring the domain of visuoconstructive abilities (54).

With regard to the four selected RCTs, three found that although vitamin supplementation may reduce the plasma Hcy levels, there was no effect regarding the cognitive tests (55-57). However, De Jager and colleagues observed that executive functions benefit from vitamin supplementation compared with the placebo. There were significant differences in semantic memory and global cognitive function (MMSE) in patients with plasma Hcy levels over 13.1 μmol/liter who received supplements compared to the placebo group (58).

Five cohort studies were included in the AD and/or cognitive impairment group, and the results were disparate. Thus, Tu and colleagues found an association between the reduced Cognitive Abilities Screening Instrument (CASI) and abstract thinking scores and the Hcy levels during six months of follow-up (59), although there were no significant correlations between the cognitive scores and the Hcy levels at the baseline and at the end of the studies. Similarly, Rozzini and colleagues showed an association between HHcy and the progression of memory impairment (60). Moreover, Oulhaj and colleagues found a concentration dependent relationship between the baseline Hcy levels and the rate of decline in the patients´ Cambridge Cognition Examination (CAMCOG) scores, where the higher the Hcy levels, the faster the decline. This relationship was significant in patients aged over 75 years who had not previously suffered a stroke (12). However, in Siuda et al., 2009, there was no relationship between the Hcy levels and the evolution in cognitive functions during one-year follow-up, even though the baseline HHcy were higher in the MCI group compared to the healthy individuals (61). Reitz et al., 2009, did not find any associations between the Hcy levels and the prevalence of MCI in either the transverse or longitudinal analyses after adjusting for ethnicity and the ApoE-Ɛ4 genotype (62).

3.2. Parkinson´s disease

Regarding the five case-control studies, three did not observe significant relationships between the plasma Hcy levels and cognitive functions in cases (63-65). In contrast, Zoccolella and colleagues showed a significant association between the Hcy levels and the prevalence of dementia in PD (66). In addition, in the study by Ozer and colleagues, the group of PD patients with Hcy levels > 14 µmol/liter had a worse performance in frontal and memory tests (67).

Two studies with cross sectional analyses of cases were included. In Annanmaki et al. 2008, there was no association between the cognitive function scores and the plasma Hcy levels (68). Conversely, the study of Martin et al. 2010 showed higher Hcy levels in PD patients with

levodopa treatment and cognitive impairment compared with those levodopa treated patients without cognitive impairment (13).

Two RCTs explored the relationship between the Hcy levels and cognition in PD. Thus, Barone and colleagues showed that elevated Hcy levels were associated with greater differences in rivastigmine-treated patients than normal/low Hcy levels. The group of rivastigmine-treated PD patients presented marked or moderate improvement in their cognitive outcomes after 24 weeks of treatment compared to the placebo group, whereas no between-group differences were found in patients with low or normal Hcy levels (69). Similarly, Litvinenko and colleagues found that PD patients with dementia and higher Hcy levels who were treated with memantine had higher scores on the MMSE, Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog), clock drawing test and Frontal Assessment Battery (FAB) by the end of study at week 24, compared to PD patients with dementia without memantine treatement or PD parkinson with dementia who were treated with memantine and who had lower Hcy levels (70).

3.3. Schizophrenia

Three studies explored the relationship between the plasma Hcy levels and cognitive function in patients with SCZ. The case-control study showed that patients had a statistically significant increase in their plasma Hcy levels. In addition, patients with SCZ exhibited a significantly increase in cognitive deficits. However, no relationship between the Hcy levels and cognitive impairment was detected (71). Moreover, the cross sectional study did not find associations between the Hcy levels and cognitive test performance in patients with SCZ (72). A randomized clinical trial observed that the Hcy levels were decreased in patients with Hcy > 15 µmol/liter and vitamin therapy compared to the placebo group. The overall neuropsychological test results, and the Wisconsin Card Sort test (WCST) results in particular, were significantly improved after vitamin treatment compared to the placebo (19).

3.4. Bipolar disorder

Three articles contemplated the relationship between the Hcy levels and cognition in euthymic patients with BD. A trend between higher Hcy levels and worse cognitive functioning was noticed. A cross-sectional study in euthymic patients with BD demonstrated that male bipolar subjects showed higher average Hcy levels than a comparison group of normal subjects, and the authors also found that poorer functioning on a task of executive function (WCST) was related to higher Hcy levels (73). There were two articles with a case-control design based on euthymic patients with BD and healthy controls. In Dittman et al., 2008, the Hcy levels were significantly higher for patients than the controls. Stepwise regression analyses revealed a significant and independent association of the Hcy levels with verbal learning, delayed memory and executive function in the patient group (18). On the other hand, Dias and colleagues showed that the Hcy levels for the euthymic patients and healthy controls were similar. Patients with higher Hcy levels performed significantly worse on all neurocognitive tests, and there was a significant association between the Hcy levels and the number of perseverations on the Stroop Color Tests and the number of moves on Hannoi Tower Test (ToH); however, a linear regression model adjusting for gender, age, education, and number of prescribed psychotropics, revealed that Hcy was not a significant predictor of neurocognitive test performance (74).

3.5. Geriatric depression

We included two case-control articles that studied cognition and Hcy levels in major depression, with contradictory results. Alexopoulos and colleagues found that depressed patients with high levels of Hcy performed better in language processing and processing speed than patients with Hcy concentrations ≤ 11.7 μmol/liter, whereas the results were opposite in the healthy control group (75). However, Ford and colleagues found that elevated plasma Hcy levels were associated with weaker performance in tests of immediate and delayed memory

and global cognitive performance compared to those with normal Hcy levels, which was independent of the presence of major depression (76).

3.6. Eating disorders

Two cross-sectional studies indicated that higher Hcy levels were related with increased cognitive impairment in patients with anorexia and bulimia nervosa. Thus, Frieling and colleagues showed a significant positive association between long term and short term memory and the Hcy levels (77). Similarly, Welheilm et al. 2010, found a significant association between low Hcy levels and cognitive deficits (78). In contrast, a RCT using folic acid versus placebo showed that the supplemented group exhibited significantly increased serum and red blood cell folate levels, reduced Hcy levels and significantly improved most of the cognitive test scores, whereas the placebo group showed no significant changes in any of the evaluated variables (79).

3.7. Cardiovascular diseases

The opposite results were found in the cross sectional studies of population with cardiovascular diseases. Two of the studies found no significant association between cognition and the Hcy levels after adjusting for demographic and medical factors (80, 81). Nevertheless, one study found a significant association between HHcy and worse cognitive performance after adjusting for age, gender, premorbid intellectual coefficient and white matter lesions (82).

Regarding the three cohort studies of patients with cardiovascular diseases, two of the studies observed a significant relationship between the Hcy levels and cognition during follow-up. Narayan and colleagues showed a positive association between higher Hcy levels and cognitive impairment in three domains (executive function, episodic memory and processing speed). The associations remained significant during a 44-month follow-up. The association with

executive function did not remain significant when folate was included as a covariate in the regression model. (83). Similarity, Jochemsen et al. 2013, observed a significant association between higher Hcy concentrations and worse executive function in patients over 65 during a longitudinal study of 3.9 years. The study highlighted that elevated Hcy levels were related to the progression of ventricular enlargement and increased the risk for a decrease in executive functioning in older persons (84). However, Silbert and colleagues showed no association between the Hcy levels and cognition at any time during a one-year follow-up, but their Hcy levels were strongly associated with age and left ventricular function (85).

3.8. Cerebrovascular diseases

In the group of cerebrovascular diseases, the results were again contradictory. Of the two articles with cross sectional analyses of cases, one study found no differences between HHcy and cognitive performance (86). Conversely, another study showed a significant inverse relationship between the plasma Hcy levels and MMSE scores (87). One study using a case-control design found that the Hcy levels were strongly correlated with cognitive decline in patients with small vessel disease (88). The controversies persisted in two cohort studies of populations with cerebrovascular diseases. One study found no relationship between the plasma Hcy levels and cognitive results after 27 months of follow-up (89). On the other hand, Newman and colleagues considered Hcy to be an independent predictor of less successful cognitive recovery in patients after stroke (90).

3.9. Kidney diseases

No significant relationship between the Hcy levels and cognitive impairment was detected in patients suffering from kidney disease (91-93). In a RCT with B vitamin supplementation versus placebo, the treatment decreased the Hcy levels by 26.7%. However, the treatment did not

improve the initial cognitive outcomes or affect the subsequent cognitive status one year later (93).

3.10. Multiple sclerosis

A case-control study showed that patients with MS had higher plasma levels of Hcy and, consequently, HHcy was associated with cognitive impairment (14). However, a longitudinal study showed that the MS patients and healthy controls had similar Hcy levels. Patients with higher Hcy levels had lower cognitive scores, as measured with the Paced Auditory Serial Addition Test (PASAT). During a four-year follow-up, higher Hcy levels were associated with decreased cognitive scores in the PASAT (94).

3.11. Other diseases

In adolescents with epilepsy, there was no relationship between the plasma Hcy levels and cognitive scores, even though the Hcy levels were significantly higher in patients with epilepsy compared to healthy subjects (95). Similarly, there was no association between the plasma Hcy levels and the MMSE or SKT scores in a sample of geriatric patients with multiple co-morbid conditions (96). There was also no correlation between the Hcy levels and cognitive results in patients with obstructive apnea sleep syndrome (97). However, in a sample of patients with multiple system atrophy, a significantly negative correlation appeared between Hcy levels and the MMSE score (98).

3.12. General population

Twenty-four articles based on the general population used a cross sectional design. From these, 17 identified significant associations between the plasma Hcy concentrations and cognitive scores. A negative association between the MMSE scores and plasma Hcy levels was found in five studies (99-103). Furthermore, two more studies found a significant relationship under special conditions, including people over 60 years (104) and in subjects who were Apo E-

ε4 carriers (105). Specifically, negative associations between cognitive performance and Hcy levels were found in psychomotor speed, coordination, manual dexterity, verbal memory and learning (106), processing speed and spatial vision (107), visual and verbal memory (108), delayed memory and attention (109), and executive functions and language (110). One study showed that the Brief Cognitive Assessment Tool (BCAT) scores were significantly impaired in people with homocysteinemia over 16 μmol/liter, specifically in the domains of perceptual speed, mental arithmetic efficacy, spatial vision and working memory (111). There were two articles conducted on post-menopausal women, which showed a significant association between higher plasma Hcy levels and worse cognition performance. In the first study, the association was significant when the working memory and the verbal memory scores were grouped in a global score (112). In the other one, the global score was based in scores of the five cognitive domains (113). In a sample of right-handed people, processing speed was also associated with the Hcy levels after adjusting for age, gender and educational level. The signification disappeared when the white matter volume was included in the regression analyses as a covariate (114). Finally, the relationship between cholesterol levels and cognitive function depends upon Hcy levels; in participants with normal Hcy levels, an inverse U-shaped relationship between the total cholesterol level and cognitive score was found, indicating that both low and high cholesterol levels were associated with lower cognitive scores. In participants with high Hcy levels, no significant association was found between cholesterol and cognition (115). In seven cross-sectional studies, there were no association between the plasma Hcy levels and cognitive performance (116-122). In one study, although the Hcy concentration was not associated with any particular domain, it was associated with global cognition. However this association did not remain significant after adjusting for the white matter volume and brain infarcts, although the significance persisted when adjusted for the total brain volume (121). Another study found no association between

cognition and the Hcy levels in subjects aged 65 years and older when results were adjusted for the folate levels (122).

From the nine randomized clinical trials in the general population, eight showed that although vitamin supplementation reduced the Hcy levels, this did not impact the cognitive test scores (123-130). However, improved cognitive performance was observed in one article where the vitamin supplementation reduced the Hcy levels. This trial was conducted with middle- and older-aged people with HHcy (131).

Finally, 13 cohort studies were conducted with the general population. From these, there were significant relationships between the Hcy levels and cognitive functions during the transverse analyses in three studies. However, during the follow-up, the Hcy concentrations were not predictors of cognitive impairment (132-134). Nevertheless, Ganguli et al., 2014, found no associations between the Hcy levels and cognitive functions during transverse analyses but there was a significant association between the Hcy levels and the executive function domain during four years of follow-up (135). In addition, five studies demonstrated a significant association between the plasma Hcy levels and cognitive function during some point of the longitudinal design (136-140). Hence, Van den Kommer and colleagues showed that higher Hcy levels at baseline were negatively associated with prolonged lower cognitive function and a faster rate of decline in information processing speed and fluid intelligence (140). Additionally, Hooshmand and colleagues found that higher plasma Hcy levels at the onset of the study were associated with poorer performance in global cognition, episodic memory, executive functions and verbal expression at a seven-year follow-up (139). These results may be comparable with the study of Strand et al. 2013, which was performed in 15-month-old children. In this study, each 2-fold increase in the Hcy concentration was associated with a two-point decrease in the mental development index score (138). Interestingly, Sharma et al., 2014, found that the plasma Hcy levels increased proportionately with the duration of

stay at high altitude and hypobaric hypoxia. Moreover, the Hcy levels were inversely correlated with the MMSE scores during across the entire follow-up period (137). Moreover, the study of de Whalley et al., 2014, supported an association between HHcy and late onset dementia during a five-year follow-up. The association between Hcy and dementia was independent of the plasma folate, B12 and antioxidant micronutrient concentrations (136). Finally, in 2014, Samaras and colleagues, found no association between the plasma Hcy levels and global cognitive function over a two-year study, but the Hcy levels were predictors of an inverse association with executive function (141). On the contrary, Tucker and colleagues showed no association between the plasma Hcy levels and cognitive scores over four years in a male sample, after adjusting for the folate and B6 and B12 vitamin concentrations (142). Furthermore, two more studies observed no association between increased Hcy levels and changes in cognitive performance (143, 144); one of them was conducted with university students, and the time of follow-up was six hours (143).

3.13 Quantitative approach

3.13.1. Case control studies

For the case-control studies, we assessed the difference in Hcy levels between cases and controls, on the one hand, and the influence of Hcy levels in MMSE scores in the case group, on the other hand. There were not enough studies assessing the influence on other cognitive scores, nor such influence for both cases and controls. Fifteen studies comparing Hcy levels in patients versus healthy population reflected that Hcy concentration is significantly higher in the group of patients with a pooled Cohen's *d* ranging between 0.30 - 1.17, depending on the population subgroup (14, 18, 39-43, 63-65, 67, 71, 74, 75, 88). Thus for most subgroups, these pooled values indicate a medium to large effect size (145) (Figure 2). This fact is particularly interesting because there is included a wide range of diverse diseases (AD, PD, BD, small vessel disease and MS). However, it is worth noting that there were some diseases that contribute to

the ES only with one study (14, 71, 75, 88). In regard to the PD group (63-65, 67), levodopa administration is a confusion factor as the treatment usually increases the Hcy levels (146).

On the other hand, three studies could be included for the case analyses of patients with AD (40, 41) and PD (64). We found that higher level of Hcy was associated with worse MMSE results in the overall analysis (ES=-0.34 [-0.63, -0.05]; significance test for ES $\neq$ 0: z=2.30, p=0.022) (Figure 3). Supplementary figure 1 depicts the effect sizes pooled by population (note that there are only two studies in AD and one in PD patients), with the AD subgroup showing also significant inverse association between Hcy and MMSE score.

3.13.2. Cross sectional studies

The effect size represents the standardized linear regression coefficient for the relationship between Hcy levels and cognitive scores: MMSE (13 studies) (47-49, 87, 98, 101-103, 107, 108, 119, 132, 144), BNT (three studies), TMT (four studies), RALVT (three studies). We have found a negative association between plasma Hcy levels and MMSE scores (ES=-0.19 [-0.27, -0.10], significance test for ES $\neq$ 0: z=4.42, p<0.001) (Figure 4). This negative association holds for all populations as shown in the subgroup analysis (Figure 5). Despite this effect across all clinical conditions, tests showed a significant between-group heterogeneity (Q=34.54, p<0.001), although the high within-group heterogeneity in Alzheimer's studies (47-49) and the small number of studies in the other subgroups render this test questionable.

No significant associations were found when Hcy levels were compared with scores of BNT, TMT, and RAVLT scores. It is worth noting that only a small number of studies could be included for each case (Supplementary figures 2-4).

3.13.3. RCT studies

Five RCT articles were included in the quantitative approach exploring the difference in cognitive scores between patients receiving vitamin for lowering Hcy levels, and those

receiving placebo (55, 56, 93, 124, 128). The effect size is the Cohen's d for the variation in scores before and after intervention, compared between vitamin and placebo groups.

Overall, there was no association between group allocation and MMSE score (ES= 0.04 [-0.06, 0.14], significance test for ES $\neq$ 0: z= 0.82 p = 0.411) (Figure 6). This lack of association holds for all populations in the subgroup analysis, with no significant between-subgroup heterogeneity (Q=1.19, p=0.552), although there were very few studies per subgroup (Supplementary figure 5). There was neither association between Hcy and RAVLT scores in the analysis that could be performed with three studies (Supplementary figure 6)

3.13.4. Cohort studies

Five cohort articles (59, 93, 139, 140, 142) were included for a quantitative exploration of the association between baseline Hcy and MMSE scores at the end of follow-up (i.e. after 6 - 84 months, 39.05 on average). Results show a negative association between higher baseline Hcy and MMSE score at the follow-up (ES=-0.08 [-0.12, -0.04], significance test for ES $\neq$ 0: z= 3.98, p <0.001) (Figure 7). In the subgroup analysis, there were significant negative associations when considering the general population (139, 140, 142) and the kidney disease (93). No significant associations in regard to the AD (59), although there were very few studies per subgroup (Supplementary figure 7).

4. DISCUSSION

Overall, our findings suggest a possible role for the plasma Hcy levels in the development or the progression of cognitive dysfunctions. More than half of the included articles (N=59) show some form of significant association between the plasma Hcy levels and cognitive functions, even when the analyses were adjusted for the relevant covariates. However, it remains unclear

whether the high Hcy concentrations are responsible for cognitive impairments, and its etiopathogenic mechanism has not been conclusively identified.

The included articles used several different instruments to measure cognitive impairment. However, the MMSE test is one of the most commonly used tests. The MMSE is frequently used as screening test for global cognition (147). The results of this systematic review include multiple studies with significant associations between the plasma Hcy concentrations and MMSE scores. Overall, the associations between the Hcy levels and cognition were negative. Although this instrument provides information on global cognitive impairment, the MMSE test does not allow us to identify the domains that are the most altered. In many other articles, more complete cognitive batteries demonstrate that the processing speed and the executive functions were the domains that were most affected by the increased plasma Hcy concentrations. Frequently, different types of memory, such as visual memory, short-term memory and explicit long term-memory, are also altered in patients with high Hcy levels. The relationship between the plasma Hcy levels and the scores representing such domains is inverse, similar to the MMSE test. Therefore, higher blood Hcy levels are associated with a worse performance in several cognitive tests. One of the most relevant prospective studies in this field from the Framingham Study cohort reported that an elevated Hcy level at baseline, in cognitively intact adults, was related to a decline in MMSE scores, but only after a follow-up period of at least four years. Furthermore, baseline Hcy was an independent risk factor for the development of dementia and AD in adults without cognitive impairment (148).

Interestingly, there are three studies showing a positive association between cognition and the Hcy concentrations (75, 77, 78). Two of them were performed in patients with eating disorders, and found a positive association between the elevated Hcy levels and memory test scores (77), with a better performance in Stroop and SKT tests (78). These results note a beneficial effect of high Hcy levels on memory, selective attention and processing speed in

eating disorder patients. This fact may indicate that the link between the elevated Hcy levels and cognition originating from a nutritional deficiency may be different than the relationship between the high Hcy levels and cognition in the elderly. Another study with similar findings was conducted with aging patients with major depression (75). In this case, the elevated Hcy concentrations were associated with a better performance in the processing speed and language processing tests. As is highlighted, there are certain results indicating that major depressive disorder may be related to a perturbation in glutamate metabolism (149, 150). Long term potentiations (LTPs) of excitatory synapses are prime candidates for learning and memory processes depending on activation of the NMDA receptors (151). In major depressive disorders, prefrontal glutamate/glutamine concentrations are abnormally reduced (152). In this context, Hcy may actually replace glutamate at excitatory synapses, acting as agonist on the glutamate binding site of the NMDA receptor (153). This linkage may avoid the direct neurotoxicity of HHcy and may generate LTPs at some specific sets of synapses mediating other forms of plasticity, attenuating the cognitive deficits caused by glutamate deficiency (152, 154-157). This theory could be similar in eating disorder patients, where there is also reported a glutamate reduction using proton magnetic resonance spectroscopy (158). This fact is supported by the evidence that dietary restriction decreases extracellular glutamate levels in striate nucleus in mice (159).

Concerning the cross sectional studies, the most affected domains by the elevated Hcy levels are executive functions, different types of memory, processing speed and global cognition. Moreover, the case control analyses revealed higher levels of Hcy in patients of diverse diseases compared with healthy controls. Also patients normally showed a worse performance in cognitive tests. In regard to the cohort studies, most of them showed an association between the Hcy concentrations and the evolution of the cognitive decline, particularly in the studies concerning the general population, AD and cognitive impairment, cardiovascular disease, cerebrovascular disease and the general conditions associated with aging. This fact

may be partially explained by suggesting cumulative effect of Hcy in the elderly, with endothelial injury and atherosclerosis (160).

Nevertheless, many of the RCTs find no evidence of B vitamin supplementation and cognitive improvement; although there was evidence that B vitamins may reduce the plasma Hcy levels to the standard values. From the 15 RCTs, the treatment with B vitamin reduced the Hcy levels in all cases, but only six studies indicated an improvement in the patients´scores on different cognitive tests (19, 58, 69, 70, 79, 131). There are two possible theories for these observations. On one hand, the effects of Hcy in the brain may be irreversible and therefore, the effects of vitamin supplementation may be limited once the pathological changes appeared (161). On the other hand, the cognitive impairment may not be caused by the elevated Hcy levels but could be produce by common mechanisms of both conditions (162, 163). Both theories could explain why the vitamin supplementation could reduce the Hcy levels, but could not reduce or prevent the cognitive impairments. It is debatable whether the earlier detection of HHcy and related factors may prevent the neurodegeneration associate with aging and dementia (164). However, as a primary preventative measure, screening for Hcy levels may protect patients from other devastating effects, such as atherosclerosis (165), hypertension (166), thrombus (167), aging-related oxidation (168) and osteoporosis (169), which are commonly associated with higher Hcy concentrations.

This review is subject to some limitations that are worth noting. The reasons why certain cognitive domains are more affected by the high Hcy concentrations in some studies but not in others are not clear. These discrepancies may be due to the differences in the cognitive batteries between studies and those inherent to the administration, as well as to the methodology employed during the experiments (170). Moreover, as noted above, the Hcy concentrations are a complex function resulting from the interaction between genetic and environmental factors (10). Fuethermore, the heterogeneity of cognitive testing used in the

studies limited the comparison and pooling of data. Therefore, this review could not elucidate the relative effect of elevated homocysteine in some cognitive domains, and instead was necessarily limited our meta-analyses to only the most commonly measured outcomes. The quantitative approach was also limited by the fact that not all the articles explained their results using an association measure, or in some cases their design made them unsuitable to summarize in a pooled estimate with the other studies, and a discrete number of study could be included in the meta-analysis. The meta-analytic results only represented a subsample of the literature summarized in the present review. Finally, it is worth noting that the small sample size (N ≤26) of the three articles with a positive relationship between cognition and the Hcy levels should be considered when interpreting the results presented here. Among the strengths of this review is the fact that, to our knowledge, it is the largest systematic effort to summarize the data on the associations between Hcy and cognition in different populations.

In conclusion, further investigations are warranted to clarify the relationship between the plasma Hcy levels and cognitive function. Treatment with vitamin supplementation often fails to reduce the cognitive impairment once it appears. Earlier detection of the elevated Hcy levels before the decline in cognitive function may be an effective intervention to prevent cognitive impairment and dementia.

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Figure 1. Flow diagram selection of study process

Figure 2. Case-control studies. Comparison of plasma Hcy levels between controls and patients. Abbreviations: CI= Confidence intervals; ES= Effect size; MS= Multiple sclerosis; N= sample size; SVD=Small vessel disease.

Figure 3. Case-control studies. Association between plasma Hcy levels and Mini Mental State Examination (MMSE) scores. Abbreviations: CI= confidence intervals; ES= Effect size; N= sample size.

Figure 4. Cross-sectional studies. Association between plasma Hcy levels and Mini Mental State Examination (MMSE) scores in the whole sample. Abbreviations: CI= confidence intervals; CVD= cardiovascular disease; ES= Effect size; MSA= Multiple System Atrophy; N= sample size.

Figure 5. Cross-sectional studies. Association between plasma Hcy levels and Mini Mental State Examination (MMSE) scores sample divided by different diseases.Abbreviations: CI= confidence intervals; CVD= cardiovascular disease; ES= Effect size; MSA= Multiple System Atrophy; N= sample size.

Figure 6. Randomize clinical trial (RCT) studies.Association between plasma group allocation and Mini Mental Examination (MMSE) scores. Abbreviations: CI= confidence intervals; ES= Effect size; N= sample size.

Figure 7. Cohort studies. Association between plasma Hcy levels and Mini Mental State Examination (MMSE) scores. Abbreviations: CI= confidence intervals; CVD= cardiovascular disease; ES= Effect size; N= sample size.

Fig 1

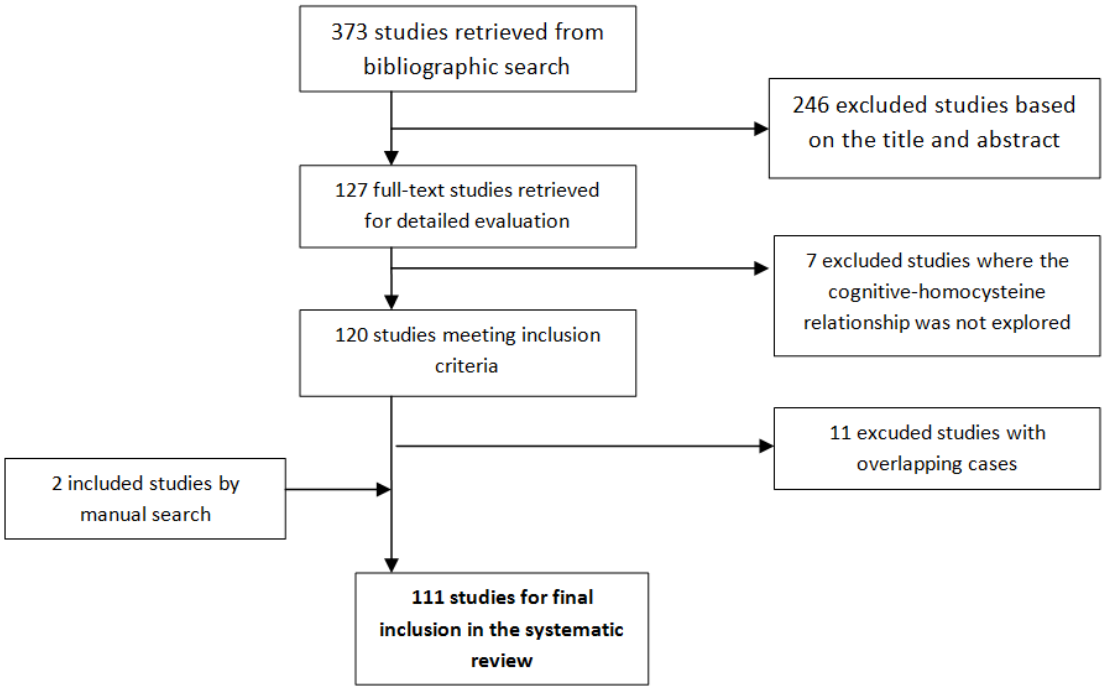

Fig 2

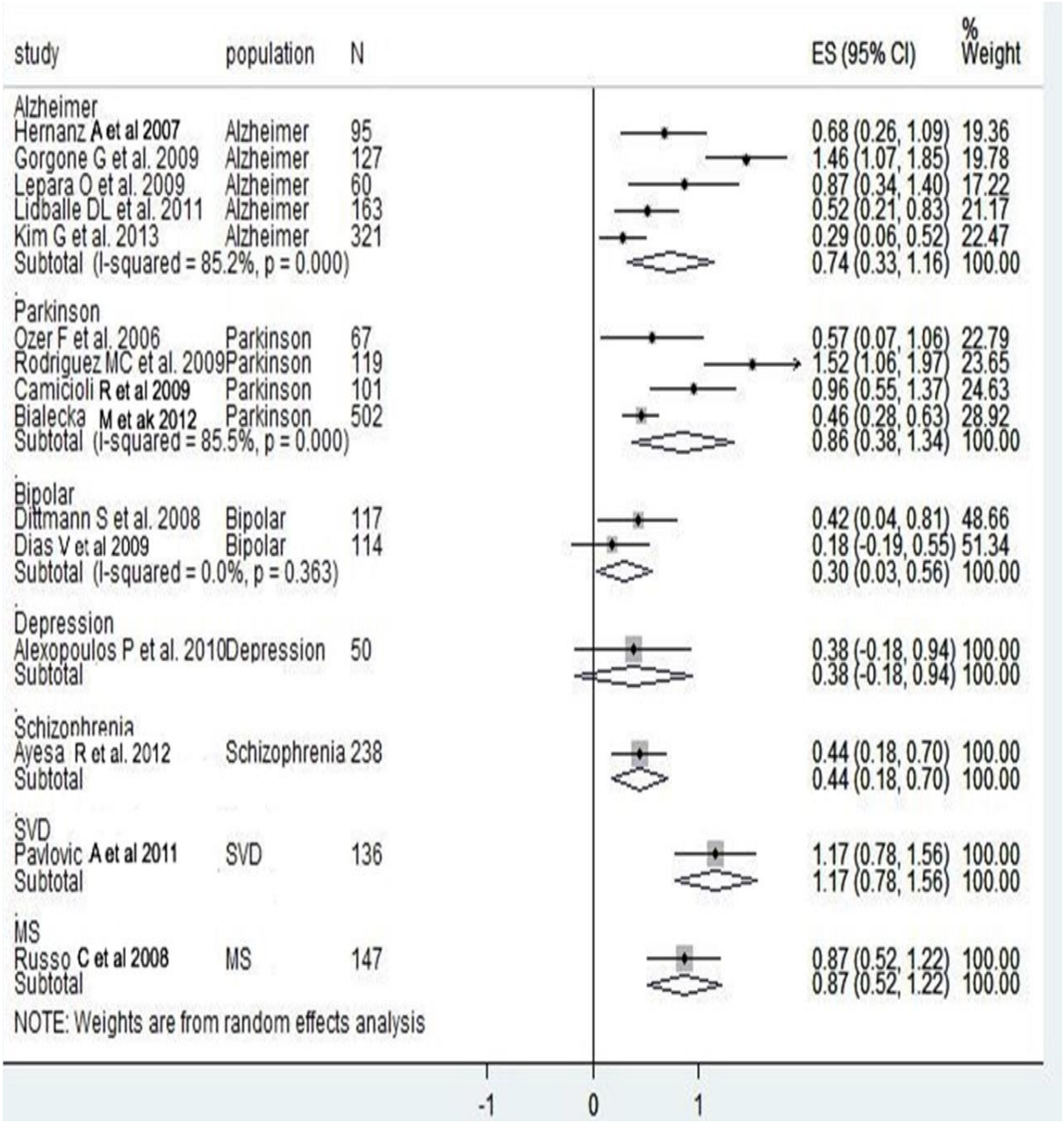

Fig 3

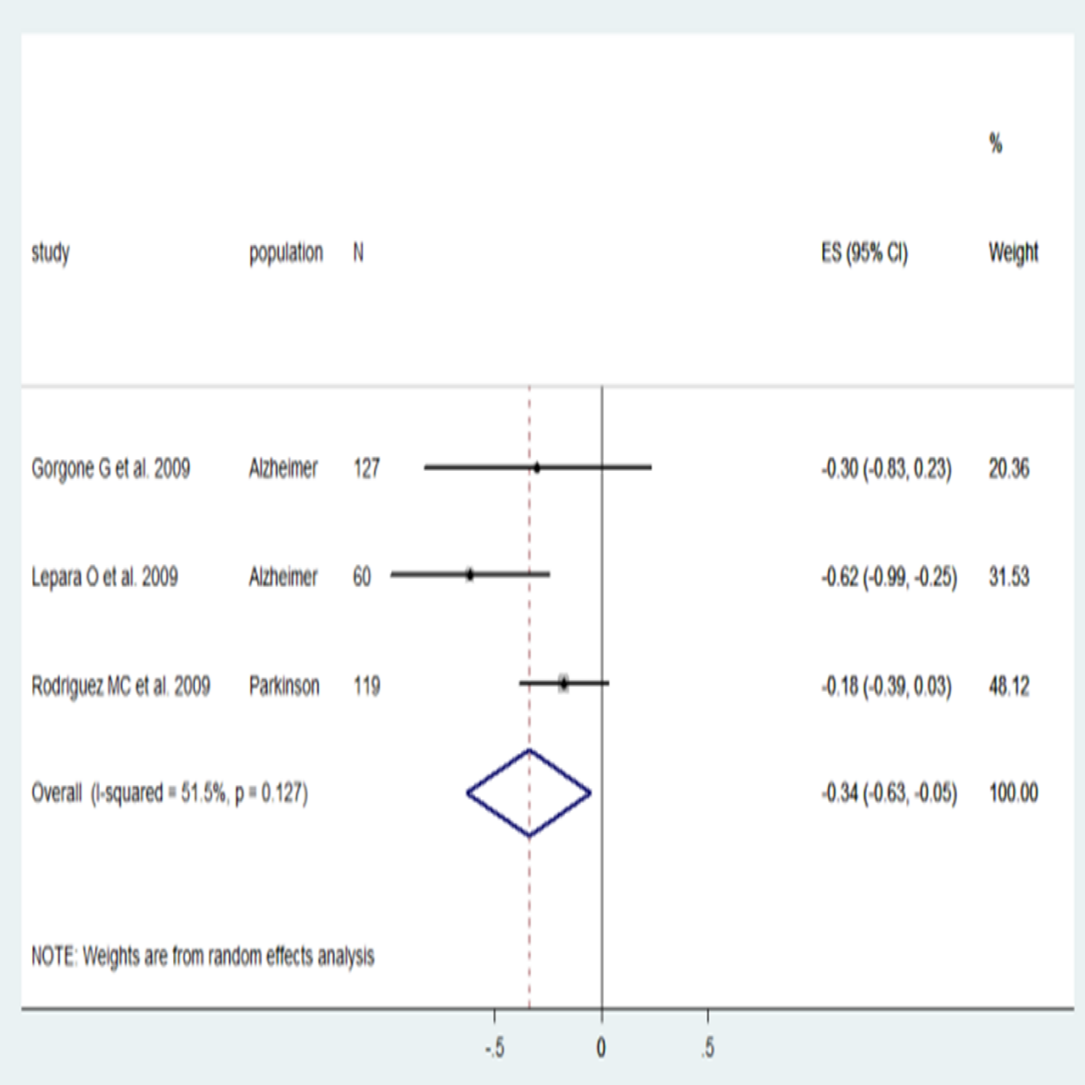

Fig 4

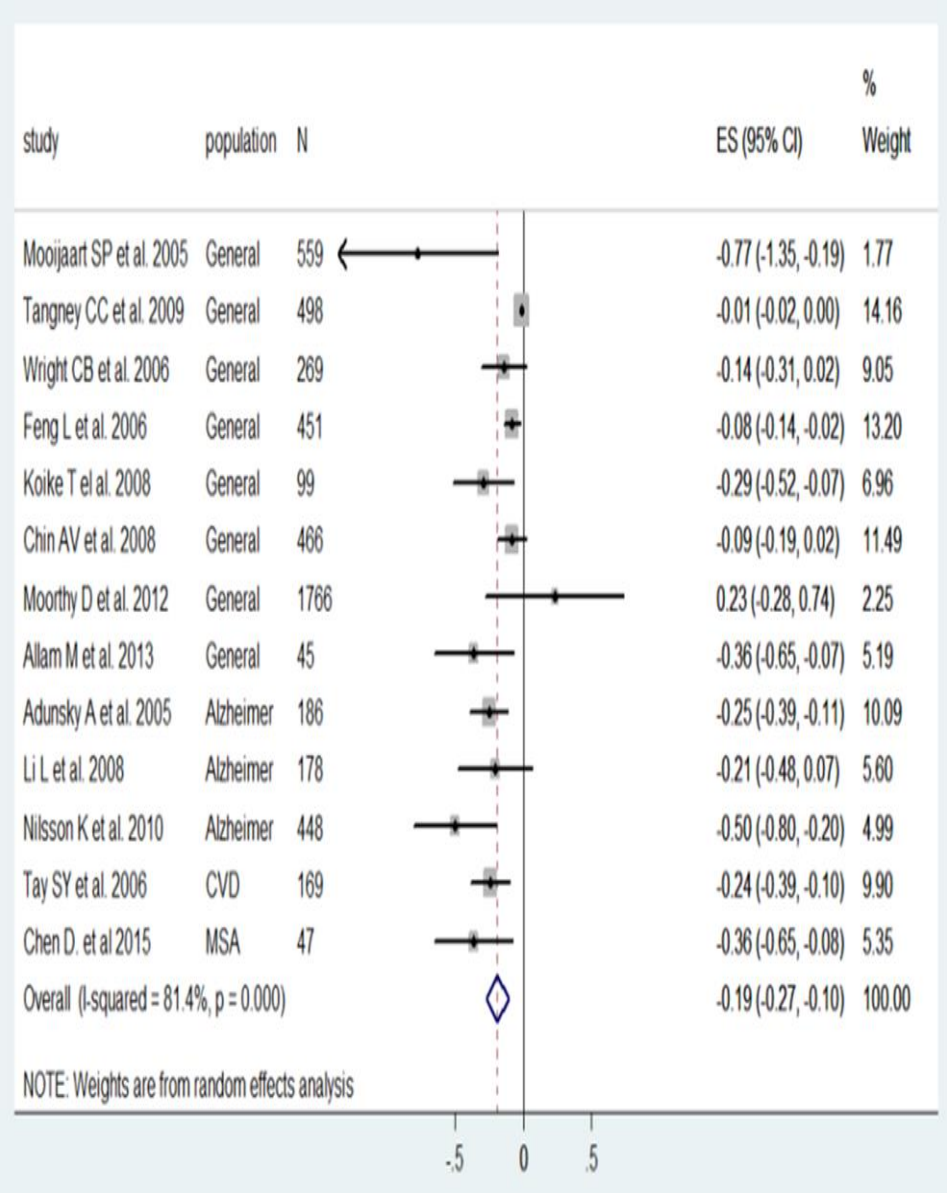

Fig 5

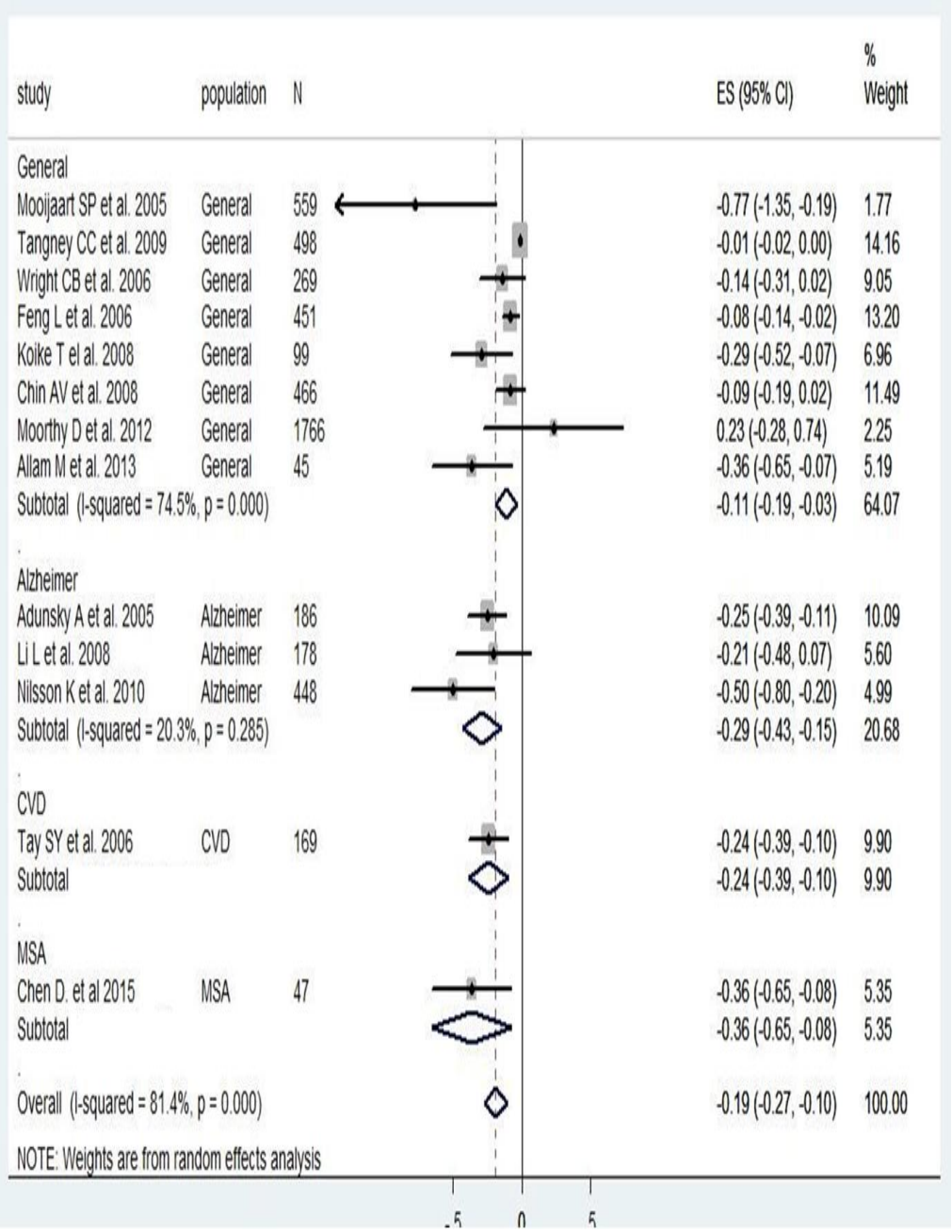

Fig 6

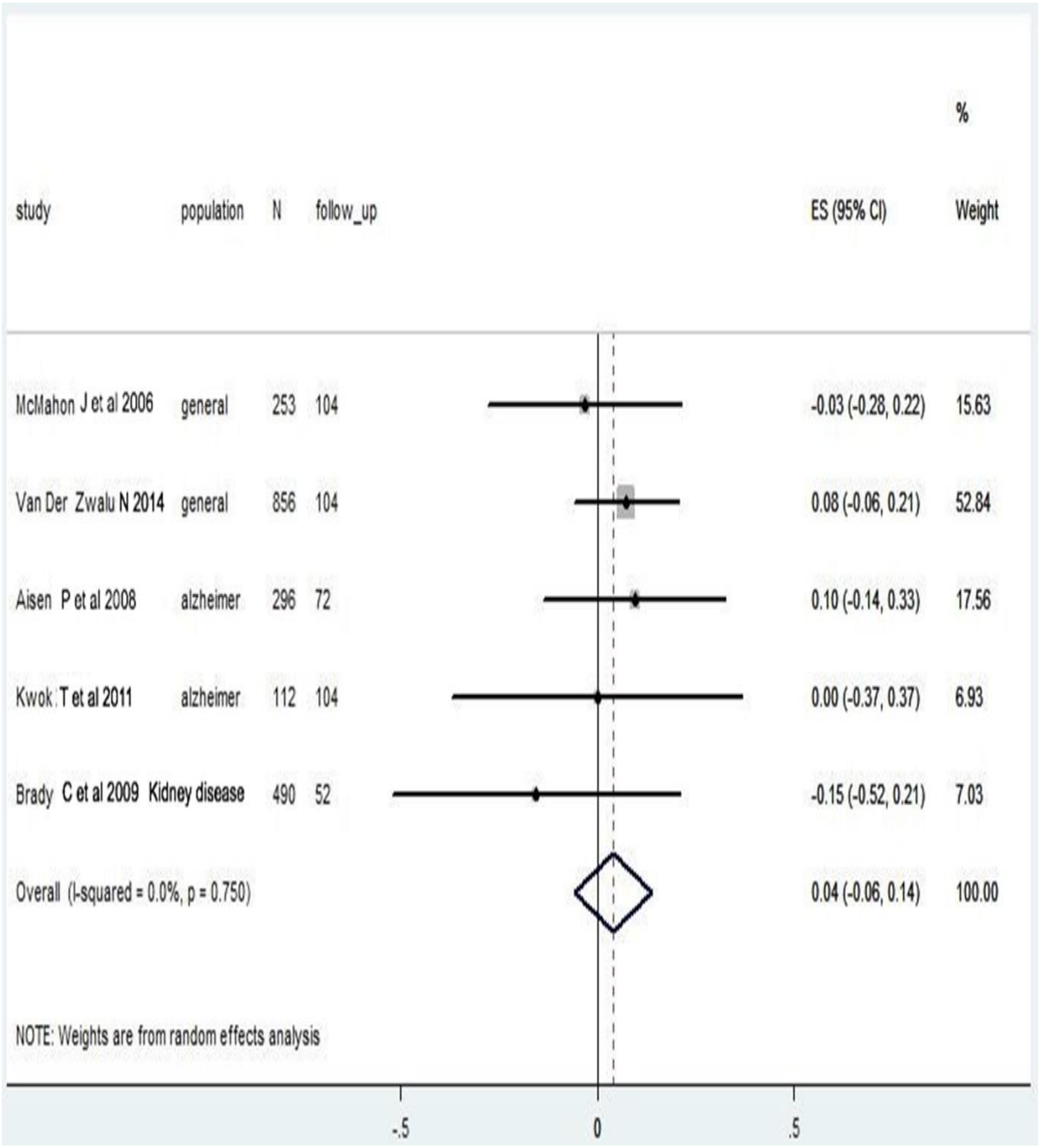

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Fig 7

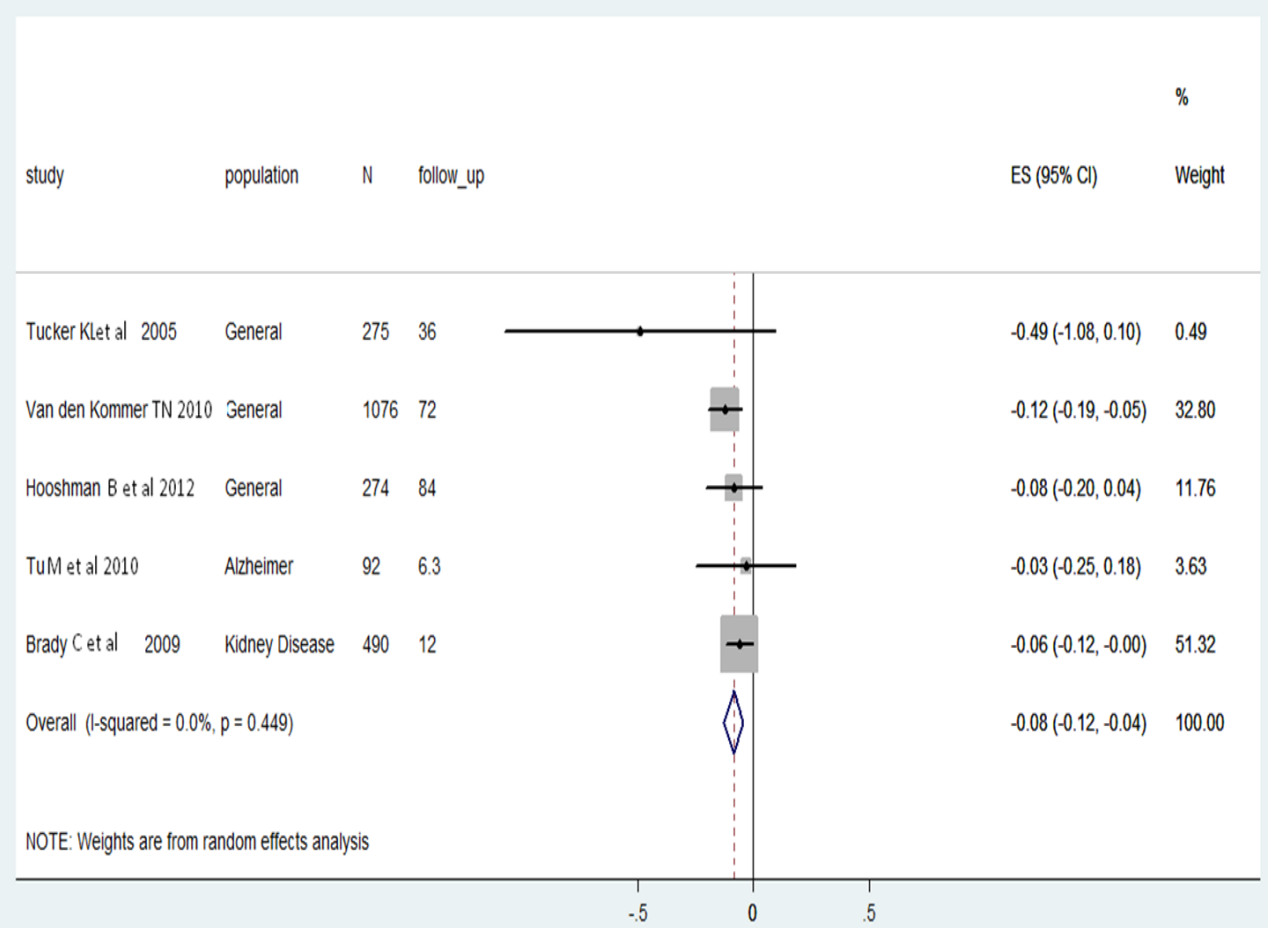

Table 1. Homocysteine and Cognition. Cohort studies

Population	Article	N	Age (years) mean (SD)	Follow-up	Hcy (µmol/l) mean (SD)	Neurocognitive tests
General	Tucker KL et al. 2005	321	67 (7)	3y	11 (5)	MMSE, Backward DS from WAIS-R, CERAD, Developmental test of VMI
	Mooijaart SP et al. 2005	559	85	4y	--	MMSE, Stroop test, LDCT, WLT
	Clarke R et al. 2007	2741	75.7 (7)	10y	14.5 (6.3)	MMSE
	Tangney CC et al. 2009	516	80 (6)	6y	11.5 (4.8)	MMSE, EBMT, SDMT
	Alexopoulos P et al. 2010	100	Group A: 23.6 (5.5)	6h	8.9 (3.2)	SKT, Stroop test, Short Test for General Intelligence
			Group B: 21.6 (2.6)		10.1(3.5)	
	Van den Kommer TM et al. 2010	1257	75.4 (6.6)	6y	13.6*	MMSE, AVLT, RCPM, Alphabet Coding Task-15
	Brown B et al. 2011	499	Group A: 74.3 (2.8)	7y	12.4 (5)	DRST, Similarities of WAIS-R
			Group B: 74.3 (2.8)		11.4 (4)	
	Hooshmand B et al. 2012	274	70.1	7y	12.2*	MMSE, LDST, PPT, Stroop Test, Immediate Word Recall Test, Fluency test.
	Strand TA et al. 2013	650	Group A: 14.8 (2) m	4m	14.7*	Bayley Scales of Infant Development II
			Group B: 15 (2) m		9.5*	
	Samaras K et al. 2014	880	DM: 78.4 (4.7)	2y	12.6 (3.9)	Digit Symbol Coding, Logical Memory and Block Design from WAIS-III, TMT, RAVLT, BVRT,
			No DM: 78.4 (4.8)		11.1 (3.9)	VFT, BNT
	Sharma VK et al. 2014	727	27.3 (2.3)	18m	8.6 (0.8)	MMSE, MSCST, RSPM, CDT, BGT, SDLT, Stroop Test, TMT, VFT
	Whalley LG et al. 2014	201	Group A: 77.2 (0.8)	5y	--	MMSE
			Group B: 77.1 (0.7)			
			Group C: 77.1 (0.6)			
	Ganguli M et al. 2014	559	77.6 (7.4)	4y	65%: >10	--
Alzheimer and cognitive decline	Rozzini L et al. 2006	74	Group A: 69.1 (7.1)	1y	--	MMSE, CDR, ADAS-cog
			Group B: 73.9 (7.3)			
	Siuda J et al. 2009	55	--	1y	--	--
	Reitz C et al. 2009	678	77.4 (5.8)	5.2y	16.8 (7.9)	MMSE, BNT, COWAT, BDAE, Similarities from WAIS-R, MDRS, RDT, BVRT, SRT
	Tu MC et al. 2010	92	73.8 (9.4)	6.3m	12.9 (7.3)	MMSE, CDR, CASI
	Oulhaj A et al. 2010	97	71.9 (8.2)	1.5-9.5y	14.2 (4.8)	CAMCOG
Cardiovascular disease	Silbert B et al. 2008	264	67.8 (7.7)	1y	10.1*	CERAD Auditory Verbal Learning Test, DSST, TMT, COWAT, VFT, GPT, NART
	Narayan SK et al. 2011	182	80 (4)	44m	--	CDR, NART, TMT, VFT
	Jochemsen HM et al. 2013	416	58 (10)	3.9y	HHcy: 22 (4)	RAVLT, ROCF, VE of TEA, BSAT, VFT, DART
					No HHcy: 12 (3)	
Cerebrovascular disease	Newman GC et al. 2007	3680	66.3 (10.8)	20.3m	13.4 (5)	MMSE
	Rowan EN et al. 2007	170	79.4*	27m	16 (5.1)	CAMCOG, CDR
Multiple sclerosis	Teunissen CE et al. 2008	219	45.1 (11.1)	4y	11.2*	PASAT

Abbreviations: ADAS-cog: Alzheimer's Disease Assessment Scale-cognitive subscale, AVLT: Auditory Verbal Learning Test, BDAE: Boston Diagnostic Aphasia Examination, BGT: Bender Visual Motor Gestalt Test, BNT: Boston Naming Test, BSAT: Brixton Spatial Anticipation Test, BVRT: Benton Visual Retention Test, CAMCOG: Cambridge Cognitive Examination, CASI: The Cognitive Abilities Screening Instrument, CDR: Cognitive Drug Research, CDT: Clock Drawing Test, CERAD: Consortium to Establish a Registry for Alzheimer´s Disease, COWAT: Controlled Word Association Test, DART: Dutch Version of the National Adult Reading Test, DM: Diabetes mellitus, DRST: Delayed Recognition Span Test, DS: Digit Span, DSST: Digit Symbol Substitution Test, EBMT: East Memory Boston Test, GPT: Grooved Pegboard Test, h: hours, Hcy: serum homocysteine, HHcy: hyperhomocysteinemia, LDCT: Letter Digit Coding Test, LDST: Letter Digit Substitution Test, m: months, MDRS: Mattis Dementia Rating Scale, MMSE: Mini-Mental State Examination, MSCST: Multi Domain Cognitive Screening Test, N: number, NART: National Adult Reading Test, PASAT: Paced Auditory Serial Addition Test, PPT: Purdue Pegboard Test, RAVLT: Rey Auditory Verbal Learning Test, RCPM: Raven's Coloured Progressive Matrices, RDT: Rosen Drawing Test, ROCF: Rey-Osterrieth Complex Figure Test, RSPM: Raven Standard Progressive Matrices, SD: standard deviation, SDLT: Serial Digit Learning Test, SDMT: Symbol Digit Modalities Test, SKT: Syndrome Short Test, SRT: Selective Reminding Test, TMT: Trail Making Test, VE: Visual Elevator Test, VFT: Verbal Fluency Test, VMI: Visual-Motor Integration, WAIS-R: Revised Wechsler Adult Intelligence Scale, WLT: Word Learning Test, y: years, *: median

Table 2. Homocysteine and Cognition. Randomize clinical studies.

Population	Article	N Treatment/Placebo	Age (years) mean (SD) Treatment/Placebo	Hcy (µmol/l) mean (SD)	Treatment	Follow-up week	Neurocognitive tests
General	Lewerin C et al 2005	126/69	75.7(4.7)/75.6(4)	17.8 (5.5)/16.1 (4.5)	0.5 mg cyanocob.+0.8 mg folic acid+3mg B-6	16	DS, block design, digit symbol and Visual Reproduction of Wechsler, Thurstone's Picture Memory Test,
	McMahon JA et al 2006	127/126	73.6 (5.8)/73.4 (5.7)	16.8 (5.4)/16.3 (4.4)	1mg folate+0.5mg B12+10mg B6	104	MMSE, RAVLT, WMS, COWAT, TMT, RSPM, NART, VFT
	Eussen SJPM et al 2007	130/65	82 (5)	1º 15.6 (6.6); 2º 14.5 (4.4)/15.8(5.6)	1º 1mg cobalamin, 2º 1mg cobalamin+0.4mg folate	24	MMSE, ROCF, TMT, DS, Stroop Test, VFT, RSPM, Similarities of Wais, AVLT, FTT
	Macpherson H et al 2012	28/28	71.9 (4.8)/70.3 (4.3)	14.1 (2.8)/15.1 (2.8)	Swisse Women's Ultivite 50+TM	16	NART, SUCCAB, CVLT-II
	Pinpigas A et al 2014	56/60	[M: 28.9 (6.9); F: 32.8(7.7)]/ [M: 30.9 (7.5); F: 31.2 (6.8)]	10.9 (1.6)/ 10.7 (1.6)	Supplementation of Multivitamin	16	SUCCAB
	Cheng D et al 2014	57/47	74.3 (9,6)/72.5 (7.0)	20.6 (6.5)/19.3 (4.2)	0.8mg folate+10mg B6+0.025mg B12	14	BCATs
	Van der Zwaluw et al 2014	2919	74.1 (6.5)	14.4*	0.4mg folate+0.5mg B12+0.015 D3	104	MMSE, RAVLT, DS, TMT, Stroop Test, SDMT,VFT
	Harris E. et al 2015	52/51	60.2(3.2)/M: 59.1(2.3); F: 60.1(3.4)	M: 15.1(3.4); F: 12.9(3)/ M: 15.5(3.9); F: 13(2.9)	Supplementation of Multivitamin	16	Stroop, Immediate and Delayed Recognition Memory, Spatial Working Memory and Contextual Memory, Reaction Time.
	Dangour A.D. et al 2015	99/102	79.9 (3.5)/80.1(3.7)	17.1(4.6)/17.2 (5.6)	1 mg Vitamin B12	52	CVLT, VFT, SLMT, Reaction Time.
Alzheimer and cognitive decline	Aisen PS et al 2008	204/140	75.7 (8.0)/77.3 (7.9)	9.2 (3.4)/9.1 (2.8)	5mg folate+ 1mg B12+25mg B6	78	MMSE, ADAS-cog
	Kwok T et al 2011	70/70	79.1 (6.7)/72.2 (7.9)	14.3 (4.3)/13.9 (3.8)	5mg folate+ 1mg methylcobalamin	104	MMSE, MDRS
	De Jager CA et al 2012	110/113	--	11.3*/11.6*	0.8mg folate+0.5mg B12+ 20mg B6	104	MMSE, HVLT-R, CERAD, CLOX, CDR, IQCODE
	Köbe T. et al 2015	13/9	70(7.2)/70 (5.2)	15.9(7)/17.6(3.6)	Omega-3+aerobic exercise+CS.	26	MMSE, AVLT, TMT, DS, VFT, Stroop
Parkinson's Disease	Barone P et al 2008	224/118	--	--	Rivastigmine	24	ADAS-cog
	Litvinenko IV et al 2010	32/30	71.2 (5.8)/72.4 (3.7)	--	20mg memantine	52	MMSE, ADAS-cog, FAB, CDT, VFT
Schizophrenia	Levine J et al 2006	20/22	40*/40*	>15	2mg folate+25mg pyridoxine+0.4mg B12	26	DS, RAVLT, WCST, ROCF or TCF
Eating Disorders	Loria V et al 2013	14/10	22.3 (7.6)/26.7 (10.0)	9.4 (2.4)/10(2)	5mg folate(Acfol)x2	26	TMT, Stroop Test
Kidney Disease	Brady CB et al 2009	339/320	--	--	40mg folate+100mg B6+2mg B12	52	TICSm, DS of WAIS, VFT

Abbreviations: ADAS-cog: Alzheimer's Disease Assessment Scale-cognitive subscale, AVLT: Auditory Verbal Learning Test, BCATs: Basic Cognitive Aptitude Tests, CDR: Cognitive Drug Research, CDT: Clock Drawing Test, CERAD: Consortium to Establish a Registry for Alzheimer´s Disease, CLOX: Executive Clock Drawing Test, COWAT: Controlled Word Association Test, CS: Cognitive Stimulation, CVLT-II: California Verbal Learning Task, DS: Digit Span, FAB: Frontal Lobe Dysfunction Assessment Battery, FTT: Finger Tapping Test, HVLT-R: Hopkins Verbal Learning Test Revised, IQCODE: Informant Questionnaire on Cognitive Decline in the Elderly, MDRS: Mattis Dementia Rating Scale, MMSE: Mini-Mental State Examination, N: number, NART: National Adult Reading Test, RAVLT: Rey Auditory Verbal Learning Test, ROCF: Rey-Osterrieth Complex Figure Test, RSPM: Raven Standard Progressive Matrices, SD: standard deviation, SDMT: Symbol Digit Modalities Test, SLMT: Symbol Letter Modality Test, SUCCAB: Swinburne University Computerized Cognitive Assessment Battery, TCF: Taylor Complex Figure, TICSm: Telephone Interview for Cognitive Status-modified, TMT: Trail Making Test, VFT: Verbal Fluency Test, WAIS: Wechsler Adult Intelligence Scale, WCST: Wisconsin Card Sort Test, WMS: Wechsler Memory Scale, y: years, *: median

Table 3. Homocysteine and Cognition. Case-control studies.

Population	Article	N	Age (years) Mean (SD)	Hcy (µmol/l) Mean (SD)	Neurocognitive tests
		Patients/Controls	Patients/Controls	Patients/Controls	
Alzheimer and cognitive decline	Irizarry MC et al. 2005	377/88	72.5/70.3(9.8)	9.1/8.7(3.2)	BDS-IMC
	Hernanz A et al. 2007	51/44	AD 73.2(7.1);	AD 14.8(7.4);	MMSE
			MCI 75.9(6.9)/	MCI 13.2(6)/	
			73.5(3.2)	10.4(2.7)	
	Gorgone G et al. 2009	63/64	75.7(9.2)/75.7(8.6)	19.1(4.4)/13.3(3.5)	MMSE, MDB
	Lepara O et al. 2009	30/30	80(0.9)/77.5(1)	16.1(1)/12.6(0.4)	MMSE
	Lidballe DL et al. 2011	80/83	83*/82*	15.6*/12.8*	MMSE
	Faux NG et al. 2011	101/172	AD 78.4(8.7);	AD [M&F 9.7(0.3)];	CVLT, RCFT, Stroop Test, VFT, Digit Symbol Coding Test, LM
			MCI 75.7(7.6)/	MCI [M 10 (0.4),F 8.9 (0.3)] /	
			70(7)	M 9.6(0.2), F 8.4(0.1)	
	Ford AH et al. 2012	431/1347	82.7(3.9)/81.2(3.5)	13.3(4.5)/12.6(4.8)	TICS
	Kim G et al. 2013	200/121	74.8(7.2)	--	MMSE, BNT, Word List Memory Test, Constructional Recall Test
Parkinson's Disease	Ozer F et al. 2006	39/28	67(9.3)/61.9(8.3)	15.2(9.6)/10.9(2.8)	STMS, CDT, SBST, WMS, BFR, JLO, Stroop Test, WCST, VFT
	Zoccolella S et al. 2009	121/154	--	17.5(10.2)/11(4.1)	--
	Camicioli R et al. 2009	51/50	71.5(4.7)/71.6/4.9)	13.6(3.8)/10.5(2.5)	MMSE, DRS
	Rodriguez MC et al. 2009	89/30	Group A 70(6.5),	Group A 14.9(4.7),	MMSE, BDS, FCSRT, CERAD Word List, BNT, APM, VFT, TMT,
			Group B70.2(5.2)	Group B 15.1(4.3)	Stroop Test, DS
			Group C 74.9(6.1)/	Group C 15.4(5.4)/	
			68.5(3)	8.5(1.9)	MMSE, WAIS-R, RCFT, DS, BVRT, TMT, AVLT, WCST, VFT
	Bialecka M et al. 2012	320/254	64.4(10.1)/64.8(9.6)	18(7.8)/14(9.6)	
Bipolar Disease	Dittmann S et al. 2008	74/42	42.5(12.2)/43(12.7)	10.2(3.2)/8.9(2.8)	TMT, German Versions of WAIS-R, LNST of WAIS-III, RBANS
	Dias V et al. 2009	65/49	37.8(10.5)/33.6(9.8)	1.4mg/l (0.4)/1.3mg/l (0.4)	WMS, SDMT, TMT, Stroop Test, Tower of Hanoi Test, COWAT, Bells Test, Comprehension and Similarities of WAIS-R
Depression	Alexopoulos P et al. 2010	25/25	69.8(5.8)/69.4(5.1)	13.3(5.5)/11.3(4.9)	Stroop test, D2-CP
	Ford AH et al. 2013	236/122	Hcy≥13: 62.1, Hcy<13: 62.4/	--	MMSE, CERAD, BNT, VFT, Word List Memory Task
			Hcy≥13: 73.9, Hcy<13: 63.8		
Schizophrenia	Ayesa R et al. 2012	139/99	32.1(10.8)/27(6.1)	13.6(7.1)/11.1(3)	RAVLT, Digit Symbol of WAIS-III, GPT, ToL, RCFT, TMT, Stroop Test, CPT, LNST and Vocabulary of WAIS-III, FAS, Zoo Map Test, Eyes Task,
Cerebrovascular disease	Pavlovic AM et al. 2011	95/41	59.8(10.9)/57.7(10.6)	14.4(5)/8.9(3.9)	MMSE, TMT, WCST, RCFT, RAVLT, BNT, Animal Naming Test
Obstructive sleep apnea	Sales LV et al. 2013	14/13	37.2(6.9)/36(6.1)	16.7(8)/10.7(2.9)	WCST, DSST, DS, RCFT, LM and Verbal Paired Association Tests, Toulouse-Pieron Attention Test, Similarities Test
Multiple sclerosis	Russo C et al. 2008	94/53	36.6(10.4)/37.1(12.1)	13.2(5.6)/9.8(2.5)	RCPM, TMT, RCFT, VFT, VSAT, PWAT, Immediate and Delayed Recall of a Short Story

Abbreviations: AD: Alzheimer's Disease, APM: Raven's Advanced Progressive Matrices, AVLT: Auditory Verbal Learning Test, BDS-IMC: Blessed Dementia Scale-Information Memory Concentration Scale, BFR: Benton's Face Recognition, BNT: Boston Naming Test, BVRT: Benton Visual Retention Test, CDT: Clock Drawing Test, CVLT: Californian Verbal Learning Task, CERAD: Consortium to Establish a Registry for Alzheimer´s Disease, COWAT: Controlled Word Association Test, CPT: Continuous Performance Test, D2-CP: D2 Concentration Performace, DRS: Dementia Rating Scale, DS: Digit Span, DSST: Digit Symbol Substitution Test, F: Female, FAS: FCSRT: Free and Cued Selective Reminding Test, GPT: Grooved Pegboard Test, Hcy: serum homocysteine, HHcy: hyperhomocysteinemia, JLO: Judgment Line Orientation, LM: Logical Memory, LNST: Letter-Number Sequencing Subtest, M: Male, MCI: Mild Cognitive Impairment, MDB: Mental Deterioration Battery, MMSE: Mini-Mental State Examination, PWAT: Paired Word Association Test, RAVLT: Rey Auditory Verbal Learning Test, RBANS: Repeatable Battery for the Assessment of Neuropsychological Status Form A, RCPM: Raven's Coloured Progressive Matrices, RCFT: Rey Complex Figure Test, SBST: Sozel Bellek Surecleri Testi, SD: standard deviation, SDMT: Symbol Digit Modalities Test, STMS: Short Test of Mental Status, TICS: Telephone Interview for Cognitive Status, TMT: Trail Making Test, ToL: Tower of London, VFT: Verbal Fluency Test, VSAT: Visual Search and Attention Test, WAIS-III: Wechsler Adult Intelligence Scale III, WAIS-R: Revised Wechsler Adult Intelligence Scale, WCST: Wisconsin Card Sorting Test, WMS: Wechsler Memory Scale, *: median.

Table 4. Homocysteine and Cognition. Cross-sectional case studies.

Population	Article	N	Age (years)	Hcy (µmol/l)	Neurocognitive tests
			mean (SD)	mean (SD)	
General	Aleman A et al. 2005	400	60.2 (11.3)	13.2 (4.0)	MMSE, DS, DSST, RAVLT, TMT, DART, VFT, D&P
	Elias MF et al. 2005	2096	GroupA: 45.3(2.7);	GroupA: 9.5(3.5);	Similarities of WAIS, WMS, LM, VR, HRNB, VOT, BNT
			GroupB: 54.6(3.2);	GroupB: 9.8 (3.7);	
			GroupC: 65.2(4)	GroupC: 10.3 (3.7)	
	Ravaglia G et al. 2005	540	G1 77.4 (8.0);	G1 14.3;	MMSE
			G2 73.1 (6.0); G3 72.1 (5.3)	G2 12.7; G3 11.1	
	Schafer JH et al. 2005	1047	59.3*	10 (4.1)	BNT, VFT, RCPM, ROCF, TMT, RAVLT, Stroop Test, PPT, FTT, Symbol Digit
	Clark MS et al. 2005	200	59.9 (2.5)	10 (2.7)	CVLT, LNST, NART, Ten Unrelated Words
	Wright CB et al. 2006	3298	66.7 (8.4)	9.2 (3.4)	MMSE
	Feng L et al. 2006	451	64.2 (6.7)	13 (4.6)	RAVLT, TMT, SDMT, VFT, VR, DS, SSP, Block Design Test
	Fischer P et al. 2006	606	75.8 (0.4)	M:14.7 (4.9)/ F: 14 (6)	MMSE
	De Lau L et al. 2007	1033	72.2 (7.4)	11.5 (4.1)	Stroop test, VFT, AVLT, MST
	Elias MF et al. 2008	911	No-ApoE-ε1:62.6 (12.9)/	No-ApoE-ε1:10 (3.6)/	MMSE, Maine-Syracuse Neuropsychological Test Battery
			ApoE-ε1:60.7 (12.3)	ApoE-ε1:9.8 (3.2)	
	Vidal JS et al. 2008	3914	74.2	15.2 (5.6)	MMSE, TMT, BVRT, IST, FWT
	Koike T el al. 2008	99	75.4 (8.1)	11.0 (4.9)	MMSE
	Chin AV et al. 2008	466	75.4 (6.1)	13.9 (6.1)	MMSE, NART-R, VFT, WMS, Digit Symbol Coding of WAIS
	West RK et al. 2011	199	86.8 (4.0)	11.81 (4.3)	TMT, VFT, BNT, Shipley Vocabulary
	Tangney CC et al. 2011	121	78.7 (5.7)	10.9 (3.1)	LM, EBMT, JLO, RSPM, SDMT, BNT, NART, DS
	Xiu LL et al. 2012	1412	>65	--	Short Portable Mental Status Questionnaire
	Moorthy D et al. 2012	1955	66.8	10.7	MMSE,
	Feng L et al. 2013	228	65.4 (6.2)	13.4 (3.8)	DS, SSP, RAVLT, VFT, SDMT, TMT, VAT, DF, OANB
	Allam M et al. 2013	45	68.1 (3.9)	18.6 (12.3)	MMSE, ACE, Clinical Dementia Rating Scale
	Strain JJ et al. 2013	210	5.6 (0.3)	6.1 (1.4)	FTT, PLS, WJ, CBCL, KBIT
	Kong HG et al. 2013	662	71.6 (8.8)	15.9 (7.3)	MMSE, BCAT
	Cheng Y et al. 2014	1889	73.4 (5.9)	17.2 (8.4)	CSID, CERAD, VFT, BNT, WLT, IUTT, Stick Design
	Aruna Agrawal et al 2015	639	--	M:12.7 (4.1) F 10.98 (3.82)	Medicaid Systems
	Raszewski G. et al 2015	170	56.45 (3.54)	14.9 (7.5)	FTT, SDMT, Continuous Performance Test, Verbal Memory, Shifting Attention Test
Alzheimer and cognitive decline	Adunsky A et al. 2005	186	82.6 (7.1)	13.2 (2)	MMSE
	Manders M et al. 2006	157	83*	16.9 (1.5)	MMSE, ADAS-cog
	Kim J et al. 2007	1215	68.7 (5.4) (60-85)	--	Mayo Clinic Criteria
		388	69.2 (5.6)	17.6 (7.4)	
		827	68.4 (5.3)	15.7 (4.8)	
	Sala I et al. 2008	325	74.4 (9.1)	12.8 (5.1)	MMSE, BDS, LM, BVRT, CERAD, BNT, Stroop Test, VFT, TMT, RSPM
	Li L et al. 2008	191	72.6 (9.2)	10.6 (3.6)	MMSE, WMS-R, CERAD, VFT, BNT, CDT, DS, WAIS-R, JLO, TMT, BVMT
	Nilsson K et al. 2010	448	75*	13.6*	MMSE
	Sachdev PS et al. 2012	757	78.5 (4.7)	11.5 (4.2)	MMSE, NART, TMT, RAVLT, LM, BNT, BVRT, VFT, BDT, Digit Symbol Coding of WAIS
	Bonetti F. et al 2015	318	G1:76.5(5.6); G2:76.8(4.9); G3:79.5(4.3); G4:78.2(4.9)	G1:11.2*; G2:12.2*; G3:24*; G4:19.2*	MMSE
Parkinson's Disease	Annanmaki T et al. 2008	40	60.8	9.3	MMSE, WAIS-R, WMS-R, WMS-III, BADS, Stroop Test, VFT
	Martin JJ et al. 2010	58	66 (8.3) (with levo: 66.8 (8.2); without levo:62.8 (8.4))	13.06; with levo 14 (5,1) without levodopa 9.8 (2.5)	MMSE, CDT, VFT, Test Barcelona, NPI
Schizophrenia	Gonzalez C et al. 2014	41	32.3 (9.1)	16.5 (9.7)	WMS-III, RAVLT, WCST, TMT, JLO
Eating Disorders	Frieling H et al. 2005	26	AN:27.8 (10.4);	12	TMT, Stroop Test, ROCF, HAWIER-R, D2, Wechsler Memory Screen Revised
			BN 24.5 (8.4)		
	Wilhelm J et al. 2010	20	AN 26.3 (8.6);	AN 12.6 (6.0);	D2, Stroop Test, SKT, MWT-B
			BN 25.5 (5.9)	BN 10.9 (1.9)	
Bipolar Disease	Osher Y et al. 2008	57	39.4 (12.7)	--	WCST, Stroop Test, BVRT, RAVLT, DS, DSST, Block Design, Animal Naming
Cerebrovascular disease	Wong A et al. 2006	57	noHHcy 68.3 (12.2) HHcy 73.0 (6.8)	--	MMSE, ADAS-cog, MDRS Initiation/Perseveration Subtest
	Tay SY et al. 2006	169	65.5 (11.7)	TACI/PACI 14.5 (5.8);	MMSE
				POCI 14.3 (4.2); LACI 13.7 (5.2)	
Cardiovascular disease	Gunstad J et al. 2006	128	69.1 (7.6)	11.7 (4.9)	MMSE, DS, GPT, COWAT, BVMT-R, BNT, VFT, CFT, VOT, Block Design, CVLT, Stroop Test, TMT, DRS, Digit Symbol Coding, Similarities
	Kloppenborg RP et al. 2011	763	59 (10) HHCY 62.6 (10.7)	M: 14.13 (6.41);	RAVLT, ROCF, VE, BSAT, VFT, DART

			NO HHCY 58.0 (9.9)	F:12.65 (4.71)	
	Ford AH et al. 2012	155	Hcy <15: 65.5 (10.1)	--	CAMCOG, CVLT, Digit Copy and Coding of WAIS
			Hcy ≥15:73.7 (7.9)	--	
Kidney Disease	Tamura MK et al. 2011	3591	58.2 (11.0)	--	3MS
	Troen AM et al. 2012	183	54 (9.5)	15.4 (5.5)	NART, TMT, Digit Symbol Coding, Block Design
Geriatric Patients	Hengstermann S et al. 2009	189	78.6 (7.3)	18.8*	MMSE, SKT
Multiple System Atrophy	Chen D. et al 2015	47	58.74 (10.18)	13.28 (4.13)	MMSE
Epilepsy	Di Rosa G et al. 2013	179	14.0 (4.2)	9.7 (3.1)	Total Intelligence quotient, Verbal Intelligence quotient, Performance Intelligence quotient

Abbreviations: ACE: Addenbrooke's Cognitive Examination, ADAS-cog: Alzheimer's Disease Assessment Scale-cognitive subscale, AN: Anorexia Nervosa, AVLT: Auditory Verbal Learning Test, BADS: Behavioral Assessment of the Dysexecutive Syndrome, BCAT: Basic Cognitive Aptitude Test, BDT: Block Desing Test, BDS: Blessed Dementia Scale, BN: Bulimia Nervosa, BNT: Boston Naming Test, BSAT: Brixton Spatial Anticipation Test, BVMT: Brief Visual Memory Test, BVRT: Benton Visual Retention Test, CAMCOG: Cambridge Cognitive Examination, CBCL*: Child Behavior Checklist,* CDT: Clock Drawing Test, CERAD: Consortium to Establish a Registry for Alzheimer´s Disease, CFT: Complex Figure Test, CSID: Community Screening Instrument for Dementia, CVLT: Californian Verbal Learning Task, DART: Dutch Version of the National Adult Reading Test, DF: *Design Fluency,* DRS: Dementia Rating Scale, DS: Digit Span, DSST: Digit Symbol Substitution Test, D&P: Doors and People Memory Test, D2: Concentration Performance, EBMT: East Memory Boston Test, FTT: The *finger-tapping test,* FWT*: The five word test,* GPT: Grooved Pegboard Test, HAWIER-R: Hamburg Wechsler Intelligence, Hcy: serum homocysteine, HHcy: hyperhomocysteinemia, HRNB: *Halstead–Reitan* Neuropsychological *Test* Battery, IST: *Isaacs Set Test, IUTT: IU Token Test, JLO: Judgment Line Orientation,* KBIT: *Kaufman Brief Intelligence Test,* LM: Logical Memory, LNST: Letter-Number Sequencing Subtest, MMSE: Mini-Mental State Examination, N: number, MST*: Memory Scanning Test,* MWT-B: Mehrfachwahl-Wortschatz-Intelligenztest, NART: National Adult Reading Test, NPI: *Neuropsychiatric inventory,* OANB*: Object and Action Naming Battery,* PLS: Preschool Language Scale, PPT: Purdue Pegboard Test, RAVLT: Rey Auditory Verbal Learning Test, RCPM: Raven's Coloured Progressive Matrices, ROCF: Rey-Osterrieth Complex Figure Test, RSPM: Raven Standard Progressive Matrices, SD: standard deviation, SDMT: Symbol Digit Modalities Test, SKT: Syndrom Kurztest, SSP: Spatial Span, TMT: Trail Making Test, VAT: *Visual* Association *Test*, VE: Visual Elevator Test, VFT: Verbal Fluency Test, VOT: The *Hooper Visual Organization Test,* VR: Visual Reproduction, WAIS-R: Revised Wechsler Adult Intelligence Scale, WCST: Wisconsin Card Sorting Test, WJ: Woodcock-Johnson Test, WLT: Word Learning Test, WMS: Wechsler Memory Scale, 3MS: Modified Mini-Mental State Exam, *: median