Metabolic syndrome over 10 years and cognitive functioning in late midlife: the Whitehall II study.

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Running Title: Metabolic syndrome and cognitive function

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ABSTRACT

Objective: Evidence that the metabolic syndrome is a risk factor for poor cognition is mixed, is mainly focused on elderly population, and it is a rare occurrence that socio-economic factors are adjusted for. We examined this association in late mid life, with particular focus on cumulative effects and the role of socioeconomic circumstances.

Research Design and Methods: Analyses were carried on 4150 white participants from the Whitehall II study. Metabolic syndrome, using the National Cholesterol Education Program Adult treatment Panel III (ATP III) criteria, was assessed three times over the 10-years follow-up (1991-2001). Cognitive function was assessed using a battery of 6 tests at the end of the follow-up.

Results: After adjusting for demographic variables, health behaviours and health status, participants with persistent metabolic syndrome (at least 2 out of the 3 screenings) over the 10-year follow-up had lower cognitive performance than participants who never had metabolic syndrome. No significant differences in cognitive function were observed between participants with non-persistent metabolic syndrome (1 out of the 3 screenings) and those who never had metabolic syndrome during the follow-up. Adjustment for adult occupational position attenuated this association by between 41% and 86%, depending on the measure of cognitive function. Adjustment for education had little effect.

Conclusion: Only persistent metabolic syndrome was associated with lower cognitive performance in late mid life. Adult occupational position, but not education, had a substantial impact on this association; these results highlight the importance of adult socioeconomic circumstances in identifying and targeting risk factors for cognitive ageing.

Cardiovascular risk factors have increasingly been recognised as important contributors to cognitive outcomes such as dementia (1). The metabolic syndrome (MS) is comprised of five cardiovascular risk factors including abdominal obesity, hypertriglyceridemia, low high density lipoprotein (HDL) cholesterol, hypertension, and hyperglycemia (2). Numerous studies have shown several of the individual components of the MS to be linked to the risk of cognitive decline and dementia (3). However, the nature of the association between MS and cognition remains unclear. There are only few studies on the MS as a whole and most of them have been limited to elderly or older populations (4-12). Furthermore, the findings are mixed: while some reports suggest that MS predicts cognitive deficit (4), cognitive decline (5; 11; 12) and dementia (8; 10), at least two studies showed MS to be associated with better cognitive performance (6) and decelerated cognitive decline (9). A further study found no significant relationship between MS and dementia (7).

Several limitations in previous studies that are possible to overcome may have contributed to inconsistencies in the evidence. First, as subclinical manifestations of dementia are believed to be present many years before the diagnosis, examining the role of risk factors, such as the MS prior to old age would provide insight into their impact on cognitive function (13; 14). Second, no previous study has examined the effects of persistent metabolic syndrome, assessed repeatedly rather than at a single time point, on cognition. Third, existing research has not taken full account of the potential for confounding by socioeconomic position.

In this field of research, socioeconomic position (SEP) may play a particularly important role as, on the one hand, it contributes to cognitive reserve (15), and on the other hand, it is associated with vascular and other risk factors for cognitive ageing (16). Although studies on the association between MS and cognition usually adjust for education, they do not take into account

the effects of later life measures of SEP. Education reflects early SEP but may not capture changes in socioeconomic circumstances in adult life. Other measures, like household income or occupational position, may better reflect adult socioeconomic circumstances.

We use data from a large prospective middle-aged cohort (the Whitehall II study) to examine the association between MS and cognitive function in mid-life. Our focus is on investigating the effect of cumulative exposure to MS over 10 years and the influence of SEP as indicated by education and occupational position.

RESEARCH DESIGN AND METHODS

Study Population

The target population for the Whitehall II study was all London-based office staff (n=10308), aged 35–55 years, working in 20 civil service departments (17). After the first medical examination (phase 1, 1985–1988), screenings by trained research staff were repeated three times over a 19-year period: Phase 3 (1991–1993), Phase 5 (1997–1999) and Phase 7 (2003–2004). Of the 10308 participants at phase 1, 584 had died before Phase 7, 1182 had withdrawn from the study and 1575 did not respond at this phase of the follow-up. The remaining 6967 participants responded at phase 7 and of these, 88.0% had data on cognitive function at phase 7 (n=6130), 71.0 % (n=4949) had data on MS at phases 3, 5 and 7 and 64.0% (n=4461) had data on all other covariates. The present analyses are based on all white participants with complete data (n=4150). Ethical approval for the Whitehall II study was obtained from the University College London Medical School committee on the ethics of human research.

Data collection

Assessment of the metabolic syndrome: The MS was defined at phases 3, 5 and 7, using the National Cholesterol Education Program (NCEP) criteria (18), based on the presence of 3 or more of the following; waist circumference: men >102 cm, women >88 cm; serum triglycerides: ≥1.7 mmol/L; HDL cholesterol: men <1.04 mmol/L, women <1.29 mmol/L; blood pressure: ≥ 130/85 mmHg; fasting glucose: ≥6.1 mmol/L. Waist circumference was taken as the smallest circumference below the costal margin. Resting blood pressure was measured using the Hawksley Random Zero Sphygmomanometer.(phase 3 and 5) and the OMRON HEM 907

(phase 7). Serum triglycerides, HDL cholesterol and fasting blood glucose were analyzed as previously described (19).

Assessment of cognitive function: Cognitive function was measured at Phase 7 and consisted of six standard tasks chosen to evaluate comprehensively cognitive functioning in middle aged white-collar workers. The tests were chosen using the following criteria: assessment of multiple cognitive domains, ability to capture effects of age and other risk factors in a middle aged population, and no ceiling or floor effects. More details on the tests, described briefly below, can be found elsewhere (20).

.*Short-term verbal memory* was assessed with a 20-word free recall test. Participants were presented a list of 20 words (one or two syllables long) at two second intervals and were then asked to recall in writing as many of the words as they could in any order.

The Alice Heim 4-I (AH4-I) is composed of a series of 65 verbal and mathematical reasoning items of increasing difficulty. It tests inductive *reasoning*, measuring the ability to identify patterns and infer principles and rules.

Vocabulary was assessed using the *Mill Hill Vocabulary test*, used in its multiple-choice format, consisting of a list of 33 stimulus words ordered by increasing difficulty and six response choices.

Phonemic and semantic verbal fluency assessed via "S" words for phonemic fluency and via "animal" words for the semantic fluency. Participants were asked to recall in writing as many words beginning with "S" and as many animal names as they could in a given period of time.

The 30-item Mini-Mental-State-Examination (MMSE) was used to assess *global cognitive status*.

Assessment of covariates: All covariates (apart from educational attainment) were measured at phase 7, concurrent with the measures of cognition. *Socio-demographic variables*

consisted of age, sex, and marital status (married or cohabiting, single, divorced, widowed). SEP was assessed using measures of education, for early SEP, and occupational position, for mid-life SEP. Highest educational attainment was measured at Phase 5 and grouped into five levels (no academic qualification, lower secondary education, higher secondary education, university degree, higher university degree). Current (or last for retired participants) British civil service employment grade, defined on the basis of salary, was used as a measure of occupational position and was grouped into 3 categories; high (senior administrators), intermediate (executives, professionals and technical staff) and low (clerical and office support staff) grades. As of August 1992 the salary range among high grade employees was £25 330 - £87 620 and among low grade employees £7 387 – £11 917.

Health behavior: smoking (current/former/non smoker), frequency of alcohol consumption (less than once per week/ at least once per week/ at least once per day), and intensity of physical activity (based on frequency and duration categorised as "high", "medium" and "low")(21).

Health measures considered in these analyses were depressive symptoms and coronary heart diseases (CHD). Depressive symptoms were measured using the four-item depression subscale (range 0–12) of the 30-item General Health Questionnaire (GHQ) (22). Participants scoring ≥4 on this depression subscale were defined as having depressive symptoms (19). Prevalent coronary heart disease (CHD) was identified using clinically verified events, including non fatal myocardial infarction and definite angina as described previously (23).

Statistical Methods

Cognitive test scores were standardized using T-scores (mean=50, standard deviation (SD)=10) in order to allow comparisons between tests. We examined the association between

cumulative exposure to metabolic syndrome, measured 3 times over the 10-year follow-up, and

cognitive functioning at phase 7. For these analyses we categorized the three measures of MS

over the 10-years of follow-up as "never" having metabolic syndrome, "non persistent" (1 out of

3 screenings), and "persistent" ($\geq$2 out of three screenings). Analysis of Covariance (ANCOVA)

was performed to calculate adjusted mean differences in cognitive T-scores across the

cumulative measure of metabolic syndrome, with "never having metabolic syndrome" as the

reference.

ANCOVA was used to assess mean differences in cognitive test scores as a function of

metabolic syndrome. For these analyses, the adjustment for covariates was carried out in three

steps. First, a basic model adjusted for age and sex; then a second model, further adjusted for

marital status, health behaviours and measures of health status. Finally, education or

occupational position was added sequentially to the basic model (Figure 2) and to the second

model (Appendix). Interaction between covariates and frequency of MS across the phases were

tested and found to be non significant. The level of statistical significance was set at p$\leq$0.05,

marginal significance was defined as 0.05<p$\leq$0.10. All analyses were conducted using the SAS

software, version 9 (SAS Institute).

RESULTS

Compared to all 6967 respondents at Phase 7, participants included in the current

analyses (n=4150) were more likely to be men (73.9% vs. 64.8%), less likely to be in low

occupational positions (7.2% vs. 17.0%) and less likely to have no academic qualification (8.1%

vs. 10.0%). Participants excluded from the present analyses had lower mean scores on all

cognitive tests ($p < 10^{-4}$) and higher prevalence of MS at phase 7 (20.0 vs. 10.9%, $p < 10^{-4}$) compared to those included.

An increase in the proportion of participants with MS was observed over the 10-year follow-up, 8.3 % at phase 3, 8.9 % at phase 5 and 11.0% at phase 7. Across the phases, 10.1 % of participants showed non-persistent MS (1 out of 3 screenings), while 7.7 % showed persistent MS (≥2 out of 3 screenings). Characteristics of the participants as a function of cumulative exposure to the MS are presented in Table 1. Participants with MS (persistent or not) were more likely to be older and more likely to be men. Smoking, low physical activity, and high prevalence of CHD were more common in participants with the metabolic syndrome. While education was not associated with the metabolic syndrome, a higher proportion of participants in the low occupational position group had MS during follow-up.

Figure 1 shows the sex- and age-adjusted mean differences in cognitive T-scores at phase 7 for cumulative exposure to the MS over the 10-year follow-up. Compared to participants who never had the metabolic syndrome, those with persistent exposure to the MS had significantly lower cognitive scores on all tests except for the MMSE. However, no significant differences were observed between participants who never had MS and those with non-persistent metabolic syndrome.

The effect of further adjustments, first for education and then for occupational position, on the score differences between participants with persistent MS and participants who never had MS over the follow-up, is shown in Figure 2. After controlling for education, participants with persistent MS had lower scores on memory, reasoning, vocabulary and semantic fluency. In contrast, adjustment for occupational position attenuated this difference by 41% for memory, 86% for reasoning, 48% for vocabulary, 65 and 47% for phonemic and semantic fluency and

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49% for the MMSE. After adjustment for occupational position, no association remained significant between persistent MS and cognitive test scores, except for that with the vocabulary test.

The analysis of the distribution of all covariates, MS and the tests of cognition as a function of occupational position showed (Appendix Table A), on one hand, that the lower the occupational position, the lower the cognitive scores and the higher the prevalence of persistent metabolic syndrome. On the other hand, occupational position was associated with all potential confounders of the metabolic syndrome-cognitive function relationship considered in this analyses.

Analyses presented in Figure 2 were repeated after taking into account the other demographic factors, health behaviours and health status (Appendix Table B). In the model including education, lower cognitive T-scores were observed in participants with persistent MS over the 10-year follow-up compared to those who never had metabolic syndrome. The associations were statistically significant for vocabulary (adjusted mean difference in T scores, $\delta m = -1.89$ (-2.87;-0.90, p=0.0002)) and semantic fluency $\delta m = -1.30$ (-2.37;-0.24, p=0.02) and marginally significant for memory ($\delta m = -0.92$ (-2.01; 0.18, p=0.10). However, these associations were substantially attenuated when education was replaced by occupational position.

All the analyses presented so far used the NCEP definition but were repeated using the International Diabetes Federation (IDF) definition, (http://www.idf.org/metabolic_syndrome) of metabolic syndrome. In general terms, the IDF definition leads to greater prevalence of MS and somewhat smaller associations with cognitive function. However, the general pattern of results was similar (results not shown but available on request).

CONCLUSION

In this prospective cohort study of a middle-aged population followed up for 10 years, participants with persistent MS had lower cognitive scores for reasoning, vocabulary, semantic fluency and, to a lesser extent, memory, compared to participants who never had metabolic syndrome. These associations remained after adjustment for demographic variables, education, health behaviour and health status. No difference in cognitive function was observed between participants with non-persistent MS and those who never had metabolic syndrome. Our study sheds light on the impact of socioeconomic position on these relationships: while education had little impact on the metabolic syndrome-cognition relationship, occupational position substantially attenuated the association.

There is increasing interest in the possible impact of vascular and metabolic disorders on dementia, and several studies have investigated this association in the elderly. Two cross-sectional studies showed that the presence of MS was associated with a higher prevalence of Alzheimer's disease (10) and also with poorer cognitive function (4). In four longitudinal studies, MS was shown to be associated with a greater cognitive decline (5; 11; 12) and increased risk of all-cause and vascular dementia (8). However another study did not show evidence of the detrimental effect of MS on dementia (7). Finally, two further studies carried out in the oldest old found the opposite, MS was associated with better cognition (6) and decelerated cognitive decline (9).

The potential explanations for the above inconsistencies include differences in the length of follow-up, the sensitivity of cognitive tests to detect a decline, the low statistical power of

several studies, and survival bias in studies involving the oldest old. Our study provides a further explanation: the measurement of the MS at one point in time may not capture the impact of long-term exposure to this syndrome as there is considerable within-individual variation in MS status over time. Our finding suggests that long term exposure to MS – persistent metabolic syndrome- rather than MS status at a given moment is associated with poor cognitive function.

As poor cognition in midlife has been shown to predict cognitive decline and dementia later in life, the examination of the role of risk factors before old age is important. It allows circumvention of the problems of survival bias and reverse causality that may be common in studies in the oldest age-groups. To date, very few studies have investigated the effects of MS on cognition in middle-age. Kalmijn et al. showed a long-term association between a cluster of 7 metabolic cardiovascular risk factors measured at middle age and the risk of dementia among men in old age(14), but a recent cross-sectional study carried out on 853 participants aged 61 years, reported no association between MS and cognitive scores (13). Thus, our observation of an association between persistent MS and cognitive function in a large middle-aged population constitutes a novel finding.

Our findings emphasize the potential importance of socioeconomic circumstances in the association between MS and cognitive function. By analysing the relationship between MS and cognition after adjusting for a measure of early SEP, here education, or alternatively a later life measure of SEP, occupational position, our study highlights the different impact of these two measures. Education, although extensively examined in relation to cognitive outcomes, has been shown in several studies, including Whitehall II, not to be associated with metabolic

syndrome.(5; 6; 13) The modest impact of education on the metabolic-syndrome-cognition relationship observed in the present study is consistent with findings from other studies. On the other hand, occupational position was strongly related to socio-demographic factors, health behaviour and several health measures, and the relationship between MS and cognition was substantially attenuated after adjustment for occupational position. To our knowledge, no other study has taken into account the effects of later life measures of SEP, such as occupational position, making comparison with other studies difficult.

The discrepant effect of adjustment for education or occupational position should be interpreted in light of the fact that these measures cover different dimensions of SEP. Compared to education, reached by the individual usually in early adult life, midlife occupational position more accurately reflects SEP conditions over the adult lifespan. SEP is an important determinant of mortality and morbidity in many countries (24) and its influence on health is believed to work in several ways. Poor SEP is seen to increase the biological vulnerability to diseases by acting directly on physiological processes but also through unhealthy behaviours (25). Our report emphasizes the importance of taking into account SEP in the metabolic syndrome-cognition relationship in order to understand the potential impact of MS on cognitive aging. Adjustment for occupational position attenuated the association between persistent MS and cognition by between 41% and 86%. There are three possible implications of our findings. One, studies on cognitive ageing that adjust for education in order to control the influence of socioeconomic factors are clearly not taking the socioeconomic environment of older adults fully into account. Two, given the size of the attenuation of the association it is possible that the observed association between MS and cognition is simply the result of confounding by socioeconomic

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factors. This would imply that the observed association is the result of the impact of adult SEP on both MS and cognitive function and there is no true causal effect of MS on cognition. Three, given the association between the components of the MS and cognition evident in the literature, it is possible that 'persistent' MS is a risk factor for cognitive function. The attenuation observed in our analysis could therefore simply be due to occupational position being a good proxy for factors mediating the association between MS and cognition. Further research is needed to delineate the precise mechanisms underlying the link between MS and cognition.

Our report has several limitations. First, the participants of the Whitehall II study are mainly office-based civil servants, not fully representative of the British population, and analysis was restricted to "white" participants which may limit the generalizability of our findings. Second, we showed that participants with lower cognitive performances or with MS were less likely to be included in our analyses. This potential selection bias would probably lead to underestimation of the relationship between MS and cognition. Finally, the use of a single assessment of cognitive function is a limitation as it does not allow conclusions to be drawn on the direction of causality between MS and cognitive decline.

In conclusion, this appears to be the first study to explore the association between cumulative exposure to the MS over a 10-year follow-up and cognitive functioning in late midlife. Our results suggest that rather than MS status at a given moment per se, the persistence of the syndrome is the factor that has adverse effects on later cognitive performances during adult life. Furthermore, our report showed the different effects of SEP measures on the relationship depending on whether education or occupational position was considered; education

had little impact but occupational position had a greater impact. These results highlight the importance of the type of socioeconomic variable in identifying and targeting risk factors for cognitive ageing.

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TABLES

Table 1. Characteristics of the population at phase 7 as a function of persistence of the MS over the 10-year follow-up (n=4150)

	Cumulative exposure to the metabolic syndrome			
	Never	**Non persistent**	**Persistent**	**p-value***
	(n=3414)	(n=418)	(n=318)	
Sex, female %	27.0	21.8	22.3	0.02
Age in years, mean (SD)	60.5 (5.9)	61.4 (5.9)	61.4 (6.1)	0.001
Marital status, married or cohabited, %	77.5	74.6	72.3	0.15
Occupational position, lowest position, %	6.8	7.2	11.6	0.01
Education, no academic qualification, %	7.8	10.3	8.5	0.24
Smoking habits, Current smokers, %	10.7	12.4	11.0	$<10^{-4}$
Alcohol consumption, > one drink per day, %	49.8	46.6	44.0	$<10^{-4}$
Physical activity, low, %	13.7	17.7	20.7	0.0004
CHD prevalence, %	5.3	8.1	12.3	$<10^{-4}$
Depressive symptoms, %	11.0	9.31	14.1	0.11
Central Obesity criteria of MS**, %	12.7	57.8	70.3	$<10^{-4}$
High triglyceride criteria of MS**, %	14.4	53.6	75.8	$<10^{-4}$
Low HDL Cholesterol criteria of MS**, %	3.7	24.6	45.0	$<10^{-4}$
Hypertension criteria of MS**, %	35.3	63.2	68.2	$<10^{-4}$
High Fasting Glucose criteria of MS **, %	6.6	29.7	52.0	$<10^{-4}$

MS: metabolic syndrome

Non persistent MS was defined as having it once out of the three screenings over the 10-years follow-up. Persistent MS was defined as having it at least twice out of the three screenings.

*Results of the chi-square tests for heterogeneity.

** Each criteria of the MS was defined using the National Cholesterol Education Program (NCEP) criteria (18). For central obesity: 8 missing values; for high triglyceride, low HDL cholesterol and hypertension criteria: 1 missing value; for high fasting glucose criteria: 5 missing values.

Figure Legends

Figure 1: Mean differences (95% confidence intervals) in cognitive T-scores across the cumulative exposure to the MS (MS) over the 10-year follow-up (n=4150), adjusted for sex and age.

□ Non Persistent MS vs. no MS ■ Persistent MS vs. no MS

* Mean difference in Cognitive T-scores statistically significant p≤0.05.

Figure 2: Mean differences (95% confidence intervals) in cognitive T-scores between participants with persistent MS and those with no MS after sequential adjustment for education and occupational position

□ M1: Analyses adjusted for sex and age
□ M1 additionally adjusted for education
■ M1 additionally adjusted for occupational position

Figure

Figure 1: Mean differences in cognitive T-scores across the measure of persistence in metabolic

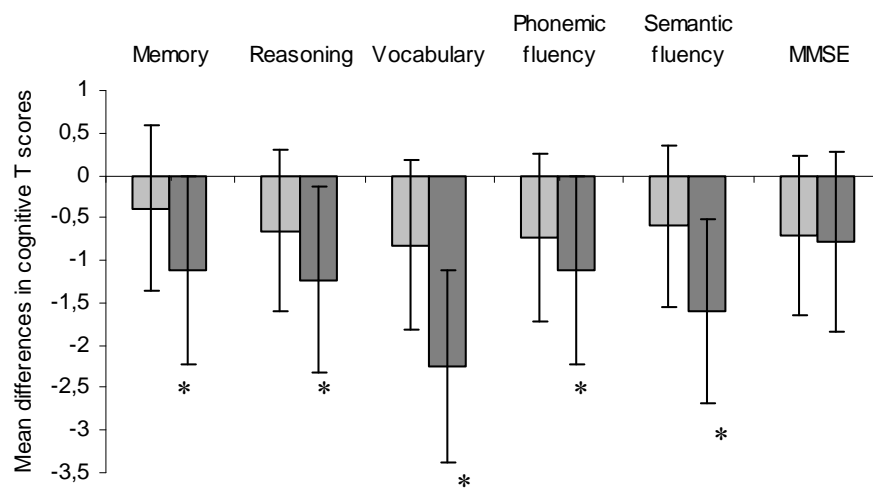syndrome over the 10-years follow-up (n=4150), adjusted for sex and age.

Figure 2: Mean differences in cognitive T-scores between participants with no metabolic syndrome and those with persistent metabolic syndrome after sequential adjustment for education and occupational grade.