# Online assessment of risk factors for dementia and cognitive function in healthy adults

J Huntley PhD[a*], A. Corbett PhD[b], K Wesnes PhD[bc], H Brooker BSc[c,] R Stenton BSc[d], A Hampshire PhD[e], C Ballard MD[b]

[a]Department of Old Age Psychiatry, Institute of Psychiatry, Psychology and Neuroscience, King's College London, UK. [b]University of Exeter, Exeter, UK. [c]Wesnes Cognition, UK. [d]Manta Software Ltd, Cambridge, UK. [e]Division of Brain Sciences, Imperial College London, London, UK. * corresponding author.

**Author Accepted manuscript**

Key Points

1) This paper analyses a large dataset of 14201 individuals to assess whether known modifiable risk factors for dementia are associated with cognitive performance in non-demented individuals in late midlife and older age (over 50 years).

2) Higher educational achievement, the presence of a close confiding relationship, moderate alcohol intake and exercise were significantly associated with better cognitive performance.

3) A diagnosis of depression, history of stroke and being underweight were significantly negatively associated with cognitive performance

4) This study provides further support for public health interventions that seek to manage modifiable risk factors for dementia across the lifespan.

Keywords: risk factors, online assessment, cognitive function, prevention

Word count: 3,497

**Abstract**

**Objective**: Several potentially modifiable risk factors for cognitive decline and dementia have been identified, including low educational attainment, smoking, diabetes, physical inactivity, hypertension, midlife obesity, depression, and perceived social isolation. Managing these risk factors in late midlife and older age may help reduce the risk of dementia, however it is unclear whether these factors also relate to cognitive performance in older individuals without dementia.

**Method**: Data from 14201 non-demented individuals aged > 50 years who enrolled in the online PROTECT study were used to examine the relationship between cognitive function and known modifiable risk factors for dementia. Multivariate regression analyses were conducted on four cognitive outcomes assessing verbal and spatial working memory, visual episodic memory and verbal reasoning.

**Results**: Increasing age was associated with reduced performance across all tasks. Higher educational achievement, the presence of a close confiding relationship and moderate alcohol intake were associated with benefits across all four cognitive tasks, and exercise was associated with better performance on verbal reasoning and working memory tasks. A diagnosis of depression was negatively associated with performance on visual episodic memory and working memory tasks, whereas being underweight negatively affected performance on all tasks apart from verbal working memory. A history of stroke was negatively associated with verbal reasoning and working memory performance.

**Conclusion**: Known modifiable risk factors for dementia are associated with cognitive performance in non-demented individuals in late midlife and older age. This provides further support for public health interventions that seek to manage these risk factors across the lifespan.

**Introduction**

Dementia is currently the commonest cause of mortality in the UK (Patel 2016). There are currently no disease modifying agents available and despite early promise, recent phase 3 pharmaceutical trials have been disappointing (Doody et al. 2014). There is therefore an urgent need for effective primary prevention and several factors have been recognized as important during mid-life that may increase the risk of developing dementia. A recent analysis has calculated population-attributable risks (PAR) of Alzheimer's disease on seven potentially modifiable risk factors for dementia. The highest PAR was for low educational attainment, followed by smoking, physical inactivity, depression, midlife hypertension, diabetes and midlife obesity (Norton et al. 2014). Although the prevalence of dementia continues to grow, both globally and in the UK, recent data suggests that the rate of increase may be slowing in some developed countries (Matthews et al. 2016). An explanation for this may be the recognition and reduction of modifiable risk factors across the life course. It is clear that the strongest risk factor for cognitive decline and dementia is age (Niu et al. 2016); however it is unclear how early modifiable factors such as cerebrovascular risk factors, depression, and lifestyle factors such as exercise and education impact on cognitive function. Therefore there is interest in how early these modifiable risk factors should be targeted to reduce dementia risk and improve cognitive function (Norton et al. 2014). Resilience to dementia has been formulated in terms of 'cognitive reserve', described as the ability of the brain to tolerate the neuropathological effects of Alzheimer's disease or cerebrovascular disease processes, without demonstrating cognitive or functional decline (Stern 2012). It is increasingly recognized that many of these underlying neuropathological processes take place many years before the clinical onset of dementia (Ritchie et al. 2016), and neuroimaging techniques, such as amyloid PET imaging have demonstrated characteristic patterns of beta amyloid deposition years before cognitive deficits are apparent (Villemagne et al. 2013). The recognition that neuropathological processes may

begin in late mid-life has increased the focus on preventative approaches to target recognized modifiable risk factors for dementia. What is less clear though, is how these risk factors may impact on cognitive function in patients without known cognitive impairment or dementia. Although each of these risk factors have been found to potentially increase risk of developing dementia, it is important to establish whether they significantly affect cognitive function either independently or in combination prior to the development of dementia. There is evidence that episodic memory and reasoning are particularly sensitive to age-related decline (Ferreira et al. 2015), however it is unclear if known risk factors for dementia specifically affect these cognitive domains.

The PROTECT Study is an online platform to investigate genetics and cognitive function in ageing. The aim is to conduct a 10- year longitudinal study with annual assessment of cognitive function, lifestyle and medical history in order to predict cognitive trajectory and risk. The use of an online platform for data collection enables the recruitment of very large numbers of people, and examination of the baseline data provides an opportunity to assess whether the presence of potentially modifiable risk factors in the study population contributes to cognitive function. This study will address the question of whether recognized risk factors for dementia are associated with cognitive function in healthy individuals > 50 years.

**Method**

*Study Design and participants:* Cross-sectional analysis of data from the ongoing online PROTECT Study (www.protectstudy.org.uk), a cohort of adults aged 50 and over, launched in November 2015. Inclusion criteria were adults over the age of 50 years, who live in the UK, have a good working understanding of English and are able to use a computer with Internet access. An established diagnosis of dementia was an exclusion criteria for the study. The study was widely publicized in the national media, in addition to

recruitment via established cohorts of older adults. Potential participants registered via the online website and downloaded the study information sheet. If they wished to participate in the study they read and signed an online consent form through an ethically approved online process.

*Demographic, lifestyle and medical data collection:* Following enrolment into the study, participants completed a series of online baseline questionnaires regarding demographic and lifestyle information. These included baseline demographic information on age, gender, education, ethnicity, medical history and current medication and a lifestyle questionnaire. For the current analysis, responses to items in the online questionnaires that provided data on the presence of risk factors for dementia were included. These factors were education, smoking, depression, physical activity, perceived social isolation, hypertension, diabetes and obesity. Additional factors in the data set that were hypothesised as being potentially relevant were also included, namely alcohol use, age, a diagnosis of heart disease or stroke, marital status and gender. Please see supplementary materials for further description of the risk factor variables.

*Cognitive assessment:* Cognitive assessment was conducted using a validated online cognitive test package consisting of four tasks (Corbett et al. 2015): 1) The Paired Associate learning task (PAL) (Owen et al. 1993) to assess visual episodic memory. 2) Self-Ordered-Search task (Owen et al. 1990) assessing spatial working memory (SWM). 3) Digit span task (DS) (Huntley et al. 2017) assessing verbal working memory. 4) Grammatical Reasoning task (Baddeley 1968) assessing verbal reasoning (VR). Participants were asked to complete each task on three occasions during one week to provide a baseline assessment. Please see supplementary methods for further details of the cognitive tasks.

*Statistical analysis:* Hierarchical multivariate regression analyses were conducted. Separate analyses were conducted with summary scores on each of the four cognitive measures as the dependent variable. Independent variables were included into the model in a hierarchy based on known risk factors for dementia from the literature (Norton et al 2014). For all variables with ordinal responses, dummy variables were created. Please see supplementary methods for further details of independent variables.

**Results**

Between November 2015 and April 2016, 14,201 participants were recruited into the study and completed all baseline cognitive tasks and baseline questionnaires enabling them to be included in the analysis. Demographics of the study participants are shown in Table 1. The mean age of participants was 62.05 (SD 7.14), range 50-101. As shown in Table 1, the participants were 71.5% female, 98.3% white, 68.5% married, 48.2% retired and 84.1% had completed at least A-level education. Participants' responses to the questions relating to each of the risk factor variables are shown in Table 2 and mean cognitive scores are shown in Supplementary Table 1.

**Overall model Summary**

Results of the hierarchical model summaries for each of the cognitive variables are shown in supplementary tables 2 - 5. For all four cognitive tasks the largest change was between model 8 and model 9 i.e. the addition of the age, gender, alcohol, marital status, stroke and heart disease variables. The overall model with all variables included was significant for all four cognitive tasks (Digit span adjusted R Square 0.037, $F(39, 14199) = 14.859$, $p < 0.001$; paired associates task, adjusted R square 0.055, $F(39, 14200) = 22.122$, $p < 0.001$; verbal learning task, adjusted R square 0.127, $F(39, 14199) =$

53.767, p< 0.001;  spatial working memory task,  adjusted r square 0.056, F (39, 14200) = 22.487, P < 0.001).

**Analysis of independent variables**

*Age and gender*

Increasing age was significantly associated with reduced performance on all cognitive tasks.  Compared to the youngest age group (50-54 years), each increase in five-year age band was associated with increasingly poor cognitive performance, with the exception of the oldest age group (>90 years).  Female gender was associated with poorer performance on the PAL (β = -0.035, p = 0.012), DS (β = -0.142, p < 0.001) and SWM (β = -0.453, p < 0.001).  Individual regression coefficients for each independent demographic variable and cognitive task are shown in Table 3.

*Education*

For all four cognitive tasks there was a significant effect of education.  Compared to the lowest level of education (GCSE), undergraduate (PAL β = 0.098 (SE 0.019) p < 0.001; VR β = 4.828 (SE 0.218) p < 0.001; DS β = 0.275 (SE 0.035) p < 0.001; SWM β = 0.400 (SE 0.055) p < 0.001) postgraduate (PAL β = 0.043 (SE 0.021) p < 0.05; VR β = 4.845 (SE 0.251) p < 0.001; DS β = 0.298 (SE 0.041) p < 0.001; SWM β = 0.174 (SE 0.063) p < 0.001) and doctorate  (PAL β = 0.102 (SE 0.036) p < 0.01; VR β = 6.460 (SE 0.422) p < 0.001; DS β = 0.387 (SE 0.069) p < 0.001; SWM β = 0.506 (SE 0.106) p < 0.001) level of education were all associated with higher cognitive scores across all tasks.  A-Level education was associated with higher performance in all tasks except spatial working memory and a vocational qualification was associated with higher performance on all tasks except paired associates learning (Table 3).

*Lifestyle factors*

Smoking was significantly associated with a higher score on verbal reasoning (β = 0.421 (SE 0.144) p = 0.003), but had non- significant negative effects on paired associates learning and spatial working memory. Recent physical exercise was associated with a significantly higher performance on verbal reasoning (β = 1.095 (SE 0.151) p < 0.001) and digit span (β = 0.130 (SE 0.025), p < 0.001). Drinking alcohol at least once per week was associated with greater performance on all four tasks compared to no alcohol intake (PAL β = 0.074, p = 0.003; VR β = 1.101, p < 0.001; DS β = 0.1, p = 0.036; SWM β = 0.238, p = 0.001). Drinking alcohol between once a month and once per week was also associated with improved performance on the PAL (β = 0.057, p = 0.046) and SWM (β = 0.170, p = 0.043) compared with not drinking alcohol (Table 4).

*Medical factors*

A diagnosis of depression was significantly associated with poorer performance on all tasks (PAL β = -0.049 (SE 0.014) p < 0.001), DS β = -0.115 (SE 0.027) p < 0.001), SWM β = -0.199 (SE 0.041) p < 0.001), except verbal reasoning. Similarly, a history of a stroke was negatively associated with performance on all tasks (VR β = -2.263, p < 0.001; DS β = -0.202, p = 0.033; SWM β = -0.423, p = 0.004) except the PAL. There was no significant association between heart disease or self-reported hypertension and cognitive performance, and a diagnosis of diabetes was only negatively associated with performance on the SWM task (β = -0.230, p = 0.014) (Table 4). Analysis of BMI demonstrated that compared to being within the normal BMI range, being underweight was significantly negatively associated with performance on all cognitive tasks except digit span (PAL β = -0.131, p = 0.025; VR β= -1.725, p = 0.013; SWM β = -0.422, p = 0.015). There were no effects of being overweight or very obese, although being obese was negatively associated with performance on the DS task (β = -0.101, p = 0.003) (Table 4).

*Social factors*

Compared to being married, being widowed was associated with increased score on PAL ($\beta = 0.054$, $p = 0.036$) and SWM ($\beta = 0.204$, $p < 0.01$), being divorced was associated with increased score on VR task ($\beta = 0.513$, $p = 0.029$), and being single was associated with increased score on the Verbal reasoning ($\beta = 0.869$, $p = 0.005$) and digit span task ($\beta = 0.147$, $p = 0.003$) (Table 3). The absence of a close confiding relationship was significantly associated with poorer performance on all four cognitive tasks, with significant improvements on all cognitive tasks seen with participants who responded that they had been in a confiding relationship 'rarely' (PAL $\beta = 0.073$, $p = 0.042$), VR $\beta = 2.645$, $p < 0.001$); DS $\beta = 0.184$, $p = 0.008$; SWM $\beta = 0.273$, $p = 0.01$); 'sometimes' (PAL $\beta = 0.064$, $p = 0.012$; VR $\beta = 2.716$, $p < 0.001$; DS $\beta = 0.228$, $p < 0.001$; SWM $\beta = 0.362$, $p < 0.001$); 'often' (PAL $\beta = 0.072$, $p = 0.006$; VR $\beta = 2.261$, $p < 0.001$, DS $\beta = 0.249$, $p < 0.001$; SWM $\beta = 0.390$, $p < 0.001$) or 'very often' (PAL $\beta = 0.96$, $p < 0.001$, VR $\beta = 2.417$, $p < 0.001$.;DS $\beta = 0.255$, $p < 0.001$; SWM $\beta = 0.435$, $p < 0.001$) (Table 4).

**Discussion**

This study examines whether recognized risk factors for dementia are associated with cognitive function in a large cohort of healthy adults over 50 years of age, and reveals a number of trends relating to risk and cognitive performance. Perhaps unsurprisingly age was a significant contributor to cognitive function, with each five-year increase in age group, except for the > 90 year group, associated with a significant reduction in score on all four cognitive tasks, compared to the youngest age group. This finding builds on previous studies which have demonstrated an age effect across a range of cognitive domains including processing speed, episodic memory and executive function (Gunstad et al. 2006), and adds robust data from a very large cohort of adults in late midlife. This also provides important validity

to the online assessment approach, in parallel with the recently published validation of other online cognitive tests being used in this study (Wesnes et al. 2017).

*Education and Lifestyle factors*

Educational attainment was significantly positively associated with cognitive performance. Previous studies have demonstrated the importance of education as a risk factor for dementia (Valenzuela, Sachdev 2006), however there are inconsistencies in the literature regarding what constitutes 'low' or 'high' levels of education. (Sharp, Gatz 2011). The sample in the current study is a highly-educated population, as the lowest level of education represented (and reference group in the analysis) is GCSE level (i.e. education up to age 16) which may highlight the challenge of targeting lower educated groups for intervention. The finding that higher education, particularly to a postgraduate level is associated with higher cognitive performance is unsurprising, however nonetheless provides further impetus for the importance of continuing education at a population level.

The positive effects of exercise and moderate alcohol intake on cognitive function have been previously documented. Physical inactivity has been estimated to account for a worldwide population attributable risk of dementia of 12.7% (Norton et al. 2014). The effects of physical exercise on cognition and dementia prevention are likely to be related to both indirect effects of exercise on other modifiable cerebrovascular risk factors and direct effects on hippocampal neurogenesis (Erickson et al. 2011), cerebral blood flow and neurotropic growth factors (Brown, Peiffer & Martins 2013). There is evidence that moderate alcohol intake (described as up to 15.0g of alcohol (about one drink) per day) can be associated with some cognitive benefits compared to non-drinkers (Stampfer et al. 2005, Ruitenberg et al. 2002) and our findings that there were benefits of drinking once per week would be in keeping with this and previous studies (Britton, Singh-Manoux & Marmot 2004). It is important to note that this analysis provides no information on drinking more heavily and there is evidence that excessive alcohol

intake is significantly detrimental to cerebrovascular health (Klatsky, Armstrong & Friedman 1989). It is also notable that smoking was not significantly negatively associated with poorer cognitive function in this sample, and indeed was associated with a greater score on the verbal reasoning task. Previous studies have suggested that nicotine may be associated with improved cognitive function (Rezvani, Levin 2001) which may in part explain this result.

*Social factors*

A more surprising result was the strong association between a lack of a close confiding relationship during adult life and cognitive ability. A perceived sense of social isolation has been found to be associated with impaired cognitive function (Cacioppo, Hawkley 2009). Previous studies have demonstrated that perceived social isolation is related to the quality rather than quantity of social interaction (Hawkley et al. 2008) and feelings of loneliness, rather than social isolation *per se*, have been shown to predict cognitive decline and risk of Alzheimer's disease (Wilson et al. 2007, Holwerda et al. 2014). Marital status was included in the model as an objective marker of some degree of social support, and these results therefore suggest that a subjectively close relationship is important in maintaining cognitive function. It is difficult to assess the causal relationship between perceived social isolation and cognition, and there is evidence that cognitive decline and early dementia may lead to increasing social isolation (Cohen-Mansfield, Shmotkin & Goldberg 2009), however there is also evidence that experimental manipulation of perceived loneliness can affect cognition in the absence of change in objective isolation (Baumeister, Twenge & Nuss 2002). Further research into the impact of subjective loneliness and isolation on cognitive decline would be useful. The increasing context of online social engagement and its potential to reduce perceived and objective social isolation in older adults also requires further investigation.

*Medical factors*

In terms of cerebrovascular and cardiovascular health and risk factors, a diagnosis of a stroke was associated with poorer performance on the verbal reasoning and working memory tasks, however there was no effect of hypertension or heart disease in this sample, and a diagnosis of diabetes was only associated with negative performance on the spatial working memory task. It is possible that the effects of cerebrovascular risk factors only become clinically apparent at a stage when they have contributed to more significant cerebrovascular disease and damage, and in this context it is perhaps unsurprising that there were no effects of these risk factors on cognitive function when examined independently and with the effects of age separately modelled. This study also found that obesity was only negatively associated with one cognitive task, whilst being underweight had significantly negative effects on short term memory, verbal reasoning and spatial working memory. This is in keeping with literature that suggests that being under-nourished can have significant effects on cognition (Sabia et al. 2009).

The gender effects found in this study are in keeping with literature that suggests that older men have advantages in visuospatial function, whilst women have advantages in language and processing speed which were not assessed in this study (Parsons et al. 2005).

The PROTECT study has been successful in recruiting a very large cohort of individuals and provides a rich source of data, however the study has several limitations. Firstly, all data on lifestyle, social and medical factors was self-reported by individuals in their own homes. It is therefore not possible to objectively verify the accuracy of some of the responses, and this issue is likely to impact most heavily on medical factors such as hypertension and depression which may not have received a formal diagnosis, or indeed be accurately reported by the individual.

Data on exercise and other lifestyle factors is based on a purposely brief lifestyle questionnaire that provides initial indications of the behavior and activities of the cohort. Whilst valuable, this limits the

depth of the data, and therefore warrants further investigation of individual factors through future research. For example, it would be interesting to explore regularity and type of physical exercise across the cohort in order to build on the data reported here. Similarly, the confiding relationship statement 'since the age of 16 I have had a close confiding relationship', encourages a subjective and categorical response, and there is no further objective data in the current data set on loneliness or social isolation to explore this variable further. It should also be noted that the overall sample is self-selected, and represents a skewed sample in which white, highly-educated women are overrepresented. Whilst this may limit the overall generalizability of the findings, the results still provide important information on the effects of these risk factors on cognition in a very large study population. It also provides valuable insight into a self-selecting cohort who are most likely to engage with online interventions and platforms, which are an increasing focus for public health approaches. Nonetheless, it will be critical to expand the recruitment of the PROTECT study to improve representation of wider demographic groupings.

Finally, the size of the R square statistic for each of the cognitive tasks remains relatively small, indicating that other variables also impact on the model, most likely individual cognitive ability amongst others. However, the findings reach statistical significance and, when applied at a population level, as is seen with the estimates of PAF for modifiable risk factors, the demonstration that some factors can have an impact on cognitive function in mid- life and old age provides greater emphasis for a preventative approach to cognitive decline.

**Conclusion**

This study provides evidence that potentially modifiable factors for dementia such as education, depression, perceived social isolation, diabetes and exercise are associated with cognitive function in

non-demented individuals in mid-life and older age. This suggests that not only should these factors be targeted to reduce future dementia risk, but also to potentially improve cognitive function and provides further support for public health interventions that seek to manage these risk factors across the lifespan.

**Disclosures**: Keith Wesnes owns Wesnes Cognition Ltd and consults for various companies involved in clinical trials. The authors declare no other conflict of interests.

**Acknowledgements:** This study was supported by the National Institute for Health Research (NIHR) Mental Health Biomedical Research Centre and Dementia Unit at South London and Maudsley NHS Foundation Trust and Institute of Psychiatry, King's College London.

**References**

Baddeley, A.D. 1968, ".A three-minute reasoning test based on grammatical transformation. ", Psychometric Science, vol. 10, pp. 341-342.

Baumeister, R.F., Twenge, J.M. & Nuss, C.K. 2002, "Effects of social exclusion on cognitive processes: anticipated aloneness reduces intelligent thought", Journal of personality and social psychology, vol. 83, no. 4, pp. 817-827.

Britton, A., Singh-Manoux, A. & Marmot, M. 2004, "Alcohol consumption and cognitive function in the Whitehall II Study", American Journal of Epidemiology, vol. 160, no. 3, pp. 240-247.

Brown, B., Peiffer, J. & Martins, R. 2013, "Multiple effects of physical activity on molecular and cognitive signs of brain aging: can exercise slow neurodegeneration and delay Alzheimer's disease", Molecular psychiatry, vol. 18, no. 8, pp. 864-874.

Cacioppo, J.T. & Hawkley, L.C. 2009, "Perceived social isolation and cognition", Trends in cognitive sciences, vol. 13, no. 10, pp. 447-454.

Cohen-Mansfield, J., Shmotkin, D. & Goldberg, S. 2009, "Loneliness in old age: longitudinal changes and their determinants in an Israeli sample", International psychogeriatrics, vol. 21, no. 6, pp. 1160-1170.

Corbett, A., Owen, A., Hampshire, A., Grahn, J., Stenton, R., Dajani, S., Burns, A., Howard, R., Williams, N., Williams, G. & Ballard, C. 2015, "The Effect of an Online Cognitive Training Package in Healthy Older Adults: An Online Randomized Controlled Trial", Journal of the American Medical Directors Association, vol. 16, no. 11, pp. 990-997.

Doody, R.S., Farlow, M., Aisen, P.S. & Alzheimer's Disease Cooperative Study Data Analysis and Publication Committee 2014, "Phase 3 trials of solanezumab and bapineuzumab for Alzheimer's disease", The New England journal of medicine, vol. 370, no. 15, pp. 1460.

Erickson, K.I., Voss, M.W., Prakash, R.S., Basak, C., Szabo, A., Chaddock, L., Kim, J.S., Heo, S., Alves, H., White, S.M., Wojcicki, T.R., Mailey, E., Vieira, V.J., Martin, S.A., Pence, B.D., Woods, J.A., McAuley, E. & Kramer, A.F. 2011, "Exercise training increases size of hippocampus and improves memory", Proceedings of the National Academy of Sciences of the United States of America, vol. 108, no. 7, pp. 3017-3022.

Ferreira, N., Owen, A., Mohan, A., Corbett, A. & Ballard, C. 2015, "Associations between cognitively stimulating leisure activities, cognitive function and age-related cognitive decline", International journal of geriatric psychiatry, vol. 30, no. 4, pp. 422-430.

Gunstad, J., Paul, R.H., Brickman, A.M., Cohen, R.A., Arns, M., Roe, D., Lawrence, J.J. & Gordon, E. 2006, "Patterns of cognitive performance in middle-aged and older adults: A cluster analytic examination", Journal of geriatric psychiatry and neurology, vol. 19, no. 2, pp. 59-64.

Hawkley, L.C., Hughes, M.E., Waite, L.J., Masi, C.M., Thisted, R.A. & Cacioppo, J.T. 2008, "From social structural factors to perceptions of relationship quality and loneliness: the Chicago health, aging, and social relations study", The journals of gerontology.Series B, Psychological sciences and social sciences, vol. 63, no. 6, pp. S375-84.

Holwerda, T.J., Deeg, D.J., Beekman, A.T., van Tilburg, T.G., Stek, M.L., Jonker, C. & Schoevers, R.A. 2014, "Feelings of loneliness, but not social isolation, predict dementia onset: results from the Amsterdam Study of the Elderly (AMSTEL)", Journal of neurology, neurosurgery, and psychiatry, vol. 85, no. 2, pp. 135-142.

Huntley, J.D., Hampshire, A., Bor, D., Owen, A. & Howard, R.J. 2017, "Adaptive working memory strategy training in early Alzheimer's disease: randomised controlled trial", The British journal of psychiatry : the journal of mental science, vol. 210, no. 1, pp. 61-66.

Klatsky, A.L., Armstrong, M.A. & Friedman, G.D. 1989, "Alcohol use and subsequent cerebrovascular disease hospitalizations", Stroke, vol. 20, no. 6, pp. 741-746.

Matthews, F.E., Stephan, B.C., Robinson, L., Jagger, C., Barnes, L.E., Arthur, A., Brayne, C. & Cognitive Function and Ageing Studies (CFAS) Collaboration 2016, "A two decade dementia incidence comparison from the Cognitive Function and Ageing Studies I and II", Nature communications, vol. 7, pp. 11398.

Niu, H., Alvarez-Alvarez, I., Guillen-Grima, F. & Aguinaga-Ontoso, I. 2016, "Prevalence and incidence of Alzheimer's disease in Europe: A meta-analysis", Neurologia (Barcelona, Spain), .

Norton, S., Matthews, F.E., Barnes, D.E., Yaffe, K. & Brayne, C. 2014, "Potential for primary prevention of Alzheimer's disease: an analysis of population-based data", The Lancet.Neurology, vol. 13, no. 8, pp. 788-794.

Owen, A.M., Beksinska, M., James, M., Leigh, P.N., Summers, B.A., Marsden, C.D., Quinn, N.P., Sahakian, B.J. & Robbins, T.W. 1993, "Visuospatial memory deficits at different stages of Parkinson's disease", Neuropsychologia, vol. 31, no. 7, pp. 627-644.

Owen, A.M., Downes, J.J., Sahakian, B.J., Polkey, C.E. & Robbins, T.W. 1990, "Planning and spatial working memory following frontal lobe lesions in man", Neuropsychologia, vol. 28, no. 10, pp. 1021-1034.

Parsons, T.D., Rizzo, A.R., Van Der Zaag, C., McGee, J.S. & Buckwalter, J.G. 2005, "Gender Differences and Cognition Gender Differences and Cognition Among Older Adults. ", Aging, Neuropsychology, and Cognition, , no. 12, pp. 78-88.

Patel, V. 2016, , Office of National Statistics. Deaths registered in England and Wales (Series DR): 2015 . Available: https://www.ons.gov.uk [2017, 3/15].

Rezvani, A.H. & Levin, E.D. 2001, "Cognitive effects of nicotine", Biological psychiatry, vol. 49, no. 3, pp. 258-267.

Ritchie, K., Carriere, I., Berr, C., Amieva, H., Dartigues, J.F., Ancelin, M.L. & Ritchie, C.W. 2016, "The clinical picture of Alzheimer's disease in the decade before diagnosis: clinical and biomarker trajectories", The Journal of clinical psychiatry, vol. 77, no. 3, pp. e305-11.

Ruitenberg, A., van Swieten, J.C., Witteman, J.C., Mehta, K.M., van Duijn, C.M., Hofman, A. & Breteler, M.M. 2002, "Alcohol consumption and risk of dementia: the Rotterdam Study", Lancet (London, England), vol. 359, no. 9303, pp. 281-286.

Sabia, S., Kivimaki, M., Shipley, M.J., Marmot, M.G. & Singh-Manoux, A. 2009, "Body mass index over the adult life course and cognition in late midlife: the Whitehall II Cohort Study", The American Journal of Clinical Nutrition, vol. 89, no. 2, pp. 601-607.

Sharp, E.S. & Gatz, M. 2011, "Relationship between education and dementia: an updated systematic review", Alzheimer Disease and Associated Disorders, vol. 25, no. 4, pp. 289-304.

Stampfer, M.J., Kang, J.H., Chen, J., Cherry, R. & Grodstein, F. 2005, "Effects of moderate alcohol consumption on cognitive function in women", The New England journal of medicine, vol. 352, no. 3, pp. 245-253.

Stern, Y. 2012, "Cognitive reserve in ageing and Alzheimer's disease", The Lancet.Neurology, vol. 11, no. 11, pp. 1006-1012.

Valenzuela, M.J. & Sachdev, P. 2006, "Brain reserve and dementia: a systematic review", Psychological medicine, vol. 36, no. 4, pp. 441-454.

Villemagne, V.L., Burnham, S., Bourgeat, P., Brown, B., Ellis, K.A., Salvado, O., Szoeke, C., Macaulay, S.L., Martins, R., Maruff, P., Ames, D., Rowe, C.C., Masters, C.L. & Australian Imaging Biomarkers and Lifestyle (AIBL) Research Group 2013, "Amyloid beta deposition, neurodegeneration, and cognitive

decline in sporadic Alzheimer's disease: a prospective cohort study", The Lancet.Neurology, vol. 12, no. 4, pp. 357-367.

Wesnes, K. A., Brooker, H., Ballard, C., McCambridge, L., Stenton, R., & Corbett, A. 2017, “Utility, reliability, sensitivity and validity of an online test system designed to monitor changes in cognitive function in clinical trials”. International Journal of Geriatric Psychiatry**, doi: 10.1002/gps.4659.**

Wilson, R.S., Krueger, K.R., Arnold, S.E., Schneider, J.A., Kelly, J.F., Barnes, L.L., Tang, Y. & Bennett, D.A. 2007, "Loneliness and risk of Alzheimer disease", Archives of General Psychiatry, vol. 64, no. 2, pp. 234-240.

**Table 1: Demographic information for all participants.**

| | Total | % |
|---|---|---|
| **ETHNICITY** | | |
| White | 13953 | 98.3 |
| Mixed | 81 | 0.57 |
| Asian | 84 | 0.59 |
| Black | 43 | 0.30 |
| Other | 40 | 0.28 |
| | | |
| **MARITAL STATUS** | | |
| Married | 9725 | 68.5 |
| Widowed | 876 | 6.2 |
| Separated | 249 | 1.8 |
| Divorced | 1536 | 10.8 |
| Civil partner | 84 | .6 |
| Co-habiting | 887 | 6.2 |
| Single | 844 | 5.9 |
| | | |
| **GENDER** | | |
| Male | 4049 | 28.5 |
| Female | 10152 | 71.5 |

| | Total | % |
|---|---|---|
| **AGE** | | |
| 50-54 | 2335 | 16.4 |
| 55-59 | 3213 | 22.6 |
| 60-64 | 3603 | 25.4 |
| 65-69 | 2957 | 20.8 |
| 70-74 | 1382 | 9.7 |
| 75-79 | 510 | 3.6 |
| 80-84 | 153 | 1.1 |
| 85-89 | 43 | .3 |
| >90 | 5 | .0 |
| | | |
| **EMPLOYMENT** | | |
| Employed full | 3089 | 21.8 |
| Employed part | 2332 | 16.4 |
| Self employed | 1511 | 10.6 |
| Retired | 6843 | 48.2 |
| Unemployed | 426 | 3.0 |

**Table 2: Risk factor variables**

| | NUMBER | % | | NUMBER | % |
|---|---|---|---|---|---|
| **EDUCATION** | | | **BMI** | | |
| GCSE | 2264 | 15.9 | underweight | 148 | 1.0 |
| A level | 1650 | 11.6 | normal | 6712 | 47.3 |
| Vocational | 2858 | 20.1 | overweight | 4801 | 33.8 |
| Undergrad | 4638 | 32.7 | obese | 2284 | 16.1 |
| Postgrad | 2311 | 16.3 | very obese | 245 | 1.7 |
| PhD | 480 | 3.4 | | | |
| | | | | | |
| **SMOKING** | | | **STROKE** | | |
| Ever smoked- no | 7576 | 53.3 | Stroke no | 13989 | 98.5 |
| Ever smoked- yes | 6625 | 46.7 | Stroke yes | 212 | 1.5 |
| | | | | | |
| **DEPRESSION** | | | **HEART DISEASE** | | |
| Depression- no | 10526 | 74.1 | Heart disease-no | 13520 | 95.2 |
| Depression- yes | 3675 | 25.9 | Heart disease-yes | 681 | 4.8 |
| | | | | | |
| **EXERCISE** | | | **HYPERTENSION** | | |
| Exercise no | 4710 | 33.2 | BP no | 10547 | 74.3 |
| Exercise yes | 9491 | 66.8 | BP yes | 3654 | 25.7 |
| | | | | | |
| **CLOSE RELATIONSHIP** | | | **ALCOHOL INTAKE** | | |
| None | 1058 | 7.5 | Never | 896 | 6.3 |
| Rarely | 617 | 4.3 | < 1 month | 1667 | 11.7 |
| Sometimes | 3080 | 21.7 | < 1 week | 2059 | 14.5 |
| Often | 2633 | 18.5 | > 1 week | 9582 | 67.5 |
| Very often | 6813 | 48.0 | | | |
| | | | | | |
| **DIABETES** | | | | | |
| Diabetes no | 13646 | 96.1 | | | |
| Diabetes yes | 555 | 3.9 | | | |

**Table 3: Multiple Regression results: Demographic variables**

| | PAL | VERBAL REASON | DIGIT SPAN | SWM |
|---|---|---|---|---|
| | **β ( Std error)** | **β ( Std error)** | **β (Std error)** | **β ( Std error)** |
| **(Constant)** | 4.541 (.046)*** | 26.167 (0.543)*** | 7.190 (0.088)*** | 8.090 (0.137)*** |
| **EDUCATION (ref GCSE)** | | | | |
| **A level** | 0.057 (0.023)* | 2.681 (0.271)*** | 0.226 (0.044)*** | 0.114 (0.068) |
| **Vocational** | 0.025 (0.020) | 2.020 (0.235)*** | 0.085 (0.038)* | 0.187 (0.059)** |
| **Undergrad** | 0.098 (0.019)*** | 4.828 (0.218)*** | 0.275 (0.035)*** | 0.400 (0.055)*** |
| **Postgrad** | 0.043 (0.021)* | 4.845 (0.251)*** | 0.298 (0.041)*** | 0.174 (0.063)** |
| **PhD** | 0.102 (0.036)** | 6.460 (0.422)*** | 0.387 (0.069)*** | 0.506 (0.106)*** |
| **AGE (yrs.) (ref 50-54 )** | | | | |
| **55-59** | -0.082 (0.019)*** | -0.998 (0.226)*** | -0.042 (0.037) | -0.167 (0.057)** |
| **60-64** | -0.163 (0.019)*** | -1.928 (0.223)*** | -0.077 (0.036)* | -0.452 (0.056)*** |
| **65-69** | -0.266 (0.020)*** | -3.155 (0.237)*** | -0.147 (0.039)*** | -0.703 (0.060)*** |
| **70-74** | -0.417 (0.025)*** | -5.435 (0.294)*** | -0.397 (0.048)*** | -1.063 (0.074)*** |
| **75-79** | -0.568 (0.036)*** | -6.981 (0.421)*** | -0.491 (0.068)*** | -1.400 (0.106)*** |
| **80-84** | -0.639 (0.060)*** | -8.441 (0.711)*** | -0.820 (0.116)*** | -1.674 (0.179)*** |
| **85-89** | -0.809 (0.110)*** | -9.623 (1.291)*** | -1.210 (0.210)*** | -2.474 (0.324)*** |
| **>90** | -0.179 (0.316) | -4.369 (3.725) | -0.892 (0.606) | -0.357 (0.936) |
| **GENDER M vs F** | -0.035 (0.014)* | 0.139 (0.164) | -0.142 (0.027)*** | -0.453 (0.041)*** |
| **MARITAL STATUS (ref married)** | | | | |
| **Widowed** | 0.054 (0.026)* | -0.093 (0.306) | 0.039 (0.050) | 0.204 (0.077)** |
| **Separated** | -0.010 (0.045) | 0.652 (0.535) | 0.020 (0.087) | 0.005 (0.135) |
| **Divorced** | 0.014 (0.020) | 0.513* (0.235) | -0.025 (0.038) | 0.109 (0.059) |
| **Civil partnership** | -0.111 (0.077) | -1.081 (0.913) | 0.032 (0.148) | -0.085 (0.229) |
| **Co-habiting** | 0.022 (0.025) | 0.269 (0.293) | 0.020 (0.048) | -0.052 (0.074) |
| **Single** | 0.031 (0.026) | 0.869 (0.307)** | 0.147 (0.050)** | -0.018 (0.077) |

***p < 0.05, **p < 0.01, ***p < 0.001, ref = reference value for regression**
**DIGIT SPAN = digit span task; PAL = Paired associates learning task; VERBAL REASON = verbal reasoning task; SWM = spatial working memory task.**

**Table 4: Multiple Regression results: Lifestyle, social and medical variables**

| | PAL | VERBAL REASON | DIGIT SPAN | SWM |
|---|---|---|---|---|
| | β ( Std error) | β ( Std error) | β (Std error) | β ( Std error) |
| **(Constant)** | 4.541 (.046)*** | 26.167 (0.543)*** | 7.190 (0.088)*** | 8.090 (0.137)*** |
| **SMOKING** | -0.019 (0.012) | 0.421 (0.144)** | 0.030 (0.023) | -0.066 (0.036) |
| **EXERCISE** | 0.020 (0.013) | 1.095 (0.151)*** | 0.130 (0.025)*** | 0.031 (0.038) |
| **CONFIDING RELATIONSHIP (ref never)** | | | | |
| **Rarely** | 0.073 (0.013)* | 2.645 (0.424)*** | 0.184 (0.069)** | 0.273 (0.107)* |
| **Sometimes** | 0.064 (0.025)* | 2.716 (0.298 )*** | 0.228 (0.049)*** | 0.362 (0.075)*** |
| **Often** | 0.072 (0.026)** | 2.261 (0.306)*** | 0.249 (0.050)*** | 0.390 (0.077)*** |
| **Very often** | 0.096 (0.024)*** | 2.417 (0.280)*** | 0.255 (0.045)*** | 0.435 (0.070)*** |
| **ALCOHOL (ref never)** | | | | |
| **< 1 MONTH** | 0.050 (0.029) | 0.036 (0.345) | -0.031 (0.056) | 0.126 (0.087) |
| **< 1 WEEK** | 0.057 (0.028)* | 0.400 (0.334) | -0.003 (0.054) | 0.170 (0.084)* |
| **>1 WEEK** | 0.074 (0.025)** | 1.101 (0.294)*** | 0.100 (0.048)* | 0.238 (0.074)** |
| **DEPRESSION** | -0.049 (0.014)*** | 0.227 (0.163) | -0.115 (0.027)*** | -0.199 (0.041)*** |
| **BP** | -0.026 (0.014) | -0.046 (0.170) | -0.053 (0.028) | -0.046 (0.043) |
| **DIABETES** | 0.009 (0.032) | 0.117 (0.371) | 0.036 (0.060) | -0.230 (0.093)* |
| **BMI (ref normal bmi)** | | | | |
| **Underweight** | -0.131 (0.059)* | -1.725 (0.692)* | -0.171 (0.112) | -0.422 (0.174)* |
| **Overweight** | 0.026 (0.014) | 0.135 (0.161) | -0.029 (0.026) | -0.009 (0.040) |
| **Obese** | 0.033 (0.018) | 0.105 (0.210) | -0.101 (0.034)** | -0.085 (0.053) |
| **Very obese** | 0.086 (0.047) | 0.349 (0.549) | -0.028 (0.089) | -0.013 (0.138) |
| **STROKE** | -0.053 (0.049) | -2.263 (0.583)*** | -0.202 (0.095)* | -0.423 (0.147 )** |
| **HEART DISEASE** | -0.053 (0.029) | -0.075 (0.338) | -0.020 (0.055) | -0.129 (0.085) |

***p < 0.05, **p < 0.01, ***p < 0.001, ref = reference value for regression**
**DIGIT SPAN = digit span task; PAL = Paired associates learning task; VERBAL REASON = verbal reasoning task; SWM = spatial working memory task.**