Accepted Manuscript

Title: Predictive Factors for Verbal Memory Performance Over Decades of Ageing: Data From the Women's Healthy Ageing Project.

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PII: S1064-7481(16)30113-0
DOI: <http://dx.doi.org/doi: 10.1016/j.jagp.2016.05.008>
Reference: AMGP 618

To appear in: *The American Journal of Geriatric Psychiatry*

Received date: 15-5-2015
Revised date: 25-4-2016
Accepted date: 11-5-2016

Please cite this article as: Cassandra Szoeki, Philippe Lehert, Victor W Henderson, Lorraine Dennerstein, Patricia Desmond, Stephen Campbell, Predictive Factors for Verbal Memory Performance Over Decades of Ageing: Data From the Women's Healthy Ageing Project., *The American Journal of Geriatric Psychiatry* (2016), <http://dx.doi.org/doi: 10.1016/j.jagp.2016.05.008>.

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Predictive factors for verbal memory performance over decades of ageing: Data from the Women's Healthy Ageing Project.

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MANUSCRIPT DETAILS: Abstract 258 words, Article 2938 words, 69 references

This analysis was funded by NHMRC grant ID 1032350, 547500 & 1062133

Acknowledgements

We would like to acknowledge the contribution of the participants and their supporters who have contributed their time and patience for over 20 years to the University. A full list of all researchers contributing to the project and the membership of our Scientific Advisory Board is available at <http://www.medrmhwh.unimelb.edu.au/Research/WHAP.html>. We are thankful to our participants, team, partners and supporters for making this study of now more than 20 years possible. Funding for the WHAP has been provided by the National Health and Medical Research Council (NHMRC Grants 547500, 1032350 & 1062133), Ramaciotti Foundation. Brain Foundation, the Alzheimer's Association (NIA320312), Australian Menopausal Society, Bayer Healthcare, Shepherd Foundation, Scobie and Claire McKinnon Foundation, Collier Trust Fund, J.O. & J.R. Wicking Trust, Mason Foundation and the Alzheimer's Association of Australia. The Principal Investigator of WHAP (CSz) is supported by the National Health and Medical Research Council and the Faculty of Medicine, Dentistry and Health Sciences at the University of Melbourne.

Abstract

Background: Abnormalities in brain structure and function can occur several decades prior to the onset of cognitive decline. It is in the preceding decades that an intervention is most likely to be effective, when informed by an understanding of factors contributing to the disease prodrome. However, few studies have sufficient longitudinal data on relevant risks to determine the optimum targets for interventions to improve cognition in ageing. In this paper we examine the timing and exposure of factors contributing to verbal memory performance in later life.

Methods: 387 participants from the population-based Women's Healthy Ageing Project, mean age at baseline of 49.6 years (45 – 55), had complete neuropsychiatric assessments, clinical information, physical measures and biomarkers collected at baseline, with at least three follow-up visits that included at least one cognitive reassessment. Mixed Linear models were conducted to assess the significance of risk factors on later life verbal memory. We explored the influence of early, contemporaneous and cumulative exposures.

Results: Younger age and better education were associated with baseline memory test performance. Over the 20 years of study follow-up, cumulative mid to late life physical activity had the strongest effect on better later life verbal memory (0.136 [.058, .214]). The next most likely contributors to verbal memory in late life were the negative effect of cumulative hypertension (-0.033 [-.047, -.018]) and the beneficial effect of HDL cholesterol (0.818 [0.042, 1.593]).

Conclusion: Findings suggest that midlife interventions focused on physical activity, hypertension control, and achieving optimal levels of HDL cholesterol will help maintain later-life verbal memory skills.

Keywords: older persons
longitudinal prospective
lifespan influence on ageing
cognition
memory
modifiable risk factors
midlife to late life health
life course research

Background

Recent research shows that abnormalities in brain tissue occur several decades prior to the onset of cognitive decline [1]. Therefore it is in these preceding decades that the influence of factors on disease evolution must be determined. As the incidence of Alzheimer's disease diagnosis doubles every five years after 65, most longitudinal studies examining risk factors and cognitive disease [2-6] recruit participants over the age of 60 or 70. Therefore ambiguity exists around the timing across the lifecourse of the proposed "earlier" therapeutic window [7, 8]. There are few research studies which have data on participants from midlife and have assessed cognition in later life. Whilst these studies were not originally designed to examine cognition, subgroup analysis indicates that this is a key period in the development of disease [9-11]. Unfortunately none of these have cognitive assessments from midlife.

There is a growing body of evidence that risk factors can impact on cognitive decline and dementia [12, 13]. Age [14], APOE4 genotype [15, 16], cardiovascular risk (lipid profile, BMI, blood pressure, smoking and fasting glucose/diabetes) [17, 18], socio-demographics (including education) [19], physical activity [2, 20], cognitive/social engagement [21] and mood [22] are all risk factors demonstrating an impact on cognitive disease [23]. Using currently available evidence it has been estimated that half the cases of dementia world-wide are potentially attributable to modifiable risk and up to 3 million diagnoses worldwide could be avoided with just a 10 -25 % reduction in known modifiable risk factors [24]. However, whilst these associations have been reported, we have yet to determine causation [25] and therefore

recommendations for appropriate lifestyle interventions remain limited by these gaps in our understanding [26]. These include a lack of information on both the lifecourse timing of risk and consideration of the interaction of all risk factors [27, 28]. Timing is important, due to the known long prodrome of cognitive neurodegenerative disease as well as the understanding of the key risk factors which, themselves, are known to exert effects significantly over time. The current known risk factors are highly correlated, therefore their influence on cognition need to be examined together in the same cohort in order to determine which are the key targets for intervention.

The large body of research examining risk factors for cognitive decline and disease has often examined only a single or small collection of risk factors [29], despite the list of known risks clearly representing multiple inter-related factors. Therefore examining all risk factors together and exploring variation in their influence on an individual over time is essential to appropriately determine causality [25, 30]. Consideration of such integrated global risk in population-based longitudinal research of adequate duration and detail is crucial to accurately describe the early long prodrome of heterogeneous cognitive decline and disease [31]. Only such multifactorial, longitudinal work can enable identification of both constant factors and timing of interventions that may delay the onset of mild cognitive impairment and dementia in those at risk and slow the progression of disease.

Objective

In this longitudinal study of more than 20 years our primary objective was to identify the key risk factors affecting cognitive decline in verbal episodic memory. Our secondary objective was to determine to what extent past (early), present (late) and cumulative factors influence cognitive decline in ageing.

Design

We studied participants enrolled in the Women's Healthy Ageing Project (WHAP) a longitudinal prospective population study of 438 women aged 45-55. The original cohort of 2001 women aged 45-55 were identified by random population sampling [32] conducted by the Roy Morgan Centre in 1990 and took part in a cross-sectional study [33]. Those women who met inclusion criteria (having a uterus and at least one ovary, menstruating and not on hormone replacement therapy) were invited to participate in the longitudinal prospective study (779) of which 438 agreed. There were no exclusion criteria. Compared to those who did not take part in the study, those agreeing to participate had a higher level of education, but were similar in age and other variables of interest [34]. Annual assessments were conducted from 1991 to 1998, followed by intermittent assessment conducted in 2002/3, 2004/5 and 2012/13. Cognitive testing of verbal episodic memory commenced in 1998 and was conducted in 2002/3, 2004/5 and 2012/13 time-points. See Figure One.

Women from the initial study on whom we had at least one cognitive time-point of verbal episodic memory and at least 3 follow-up time points were included in the analysis. The longitudinal analysis was based on 6 periods of examination, 1991-1993; 1994-1997; 1998/9; 2002/3; 2004/5; 2012/13 providing approximately the same time difference between the examined periods. The primary outcome measure was the delayed recall of a 10 item supraspan word list score from the Consortium to Establish a Registry for Alzheimer's Disease (CERAD-DR) [35], a measure of verbal episodic memory, a domain known to be sensitive to early Alzheimer's disease changes.

The details of questionnaire, clinical, physical and biomarker measures have been described in previous publications [32, 33, 36]. The list of clinically relevant potential predictors was established from

the literature eg. [29, 37]. We include a brief description on the key variables of interest in this analysis. These variables were recorded at each follow-up year unless otherwise specified:-

Sociodemographic: Education in years, marital status, employment status voluntary work, age of menarche, number of pregnancies, number of births and number of children.

Lifestyle: Physical activity as the number of days a week participants engaged in physical activity for recreation or leisure. Alcohol consumption, as the number of standard drinks in the preceding 2 weeks. Cigarette smoking as the number of cigarettes per day smoked.

Clinical and Vascular Risk Factors including biomarkers: Height, weight, body mass index (BMI), systolic blood pressure (SBP) and diastolic blood pressure (DBP), (mmHg). In order to be eligible for the study at outset, the women had to be premenopausal and not taking hormone therapy. Later hormone therapy use (HT) was recorded. Women who reported the use of only topical oestrogens were not classified as users. Participants had fasted overnight for at least 10 hours prior to blood collection. Samples were forwarded to a clinical pathology laboratory for biomarkers including cholesterol, low density lipoprotein (LDL), high density lipoprotein (HDL), triglycerides (TG); glucose; follicle stimulating hormone, estradiol and testosterone. APOE genotype was determined. PROCAM cardiovascular risk scores were calculated [38].

Co-morbidity: Participants were specifically asked about a number of neurological, psychological and vascular conditions, significant symptoms and family history of neurological, psychological and vascular diseases and events. Occurrence of any reported conditions were considered in the analysis as a morbidity index.

Psychological: Semi-structured interview and mood scales. The Affectometer 2 – Negative Mood Score [39] a 10 item measure. The Centre for Epidemiological Studies Depression (CESD) Scale [40] administered since 2002.

Cognitive Testing: A number of studies indicate the earliest change to cognition is in verbal episodic memory. The primary outcome measure used in this analysis was a modified version of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) [41] 10-item supraspan word list score-delayed recall (CERAD-DR)[42]. This was the initial neuropsychological test of cognition first completed in the 1998 follow-up. CERAD-DR has been reported to be sensitive to early changes associated with dementia [43, 44]. This task consisted of ten unrelated nouns of 1-2 syllables and the word order for each of the three learning trials was varied [45].

The other tests which were tested in the model were the CERAD-immediate recall sum of 3 trials (CERADI) and the Californian Verbal Learning Task – II(CVLT) -immediate (CVLTI) and CVLT-delayed recall (CVLTD) [46]. We have previously reported Australian normative data for these tests from the 2002/3, 2004/5 and 2012/3 follow-up years. Clark (2004) reported that both tests measure the same cognitive construct, auditory verbal memory, and noted a trend for decline in both performances with age [45]. Details on each test administration have been described in detail elsewhere [32, 45].

Statistical Analysis

CERAD-DR was the main endpoint. Three other endpoints (CERADI, CVLTD and CVLTI) were considered as secondary endpoints. Women with at least one post-baseline follow-up were included in the analysis. Our main analysis used a mixed linear model considering CERAD-DR as the dependent variable, in assuming a first order autocorrelated model AR(1) adapted for continuous time and different inter-visit time and age and education level as fixed covariates. We first analyzed CERAD as a continuous scale by a Mixed Linear model. Predictors previously identified in the literature and available in our database with a minimum of missing data (<5%) were considered as the candidate covariates in the main model; predictors

identified in the literature but with more missing data were tested in secondary supportive models. Except for education level, and parity, being constant covariates, all the other variables were considered changing in time. The final model was built following three stages: during stage 1 the effect of each covariate was separately tested in adjusting for these constant covariates; the main effect was tested following three hypotheses: simultaneous (X at time t impacts the endpoint Y at the same time t), lagged (the endpoint is affected by values of X at time t-1 or earlier), and cumulative (the endpoint is affected by the mean value of prior values of X). For the cumulative effect, we added each period as separate covariates each adjusted for age and educational level to provide an equality of weight of each period. We compared the effects estimated by the mean restrained to midlife period (<55 years), late periods (>55y) and the unweighted mean across the whole follow up. For each analysis, we tested the main effect and its first-order interaction with age and education. The hypothesis minimizing the Akaike Information Criterion AIC was chosen. During a second stage, all the previously identified significant effects were included into the model and entered a backward strategy in removing non-significant covariates, based on both likelihood Ratio Test LRT and decrease of AIC. At last stage, the first order interactions between each pair of the identified predictors and between each predictor and age and education level were added and tested in separate analyses. For sensitivity purposes, we conducted final supportive analyses: the model was re-assessed by using a forward/stepwise strategy instead backward. For the most important potential predictors, instead of considering them as continuous, we conducted sensitivity analyses based on cut-off values. For pressures we measured time during which systolic pressure was >140mmh and diastolic <90mmH. For Physical activity, instead continuous value we considered as binary value (no activity at all versus other). Data were considered as missing at random and no missing data imputation was used [47]. All the tests were two-tailed at significance level $p<.05$ for main effects and $p<.20$ for interaction effects given their expected lower power. The statistical analysis was conducted with the statistical package R (version 3.0.2),

Results

387 women (89%) had at least one cognitive time point and at least three fully documented visits. Characteristics of this cohort are displayed in Table 1. The 51 women who were lost to follow-up over the 22 years of the study were more likely to be less educated, and suffer poorer health than those who were retained (data not shown). Likewise those participants remaining in the cohort at the end of the study were more likely to be healthier than those who dropped out earlier in the study. Over the duration of the study 3 participants developed dementia, all of the Alzheimer's type, 12 Mild Cognitive Impairment and 7 normal cognition with MMSE <28.

(Insert Table 1 about here)

The variation of CERAD over time was studied as a continuous variable. Age and education were considered as obvious adjustment covariates of cognition: a constantly decreasing value of the CERAD-DR score of -0.122 ([-149,-0.095], $p<.001$) per year was observed with age, and CERAD-DR value at any time was shown correlated with its previous value at the last examination (auto-regressive correlation $r=0.25$, 95 CI= (0.08, 0.56)). Education level constituted another important covariate, higher educational level improving the CERAD-DR score by 0.38 [0.20, 0.55]

Influence on memory performance over time

Among all the candidate changing covariates in time, physical activity showed the most determinant effect on cognition. More physical activity was associated with better verbal memory. The mean value of physical activities from all years from the past to the present represented the greatest determination with a mean increase of CERAD of 0.136 [0.058, .214] $p<.001$ per mean day of physical activity.

HDL was the next most significant predictor of cognitive performance. Mean HDL of all measures over the past years (from early menopausal years) was observed to increase memory score by 0.818 [0.042, 1.593] $p < .001$ per unit (mmol/L) of HDL. Both high systolic and high diastolic blood pressure negatively affected verbal memory performance over time. Mean arterial pressure MAP [48] was the best estimate of the overall effect of blood pressure. The mean MAP over all the years since premenopause is associated with a mean decrease of 0.033 [-0.047, -0.18]; $p < .001$ per mmHG.

The influence of hormone therapy (HT) administered at a given time missed reaching a significant effect (0.27 [-0.02, .555]; $p = .06$). High Fasting Blood Glucose and low Testosterone were identified to have a negative effect on cognition. However, these variables were characterized by a large proportion of missing data (45.5%) and therefore could not be included in the model. No other covariate was found to be determinant in the model. In particular, the other lipid values (triglycerides, low density lipoprotein or total cholesterol) were not significant predictors. Likewise, the composite cardio-vascular scores did not significantly impact verbal memory performance. Morbidity was not significant.

For the changing variables retained in the final model (physical activity, Blood pressure, HDL), the cumulative effect was predominant compared with the simultaneous or lagged effects based on only the pre- or post-menopausal periods (the effect size of estimate roughly doubled and only cumulative effects provides a highly significant effect ($p < 0.001$) for physical activity and blood pressure). Sensitivity analyses based on binary values of Blood pressure, physical activity, or HDL, instead of continuous mean values, provided the same results.

Based on the same mixed model, we failed to find a significant effect for negative or positive mood score or APOE genotype (only available on 218 patients). Finally, no interaction was found significant at the pre-determined level ($p < .2$). A forward and stepwise strategy re-applied to the model provided the same results. Table 2 summarizes the identified main effects in our predictive model of cognition decline measured by CERAD-DR. (Insert Table 2 about here).

The three other endpoints (CRDI, CVLTD and CVLTI) were analysed separately as secondary endpoints. The CVLT delayed (CVLD) and immediate recall scores (CVLTI) were reported only at year 11, 13 and 21. A separate analysis was carried out on these endpoints based on the same model, and as these endpoints were positively correlated, we repeated the same analysis on a Z-score to combine the four endpoints. Very similar and consistent results were found, the largest difference on the standardized coefficient was 7.6% (Supplement Table S1, S2 & S3). The 15 participants who were classified with cognitive disease (MCI or AD) over the duration of the study were excluded from the analysis with no significant change in results. The sample size of those developing disease in this healthy cohort is insufficient for independent analysis.

Discussion

Whilst the relationship between ageing and decrements in verbal memory is known, our study describes that modifiable risk factors which can influence the magnitude of this decline during ageing. This lifecourse approach to the influence of modifiable risk factors on verbal memory decline in ageing has shown that the most significant and persistent influence on improved memory scores observed in later life is physical activity. The most significant vascular risk factors associated with verbal memory decline were sub-optimal HDL and high BP. These were cumulative in nature with optimal HDL showing an aggregate protective effect and high blood pressure, both systolic and diastolic, having an aggregate deleterious effect over time. As the combined risk from all previous years determines the greatest impact on cognitive decline, there is the potential for later life change to offset earlier life risk. Comparison of relevant β values (see Table 2) indicates that the modifiable variables explain a significant part of the variance in cognition at any age. The beneficial influence of physical activity and blood pressure together approximately compensates the negative influence of age.

Whilst there are a variety of conflicting reported associations between individual cardiovascular risk factors and cognitive decline, longitudinal studies support the role of blood pressure[49]. The few available longitudinal studies which have examined more than one modality have found similar relationships, with physical activity [50, 51] and HDL [51-53] showing the most prominent influence on cognitive change. The Cooper Center Longitudinal Study following over 20,000 participants, which showed that poor midlife fitness was associated with the later development of dementia is further evidence that lifecourse physical activity warrants further consideration [54]. Not all studies involving lipids have analysed HDL and our work and that of others suggests that HDL has the dominant lipid effect on cognition. Large population autopsy studies which have examined the correlation of lipid profile with measured brain plaques of a large population have found similarly that HDL was the key lipoprotein of influence[55]. Given that lipoproteins, triglycerides and cholesterol are all highly correlated any one of these may demonstrate an association which is in fact caused by another. This may explain the conflicting observational and intervention lipid research results.

Our results add to the growing consensus that there is a clear distinction between cardio-vascular and cerebro-vascular risks. Of cardiovascular risk, cholesterol, LDL, BMI and even risk scores were not found to be independently significant once the influence of the physical activity, HDL, BP and fasting glucose were accounted for. We also observed a different pattern of influence of LDL on cognition to that ascribed to cardiovascular health, with LDL not having a linear negative association with verbal memory performance over time. There is evidence that some “cardiovascular” risk factors have an important influence on cognition which indicates they are also “cerebrovascular” risk factors. Our findings indicate that the way vascular risk factors influence cognitive decline is not necessarily the same as occurs in the development of cardiac disease. These differences, together with the timing of different studies, may account for the many conflicting reports in the association between “cardiovascular risk factors” and cognition [56]. The linear mixed model found that mood and APOE influence were not significant over and above the effects of physical activity, HDL and BP. The mechanism of APOE conferred risk is unknown and hypothesised to be vascular which may well be mitigated by the primary factors found to be driving cognitive decline in this study (Physical activity, HDL and BP). Whilst mood was not a significant contributor to cognitive decline, these were healthy women, with few scoring in the “at risk” category. The literature supports a relationship between mood disorders and cognition, but within the healthy spectrum of mood in our cohort we found no significant relationship..

The strong pathophysiological evidence that hormonal exposure influenced cognition was questioned when the Women’s Health Initiative was unable to demonstrate a cognitive benefit for hormone therapy (HT). However there is interest in examining the role of hormones on cognition in healthier mid-aged women[57] given the evidence there may be a therapeutic window for benefit [58-60]. In our study commencing HT improved cognitive performance and ceasing therapy reduced cognitive performance but this effect of HT use did not reach statistical significance. This finding needs further research to understand the importance of the timing and duration of therapy.

Limitations and Further Work

Attrition bias needs to be considered in all studies of long duration. Those remaining in the study have a higher education, less morbidity and lower age. This healthy bias reduces the power of our study to detect change. Therefore we were likely to underestimate the effect of factors on cognitive decline and results may not be directly generalisable. Measures of physical activity were self-reported, rather than measured by actigraph. Whilst direct measurement has greater accuracy, it is un-blinded. Therefore people may exercise more when wearing the monitor compared to when they are not wearing it. The average of almost 3 days a week where activity was done in our cohort is comparable to the Australian Bureau of Statistics 2011/12 survey which reported 43% of Australian adults did “at least 30 minutes of activity” on most days of the week [61]. Important factors in cognitive health which were not measured in

this study include social engagement, diet and cognitive activity which may also have an influence. As this is a cohort study based on Australian born women the relevance of the results to other populations will need to be determined.

The capacity to examine the influence of these factors over 20 years sheds some light on the conflicting literature reporting relationships between individual modifiable risk factors and cognition. The important effect of the six predictors (as shown in table 2) on cognitive decline, and their knowledge over a long period are necessary to evaluate the impact of risk factors like physical activity, blood pressure and HDL, which our study shows has a lifecourse cumulative influence on later life verbal memory.

Whilst the identification of risk factors constituted our main objective, our secondary objective was to assess the early, late and cumulative effect of these predictors on cognition. This provided clinical utility, for instance, does regular physical exercise practiced since the early years of pre-menopausal period provide a more beneficial effect than the same intensity of exercise, but only practiced for a few years? A methodological limitation of comparing cumulative and simultaneous effects of each predictor is whether one can interpret measures averaged across all available timepoints as unequivocally representing a longer duration for risk factor than is captured by measures based on fewer timepoints. Notwithstanding these limitations, we provide some evidence of the greater impact of cumulative effect of almost all the identified risk factors, compared with any simultaneous effects. This finding is also supported by the observed strong autocorrelation of cognition values ($R=.25$) which of course includes the indirect effect of each risk factor at earlier periods.

A last limitation is that all the detected predictors (blood pressure, lipids, hormones) are present all the time throughout one's life, and we only dispose of values at several discrete time points. Our approximation was to consider that these values did not change between any two examinations. Meanwhile before using these values as continuous variables, we also conducted analyses based on cut-off values. For pressures we measured time during which systolic pressure was $>140\text{mmHg}$ and diastolic $<90\text{mmHg}$. For Physical activity, instead continuous value we considered as binary value (no activity at all versus other). All these analyses provided very similar results compared with results based on continuous values. As these results were similar and do not need arbitrary cut-off values, we preferred to report results based on continuous values.

These findings need to be validated in other longitudinal prospective studies to examine the influence of cultural, demographic and regional impacts on this model. A similar study and analysis should be conducted for men. Further work should also explore the likely mechanisms by which high HDL and physical activity exert their strong positive influence on verbal cognition and also examine influence on other cognitive parameters. Exploration of cerebral microvascular change over decades could provide information on the presumed influence of improving vascular health and thus improving cerebral blood flow, reducing microvascular damage and improving neuronal integrity. A larger battery of neuropsychiatric testing could broader impacts on the various cognitive domains.

Conclusion

As global collaborations draw together around a much needed intervention, it is important to consider the timing to commence such intervention. There is no doubt that intervention is better late than never, but the results of our work indicate that an intervention after 65 will have missed at least 20 years of aggregate risk. Unlike the capacity of muscle and vessels to remodel and reverse atrophy and damage, neuronal cells are not nearly so versatile with damage and cell loss irreversible. The recent finding reporting that cardiovascular risk in young adults is associated with cognitive performance suggests the therapeutic window for change may be even earlier [62]. Our results in conjunction with recent work demonstrating amyloid accrual already present in 50 year olds [63] argue strongly for earlier life intervention to prevent losing our cognitive capital. The additive effect of lower blood pressure, increased

high density lipoprotein and increased physical activity was observed to compensate for the effect of advancing age.

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SUPPLEMENTARY TABLES

Table S1: Immediate CERAD recall score (CERADI) - Linear Model, Sample Size=389, 4 repeated measures of cognition

.	Coef	95%	CI	Pval
Intercept	9.058	8.036,	10.079	<.001
Age	-0.046	-0.060,	-0.031	<.001
Education Level	0.330	0.226,	0.434	<.001
Cumulative Higher Physical Activity	-0.053	-0.096,	-0.011	0.014
Cumulative High HDL level	0.479	0.041,	0.918	0.032
Cumulative mean arterial pressure	-0.013	-0.021,	-0.006	<.001
Starting hormone therapy	-0.015	-0.162,	0.131	0.837

Table S2. Delayed CVLT recall score (CVLTD) - Linear Model, Sample Size=305, 3 repeated measures of cognition

.	Coef	95%	CI	Pval
Intercept	-0.156	-4.022,	3.710	0.937
Age	0.117	0.063,	0.172	<.001
Education Level	1.371	0.977,	1.765	<.001
Cumulative Higher Physical Activity	-0.226	-0.376,	-0.075	0.004
Cumulative High HDL level	2.609	0.868,	4.351	0.004
Cumulative mean arterial pressure	-0.005	-0.034,	0.024	0.171
Starting hormone therapy	-0.559	-1.121,	0.002	0.052

Table S3. Immediate CVLT recall score (CVLTI) - Linear Model, Sample Size=305, 3 repeated measures of cognition

.	Coef	95%	CI	Pval
Intercept	5.816	3.301,	8.331	<.001
Age	0.036	0.001,	0.071	0.048
Education Level	0.870	0.606,	1.133	<.001
Cumulative Higher Physical Activity	-0.285	-0.388,	-0.183	<.001
Cumulative High HDL level	1.771	0.606,	2.936	0.003

Cumulative mean arterial pressure -0.005 -0.025, 0.014 0.160

Starting hormone therapy -0.519 -0.900, -0.138 0.008

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1 TABLES AND FIGURES

Figure 1: Progression of participants through the Women's Healthy Ageing Project

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit www.prisma-statement.org.

Table 1: Description of the cohort's 387 participants at baseline, values are mean or % $\pm$ SD or (count)

Age	49.62	$\pm$ 2.54
Education	Level	
- Low	1.8%	(7)
- Intermediate	39.1%	(151)
- High	22.0%	(85)
- University	37.1%	(143)
Married	76.7%	(296)
Employed	59.1%	(228)
Sexually active	73.3%	(283)
Number of Std Drinks/7days	3.76	$\pm$ 3.84
Number of cigarettes/day	2.28	$\pm$ 7.33
Physical Exercise (N of days / week)	2.71	$\pm$ 2.76
Age at menarche	13.04	$\pm$ 1.51
Number of children	2.95	$\pm$ 1.30
Hormone Therapy (HT) use	18.5%	(386)
Body Mass Index (BMI)	26.94	$\pm$ 8.32
Follicle Stimulating Hormone (FSH) IU/L	58.31	$\pm$ 44.79
Cholesterol mmol/L	5.82	$\pm$ 1.05
Glucose mmol/L	5.29	$\pm$ 1.22
High density lipoprotein (HDL) mmol/L	1.55	$\pm$ 0.42
Triglycerides (TG) mmol/L	1.33	$\pm$ 0.85
Systolic Blood Pressure (SBP) mmHg	127.98	$\pm$ 20.68
Diastolic Blood Pressure (DBP) mmHg	78.24	$\pm$ 11.81
Classifications at followup		
- Healthy Cognition (HC)	94%	(237)
- Mild Cognitive Impairment (MCI)	4.8%	(12)
- Alzheimer's Disease (AD)	1%	(3)
APO E Genotype E4 positive (n=304)	23%	(77)
CERAD Score		
- CERAD delayed	7.67	$\pm$ 1.53
- Mean of Immediate CERAD trials	7.24	$\pm$ 1.10
CVLT Score		
- CVLT delayed	8.81	$\pm$ 3.23
- Mean of Immediate CVLT trials	8.77	$\pm$ 2.06

Table 2: Factors influencing delayed CERAD score.

Covariates	Coef	95%	CI	β	P
Intercept	6.276	5.641	6.911		<.001
Age	-0.122	-0.149	-0.095	-.285	<.001
Education Level	0.377	0.200	0.555	.152	<.001
Physical exercise	0.144	0.065	0.223	.120	<.001
HDL	0.818	0.042	1.593	.071	0.039
Blood pressure MAP	-0.033	-0.047	-0.018	-.163	<.001
HRT	0.268	-0.017	0.552	.117	0.066

Continuous delayed CERAD score (mixed Linear Model). Education level from lowest (0) until highest (3), Physical exercise measured by the mean number of days per week reported over the whole follow-up. HDL is the mean value of High density cholesterol measured over the whole follow up, Blood pressure is the <MAP value (2/3 systolic BP+ 1/3.Diastolic BP) over the whole follow up period. Intercept is the estimated constant value of the model when all the covariates have 0 value, corresponding to age=50 years, lowest education level, no physical exercise, Blood pressure MAP=90mmgh, and no HRT use. OR designates Odds Ratio.

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Title:

Predictive Factors for Verbal Memory Performance Over Decades of Aging: Data from the Women's Healthy Ageing Project

Date:

2016-10-01

Citation:

Szoeke, C., Lehert, P., Henderson, V. W., Dennerstein, L., Desmond, P. & Campbell, S. (2016). Predictive Factors for Verbal Memory Performance Over Decades of Aging: Data from the Women's Healthy Ageing Project. AMERICAN JOURNAL OF GERIATRIC PSYCHIATRY, 24 (10), pp.857-867. <https://doi.org/10.1016/j.jagp.2016.05.008>.

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