Vitamin intake is associated with improved visuospatial and verbal semantic memory in middle-aged individuals

Miles Flitton, Ian A. Macdonald, Helen M. Knight

School of Life Sciences, University of Nottingham, Nottingham NG7 2UH, UK

Objectives: Factors maintaining cognitive health are still largely unknown. In particular, the cognitive benefits associated with vitamin intake and vitamin supplementation are disputed. We investigated self-reported vitamin intake and serum vitamin levels with performance in cognitive factors sensitive to dementia progression in two large middle-aged general population cohorts.

Methods: Survey data were used to assess regular vitamin intake in 4400 NCDS 1958 and 1177 TwinsUK cohort members, and serum homocysteine and B vitamin levels were measured in 675 individuals from the TwinsUK study. Principal component analysis was applied to cognitive test performance from both cohorts resulting in two dementia-sensitive cognitive factors reflecting visuospatial associative memory and verbal semantic memory.

Results: In both cohorts, individuals who reported regular intake of vitamins, particularly B vitamins, showed significantly better performance in visuospatial associative memory and verbal semantic memory ($P < 0.001$). A significant association was also found between homocysteine levels, vitamin serum concentration and visuospatial associative memory performance which indicated that individuals with high B vitamin and homocysteine levels showed better visuospatial associative memory performance than individuals with low vitamin B levels ($P < 0.05$).

Discussion: The findings demonstrate that early dementia-sensitive cognitive changes can be identified in middle-aged asymptomatic individuals and that regular vitamin intake is associated with improved cognitive performance. These findings reinforce the potential cognitive benefits of regular vitamin intake, which should be considered as an economically viable therapeutic strategy for maintaining cognitive health.

Keywords: Vitamins, Visuospatial associative memory, Verbal semantic memory, Cognitive reserve, Homocysteine

Introduction

The burden of dementia on the medical profession and on society as a whole has led to increased research efforts aimed at understanding the earlier stages of cognitive disease. It is now widely accepted that disease pathology may occur decades before clinical symptoms and a diagnosis of dementia. Mild cognitive impairment (MCI), which commonly presents in late middle-age (>60 years), is argued as a prodrome stage of Alzheimer’s disease (AD) as both MCI and AD present with particular deficits in mnemonic domains. However, individuals who develop MCI can remain in a stable clinical phenotype without developing AD or other neurodegenerative disorders while some individuals even improve back to a pre-impairment level of memory performance. Identifying factors that underlie protection against the onset of cognitive decline in middle-age is of great promise to medical science.

Cognitive reserve describes resilience to cognitive decline either due to increased biophysical tolerance to pathology within the brain or improved mental adaptation to cognitive processing. Many neurobiological, genetic, and environmental factors could contribute to cognitive reserve, including lifestyle factors such as exercise and diet. The influence of diet is often studied by assessing the effect of vitamin supplements in randomized controlled trials, or through association with self-reported vitamin consumption in longitudinal cohorts. While the relationship between cognitive function and clinical trial vitamin supplementation appears inconclusive, self-reported vitamin intake and measurements of vitamin levels have been associated with favourable cognitive outcomes.

Numerous dietary supplements have been assessed in both healthy and at-risk groups but no clear consensus has emerged about the specific effects of vitamin...
supplementation or intake on brain function and cognitive performance. The most popular candidates for vitamin studies have been B vitamins, most commonly combinations of vitamin B6, vitamin B12, and folate. Clinical studies investigating B vitamin supplements in individuals with MCI have consistently reported reductions in levels of homocysteine (Hcy) (a substance associated with risk for dementia and cognitive impairment), as well as improved cognitive performance and reduced rate of brain atrophy. In contrast, B vitamin supplementation has been largely ineffective in studies of AD, as exemplified by a large clinical trial which resulted in significantly reduced Hcy levels but no slowing of cognitive decline. Research examining the effect of vitamin supplementation on cognitive performance in healthy control individuals have also produced incongruous results. B vitamin supplementation studies in healthy controls have reported results ranging from no influence on cognitive performance to beneficial effects for multiple cognitive domains. However, in contrast to B vitamin supplements, assessment of B vitamin serum levels and self-reported vitamin intake has been much more consistent in reporting positive links with cognitive performance.

A number of studies which have examined other nutritional supplementation targets such as vitamin D and polyunsaturated fatty acids (PUFAs) also show discrepancy between vitamin supplementation and studies of self-reported vitamin intake or biochemical measurement of vitamin levels. For instance, low vitamin D levels have been linked with increased risk of cognitive impairment. However, the supplementation of vitamin D has proved largely ineffective. This pattern is also observed for vitamin E, where biochemical measures of vitamin levels or reported vitamin intake have correlated with cognitive performance but vitamin supplementation as a potential treatment has had only mixed success in individuals with dementia. In contrast, treatment with, or high recorded levels of, PUFAs appear to have largely beneficial effects on cognition in individuals with dementia or at risk of dementia, particularly if combined with B vitamins.

In the current study, we conducted an analysis of self-reported vitamin intake and vitamin biochemical measurements from two large middle-aged general population cohorts, the National Child Development Study (NCDS) 1958 birth cohort and the TwinsUK cohort. We focused on the relationship between vitamin intake and performance in mnemonic domains sensitive to the progression of dementia, thus aiming to provide a clinically sensitive measure of early cognitive decline.

Methods
Study populations
Access and ethical permission were granted by the UK Data Service and the TwinsUK Resource Executive Committee to obtain data including cognitive variables, biomedical measures, and vitamin intake information by means of two longitudinal cohort studies, the NCDS 1958 and TwinsUK. As the individuals from both cohorts were surveyed multiple times over the years, the data from each cohort is associated with multiple age points. This is discussed in greater detail throughout the methods.

The NCDS 1958 is an ongoing longitudinal study of approximately 17 000 British individuals born within the same week in March 1958. This cohort includes comprehensive survey and assessment data for a wide range of variables, providing a rich resource for examining health across the lifespan. NCDS 1958 was approved by the UK Multi-Centre Research Ethics Committee. Data collection procedures for the NCDS surveys have been described elsewhere. Of the multiple surveys carried out in this cohort, we utilized data from the NCDS 1958 Sweep 8 taken from 2008 to 2009 and the Biomedical Survey taken from 2002 to 2004.

The TwinsUK cohort is a repository of approximately 12 000 monozygotic and dizygotic British twins who have been serially assessed for health traits since 1992. Procedures used for sample and data collection have been described previously. TwinsUK was approved by the Guy’s and St Thomas’ Ethics Committee. Data for TwinsUK were requested and approved through the TwinsUK Resource Executive Committee based at the Department of Twins Research and Genetic Epidemiology at Kings College London.

Data processing
In total, 9790 individuals were made available from the NCDS 1958 study and 1870 individuals were made available from the TwinsUK study. The removal of missing data was then performed on each of the variables used in our analysis (supplementary Figure 1). A summary of variables and descriptive statistics for each cohort is presented in Table 1.

In the NCDS 1958, self-reported questionnaire variables were obtained for daily use of single vitamins, combined vitamins, and folate intake. No further information was available from which to ascertain actual amounts of specific single or combined vitamins taken by cohort members. For our analysis, we derived a new vitamin intake variable from this data by categorizing individuals as having ‘regular vitamin intake’ if they took single vitamins, combined vitamins, or folate more frequently than three times a week. We categorized individuals as having ‘irregular vitamin intake’ if they took single vitamins, combined
vitamins, or folate less frequently than two times a week. Finally, we categorized individuals with no available data for single vitamins, combined vitamins, and folate as ‘non-reported vitamin intake’. We cannot say that these individuals categorically did not take vitamins, but that there was an absence of evidence regarding their vitamin intake. After data processing, 4400 individuals from the NCDS 1958 cohort were categorized as belonging to these three vitamin intake groups (Fig. 1).

In the TwinsUK, self-reported questionnaire variables were obtained on whether people had taken vitamins every day for a month at the time of the survey. For our analysis, we used this vitamin intake variable and categorized those who took vitamins every day for a month as ‘regular vitamin intake’. We categorized individuals who did not take vitamins every day for a month or individuals with no available data as ‘non-reported vitamin intake’. This left 1177 individuals from the TwinsUK cohort (Fig. 1). Further self-reported information describing specific vitamin intake was provided for some of the individuals in the questionnaire data. We assessed this data to ascertain whether individuals were taking any supplements that included B vitamins compared to other supplements that did not include B vitamins and derived a new variable classified as specific B vitamin intake.

In addition to the survey questionnaire data, serum concentrations of homocysteine, vitamin B12, and folate were taken during biomedical visitations in the TwinsUK cohort. Previous cohort studies assessing Hcy levels and vitamin levels have grouped these variables as high or low in terms of their median values. We cannot say that these individuals categorically did not take vitamins, but that there was an absence of evidence regarding their vitamin intake. After data processing, 4400 individuals from the NCDS 1958 cohort were categorized as belonging to these three vitamin intake groups (Fig. 1).

Table 1 Descriptive statistics and mean cognitive test performance of the NCDS 1958 and TwinsUK cohort variables

| Variables                  | NCDS 1958  | TwinsUK  |
|----------------------------|------------|----------|
| Number                     | 4400       | 1177     |
| Sex                        |            |          |
| Male                       | 2174       | –        |
| Female                     | 2226       | 1177     |
| Age                        |            |          |
| Vitamin intake             | 45         | 56 ± 11.5|
| Vitamin levels             | –          | 49 ± 10.8|
| Hcy levels                 | –          | 57 ± 11.2|
| Cognitive tests            | 50         | 51 ± 10.6|
| Vitamin intake             |            |          |
| Regular                    | 732        | 755      |
| Irregular                  | 160        | –        |
| Non-reported               | 3508       | 422      |
| Vitamin levels             |            |          |
| Vitamin B12 (pmol/l)       | –          | 595.3 ± 286.4|
| Folate (nmol/l)            | –          | 12.7 ± 6.1|
| Hcy levels (µmol/l)        | –          | 12 ± 4.1 |
| Cognitive tests            |            |          |
| Word recall                | 6.6 ± 1.5  | –        |
| Delayed word recall        | 5.5 ± 1.8  | –        |
| Animal naming              | 22.5 ± 6.3 | –        |
| Ps & Ws scanning           | 25.9 ± 7.3 | –        |
| Ps & Ws identified         | 21.7 ± 5.9 | –        |
| Delayed matching to sample latency | – | 3686.5 ± 1199.1 |
| Delayed matching to sample correct | – | 17.2 ± 1.8 |
| Pattern recognition memory latency | – | 2176.3 ± 631.5 |
| Pattern recognition memory correct | – | 20.9 ± 2.4 |
| Paired associates learning errors | – | 20.3 ± 17.3 |
| Spatial span length        | –          | 5.5 ± 1.1 |

Information on vitamin intake, biochemical measurements cognitive data was taken from multiple time points in each cohort as explicated by the ages associated with each variable. No vitamin or homocysteine levels were available from NCDS 1958. Hcy, homocysteine.

Details of the NCDS 1958 demographic variables have been presented in detail in previous work while the impact of vitamin intake on cognitive performance has not. Variables such as ethnicity, socio-economic status, exercise, BMI, and further dietary details were not within the scope of our analysis. However, sex and age were both included as covariates where appropriate. All TwinsUK members were female and so sex was not analysed in this cohort. In NCDS 1958, 2174 (49.5%) of the 4400 processed individuals were male and 2226 (50.5%) were female. As the members of NCDS 1958 were all born within the same week in 1958 and hence they are all the same age, age was not analysed in this cohort. However, it should be emphasized that the NCDS 1958 cohort members were 45 years old when they provided self-reported vitamin intake data and 50 years old when they provided cognitive data. TwinsUK members were surveyed on multiple occasions for vitamin intake, vitamin levels, Hcy levels, and cognitive data over the course of the original study. These individuals were on average 49 years old (SD 10.8) when measured for vitamin levels, 57 years old (SD 11.2) when measured for Hcy levels, 51 years old (SD 10.6) when cognitive testing was conducted, and 56 years old (11.5) when providing self-reported vitamin intake data. Owing to the multiple age variables associated with this data, we used the variable with the most complete age information available from this cohort, namely the age at which Hcy measurements took place. This was used as a proxy variable for the effect of age in this cohort.

Cognitive tests

Cognitive test batteries were conducted during visitations in NCDS 1958 and TwinsUK studies with specific
data from these batteries utilized in our analysis. In the NCDS 1958, Word Recall and Delayed Word Recall involved recalling a list of 10 words both immediately and after a delay at the end of the testing session. Animal Naming is a standard semantic fluency test where participants must name as many words as possible from a selected category. The category selected was animals. The Letter Cancellation task is designed to measure attention and visual-spatial scanning abilities. Here, participants are required to scan a page of letters and the number of P’s & W’s they identify (accuracy) and the time taken to do so (speed) are recorded.21

The TwinsUK cohort battery of tests included four Cambridge Neuropsychological Test Automated Battery (CANTAB) tasks; Delayed Matching to Sample (DMS), Paired Associates Learning (PAL), Pattern Recognition Memory (RPM) and Spatial Span (SSP). The CANTAB battery has been widely used in psychological testing and has been noted for its sensitivity to age-related cognitive change.22 The Delayed Matching to Sample task assesses visuospatial memory by presenting a pattern to participants, followed by a delay, before asking participants to identify the pattern from a selection of four. Pattern Recognition Memory presents a series of abstract visual patterns to participants before asking the participants to identify a pattern they had seen as well as a novel pattern they had not seen. Paired Associates Learning also assesses visuospatial memory by displaying ‘boxes’ on the screen that cover one or more patterns. After having seen beneath each ‘box’ on the screen, a pattern is presented in the centre and participants must identify which ‘box’ covers this pattern. Spatial Span is a memory task in which a series of boxes change colour and participants are asked to recall the specific order of colours that appeared. Cognitive test output measures used were Paired Associates Learning Total Errors score, Delayed Matching to Sample Total Correct score and latency, Pattern Recognition Memory Total Correct score and latency, and Spatial Span Length score. In total, cognitive test data were available for 4400 individuals in NCDS 1958 and 196 or 204 individuals in TwinsUK for vitamin supplement intake or vitamin serum levels, respectively.

**Statistical analysis**

Principal component analysis (PCA) is a transformative procedure used to identify the major sources of variance within a select number of variables. PCA was applied to cognitive test performance scores generated separately in the NCDS 1958 cohort and TwinsUK cohort using Varimax rotation. The output values were measured with the Kaiser–Meyer–Olkin (KMO) measure of sampling adequacy and Bartlett’s test of sphericity. Retaining components with an eigenvalue >1 were taken to indicate a single underlying factor. This resulted in the identification of three PCA derived factors reflective of verbal semantic memory (NCDS 1958), visuospatial associative memory (TwinsUK), and visual scanning (both cohorts) as detailed in supplementary Figure 2.

Normal distribution of all available data was assessed using the Kolmogorov–Smirnov and Shapiro–Wilk normality tests. Logarithmic transformation was subsequently applied to variables which were not normally distributed and geometric means
presented in these cases. One-way ANOVAs were performed to assess simple associations between vitamin intake or vitamin levels and cognitive performance. Cohen’s $d$ was used to estimate effect sizes for these associations. For analyses incorporating the influence of Hcy in addition to vitamin intake or vitamin levels, as well as taking into account the covariate effects of age and sex, univariate linear models with *post hoc* correction for multiple comparisons were applied. All analyses were two-tailed and a $P$-value $<0.05$ was considered statistically significant. Statistical analysis was principally carried out using SPSS Statistics version 22.0 and R version 3.2.3.

**Results**

*Measurement of dementia-sensitive cognitive domains*

To evaluate cognitive performance relevant to the progression of dementia, we applied a dimensional reduction technique, PCA, to identify the major sources of variance within the cognitive tests from the NCDS 1958 cohort and the TwinsUK cohort. This led to the emergence of four derived cognitive factors which we construe to reflect three classes of cognitive processing. The first PCA model identified in the NCDS 1958 cohort included Word Recall (0.874), Delayed Word Recall (0.874), and Animal Naming (0.543), and had an eigenvalue of 1.55 accounting for 30.98% of the variance. As the main components assess verbal and semantic memory processing, we named this derived factor ‘verbal semantic memory’. The second PCA model identified in the TwinsUK included Delayed Matching to Sample (0.738), Pattern Recognition Memory (0.714), Paired Associates Learning (−0.685), and Spatial Span (0.671), and had an eigenvalue of 2.38 accounting for 26.50% of the variance. The relationship between measures was in the expected directions, i.e. higher correct scores and lower number of errors made. As the components evaluate visual spatial relationships and recall of visual objects and patterns, we interpreted this factor to reflect ‘visuospatial associative memory’.

The third PCA factor identified in the NCDS 1958 cohort was comprised of the two letter cancellation outcome measures (P’s & W’s Scanned (0.956) and P’s & W’s Identified (0.948) and had an eigenvalue of 2.14 accounting for 42.78% of the variance. The fourth PCA model was generated from the TwinsUK data an included latency scores for Delayed Matching to Sample (0.869) and Pattern Recognition Memory (0.714) and had an eigenvalue of 1.39 accounting for 15.41% of the variance. Both the third and fourth factor we interpret as reflecting one form of cognitive processing, ‘visual scanning’ (Fig. 1). Correlation coefficients support the relationship between these derived cognitive factors and their constituent cognitive tests (values presented in supplementary Figure 2).

Two of these derived cognitive factors, visuospatial associative memory and verbal semantic memory, have previously been associated with sensitivity to dementia progression. Visuospatial associative memory tests have been highlighted in predicting progression from questionable dementia to AD as well as for classifying individuals with MCI. Verbal semantic tests have also been used to predict progression to AD as well as distinguishing between amnestic and non-amnestic diagnoses of MCI. In contrast, visual scanning is a more fundamental measure of general attention, providing a useful comparison to the dementia-sensitive factors.

*Influence of vitamins on cognitive performance*

Using these dementia-sensitive derived cognitive factors, we assessed self-reported vitamin intake and cognitive performance in the NCDS 1958 and TwinsUK general population cohorts. In the NCDS cohort, self-reported regular vitamin intake was associated with significantly better performance on both verbal semantic memory (regular intake = 0.23 versus non-reported = −0.06, $F = 26.932$, $P < 0.001$, $d = 0.29$) and visual scanning (regular intake = 0.09 versus non-reported = −0.02, $F = 4.314$, $P = 0.01$, $d = 0.12$). Females performed better than males in both verbal semantic memory ($P = 0.014$) and visual scanning ($P = 0.003$), irrespective of vitamin intake. In the TwinsUK cohort, self-reported regular vitamin intake was associated with significantly better performance on visuospatial associative memory (regular intake = 0.14 versus non-reported = −0.44, $F = 15.454$, $P < 0.001$, $d = 0.61$) (Fig. 2A). Moreover, individuals who specifically reported taking B vitamins showed better visuospatial associative memory performance compared to those who took other vitamins (B vitamins = 0.37 versus other vitamins $= −0.02$, $F = 5.170$, $P = 0.025$, $d = 0.42$). No influence of vitamin intake was observed for visual scanning (regular intake $= −0.03$ versus non-reported $= 0.001$, $F = 0.060$, $P = 0.8$, $d = 0.03$).

Assessment of serum concentrations of vitamin B12 and folate in TwinsUK showed no association with visuospatial associative performance (high vitamin B12 or folate $= −0.16$ versus low vitamin B12 and folate $= 0.11$, $F = 1.221$, $P = 0.120$, $d = 0.17$), contrasting with the self-reported regular vitamin supplement findings in these cohorts. Age was found to be significantly associated with cognitive performance in TwinsUK, but did not influence the aforementioned relationships between vitamin supplement intake and visuospatial associative memory ($P < 0.001$) or visual scanning ($P = 0.723$) performance.
Interactive influence of vitamins and homocysteine on cognitive performance

Previously published findings have identified Hcy as a major risk factor for dementia and MCI. Measurements of Hcy were unfortunately not taken in the NCDS 1958 cohort. However, both self-reported regular vitamin intake (regular intake = 12.07 µmol/l versus non-reported = 11.08 µmol/l, \( F = 19.905, P < 0.001, d = 0.27 \)) and high serum levels of vitamin B12 and folate (high vitamin B12 and folate = 11.48 µmol/l versus low vitamin B12 and folate = 10.17 µmol/l, \( F = 6.364, P = 0.001, d = 0.31 \)) were associated with significantly lower levels of Hcy in TwinsUK (Fig. 2B).

Interestingly, an interaction was found between Hcy levels, serum vitamin levels, and visuospatial associative memory performance, where individuals with the highest levels of Hcy and high vitamin B12 levels performed significantly better than those with low vitamin B12 levels \( (P = 0.032) \) (Fig. 2C). Moreover, the addition of age as a covariate increased the statistical significance of this finding \( (P < 0.001) \). As predicted, individuals with low vitamin B12 levels and lower Hcy performed better than those with low vitamin B12 levels and high Hcy, but this difference did not reach statistical significance \( (P = 0.110) \). No such interaction was seen for the visual scanning factor suggesting that the observed relationship between Hcy and B vitamins is specifically relevant to dementia-sensitive cognitive performance.

Discussion

Using well-collated survey and biomedical datasets from the NCDS 1958 and TwinsUK general population...
cohorts, our analysis revealed evidence of a positive association between self-reported regular vitamin intake and cognitive performance that was particularly significant in the dementia-sensitive visuospatial associative and verbal semantic memory factors. Moreover, we found that individuals with the highest levels of Hcy and high levels of B vitamins showed better visuospatial associative memory performance than those with low levels of B vitamins. These findings suggest that cognitive domains sensitive to dementia progression can be assessed in general population cohorts before the clinical onset of cognitive decline seen in MCI, and that performance in these domains can be altered through regular vitamin intake.

The mnemonic benefits associated with middle-age vitamin intake in this study imply early protection against cognitive impairment, long before the age where vitamin intervention treatments are commonly studied in randomized control trials. B vitamin intake particularly follows a non-linear trajectory, as high levels of folate in elderly individuals have been associated with cognitive decline while moderate levels of supplementation resulted in health benefits. This supports the suggestion that moderate B vitamin use in middle-age could boost cognitive reserve before encountering age-associated cognitive risk. A similar argument has also been put forward with regards to cognitive enhancing nootropic drugs.

The use of cohort studies comes with inherent strengths and limitations. Variables are commonly collected during a number of surveys and hence obtained at different time points. However, while we acknowledge that this was the case for the NCDS 1958 and TwinsUK cohorts, this has not impeded the study of cognition using longitudinal cohort data.

As with previous work exploring the relationship between vitamins and cognition, some incongruence between the qualitative measure of self-reported vitamin intake and the quantitative measure of serum vitamin levels was evident in our analyses. Specifically, self-reported supplement intake showed significant associations with cognitive performance, whereas vitamin levels did not. However, deeper analysis of B vitamin levels coupled with Hcy levels confirmed a positive association with cognitive function. This alludes to a mechanism of action via B vitamins and Hcy, either through excitotoxicity, impeded neural circuitry, or perturbed molecular pathways. Indeed, disturbance of the one-carbon cycle – which metabolizes Hcy and requires B vitamins – could influence cognitive function via disrupted methyl donation for DNA, histone, and non-histone protein methylation pathways.

It is possible that self-reported vitamin intake data, rather than highlighting a causal relationship between vitamin use and cognition, acts instead as a proxy for other environmental factors. As further nutritional and lifestyle information was not available from either NCDS 1958 or TwinsUK, we can only speculate as to any possible underlying relationships. For example, individuals who report taking vitamin supplements may be more health-conscious and more likely to exercise regularly, behaviour that is generally agreed to benefit cognition. Simply taking supplements could also have a placebo effect, as reported in previous vitamin trials. While studies of multivitamin supplementation have had varied results, the qualitative self-reporting data analysed in this study demonstrates that multivitamin intake as opposed to any single vitamin is most likely to benefit cognitive function. However, further randomized controlled trials assessing single and multivitamin supplementation will be needed to reach a firm conclusion surrounding vitamin intake and cognitive function.

As the focus of dementia research shifts from treatment options to intervention strategies, individuals in middle-age who are asymptomatic for cognitive decline will become the targets for boosting cognitive reserve. The sensitivity of visuospatial associative and verbal semantic memory to early changes in cognition should prove valuable for both academic and therapeutic work in dementia prevention. The importance of regular vitamin intake highlighted in this study suggests that supplementation should be advocated in healthy middle-aged individuals, particularly those with elevated Hcy levels who are at higher risk of developing dementia. With credible pharmacological treatments for dementia currently beyond the horizon, vitamin supplementation may provide a practical and economically viable alternative in the effort to prevent dementia-related cognitive decline.

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