Inflammatory markers and cognitive function in middle-aged adults: The Whitehall II study.

David Gimeno, Michael G Marmot, Archana Singh-Manoux

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Gimeno David [1 2 *] **, Marmot Michael G** [1] **, Singh-Manoux Archana** [1 3 4]

[1] *Department of Epidemiology and Public Health University College of London (UCL), 1-19 Torrington Place London WC1E 6BT,GB*

[2] *The University of Texas School of Public Health The University of Texas School of Public Health, San Antonio Regional Campus, Texas,US*

[3] *Centre de gérontologie AP-HP, Hôpital Saint Périne, FR*

[4] *Santé publique et épidémiologie des déterminants professionnels et sociaux de la santé INSERM : U687, IFR69, Université Paris Sud - Paris XI, Université de Versailles-Saint Quentin en Yvelines, Hôpital Paul Brousse 16, av Paul Vaillant Couturier 94807 VILLEJUIF,FR*

* Correspondence should be adressed to: David Gimeno <d.gimeno@ucl.ac.uk>

Abstract

Objectives

To assess whether C-reactive protein (CRP) and interleukin-6 (IL-6) are associated with low cognitive performance and decline in middle-aged adults.

Design/Setting

The Whitehall II study; an ongoing large-scale, prospective occupational cohort study of employees from 20 London-based white-collar Civil Service departments.

Participants

Data from over 3000 males and 1200 female employees.

Measures

Inflammatory makers measured in 1991–93 and five cognitive tests (short-term verbal memory, inductive reasoning (AH4-I), vocabulary (Mill Hill), and phonemic and semantic fluency) performed in 1997–99 and 2002–04. Performance in the lowest sex-specific quintile indicated low cognitive performance or decline. Covariates included sociodemographics, health behaviours and health conditions.

Results

In age-adjusted analyses both CRP and IL-6 were associated with all cognitive measures in 1997–99, even though the association with memory was not consistent. After extensive adjustment raised CRP levels were only associated with poor cognitive performance on the AH4-I (OR=1.38; 95% CI: 1.05–1.82) and Mill Hill (OR=1.52; 95% CI: 1.14–2.03) and IL-6 on semantic fluency (OR=1.27; 95%CI: 1.14–2.03). Associations were more evident in men than in women. No clear relationship was observed for decline.

Conclusions

Our results suggest that raised levels of inflammatory markers in midlife are moderately associated with lower cognitive status, but little with cognitive decline.

MESH Keywords Adult ; Biological Markers ; blood ; C-Reactive Protein ; metabolism ; Cognition ; physiology ; Cohort Studies ; Diabetes Mellitus, Type 2 ; blood ; Female ; Humans ; Inflammation ; blood ; psychology ; Interleukin-6 ; blood ; Life Style ; Longitudinal Studies ; Male ; Middle Aged ; Neuropsychological Tests ; Prospective Studies ; Risk Factors

Author Keywords inflammation ; C-reactive protein ; interleukin-6 ; cognitive aging ; prospective study ; midlife

INTRODUCTION

Several studies suggest that raised levels of inflammatory markers are associated with cognitive deficit and dementia (Kuo et al., 2005; Dziedzic, 2006). Among the vast array of serologic markers of systemic inflammation, the two most frequently investigated are C-reactive protein (CRP)(Teunissen et al., 2003; Yaffe et al., 2003; Tilvis et al., 2004) and interleukin-6 (IL-6) (Weaver et al., 2002; Rafnsson et al., 2007; Schram et al., 2007), which regulates the synthesis of CRP and may be a more sensitive and appropriate marker of systemic inflammation (Gabay, Kushner, 1999). Some prior studies have exclusively used measures of global cognitive function (Weaver et al., 2002; Yaffe et al., 2003; Tilvis et al., 2004; Yaffe et al., 2004), but increasingly multiple measures of cognition are being examined to identify specific cognitive function domains associated with inflammation (Teunissen et al., 2003; Dik et al., 2005; Weuve et al., 2006;

Rafnsson et al., 2007; Schram et al., 2007; Alley et al., 2008). Besides a few studies (Dik et al., 2005; Weuve et al., 2006; Alley et al., 2008), many support the idea that inflammatory markers might be useful to detect people at greater risk of cognitive impairment and, if the relationship proves to be causal, to both develop preventive strategies and, as a minimum, intervention therapies to defer the onset of the impairment.

Most of the earlier studies have focused on people 65 years-old or older (Weaver et al., 2002; Yaffe et al., 2003; Tilvis et al., 2004; Yaffe et al., 2004; Dik et al., 2005; Rafnsson et al., 2007; Schram et al., 2007), while one had a very small sample (n=65) of middle-aged adults (mean age 54 years) (Teunissen et al., 2003). Increasingly, risk profiles in middle age are recognized as being important for dementia in later life (Kivipelto et al., 2006). Thus, the 'life-long' view of dementia stresses the importance of risk factors in midlife. Evidence of an association between inflammatory markers and cognition in middle age would support the hypothesis that inflammation is involved in the pathogenesis of preclinical cognitive deficit and decline. This study aims to assess whether serum concentrations of CRP and IL-6 are associated with low cognitive performance and decline in middle-aged adults using multiple measures of cognitive function. To achieve this, we used data from the Whitehall II study, an ongoing large-scale prospective occupational cohort study of employees with the potential of adjusting for many possible risk confounders.

METHODS

Design/setting and participants

The Whitehall II study recruited 6895 men and 3413 women at Phase 1 (1985–88), response rate 73%. True response rate is likely to be higher since around 4% of the invited were ineligible. Participants were all office staff, aged 35 to 55 at study inception, from 20 London based Civil Service departments. Since Phase 1 there have been seven further data collection phases. Even phases are questionnaire only, while odd phases include a clinical examination (Marmot, Brunner, 2005). Informed consent was obtained from all participants. The University College London Medical School Committee on the Ethics of Human Research approved the protocol.

We used data from the third (1991–93), fifth (1997–99) and seventh (2002–04) phases of the Whitehall II study. Inflammatory makers were measured at Phase 3 while cognitive testing was performed at phases 5 and 7. Mean follow-up from Phase 3 to Phase 5 was 6.4 years (range 4.1 to 8.8) and to Phase 7 was 11.8 years (range 9.6 to 13.8). This study included participants with available measures of inflammatory markers at Phase 3 who completed at least one of the five tests of cognitive function either at Phase 5 or at both Phases 5 and 7 (see Figure 1). Participants were excluded if at Phase 3: 1) reported an 'ever' doctor diagnosis of stroke; 2) reported having a recent cold/flu or had high CRP values (i.e., >10 mg/L) and, 3) had missing covariate data. Participants reporting stroke were excluded because cognitive impairment is frequent after stroke (Tatemichi et al., 1994). Stroke participants had higher levels of CRP (1.26 mg/L vs. 1.11 mg/L, p=0.28) and IL-6 (1.98 pg/mL vs. 1.58 pg/mL, p=0.008) and, overall, they were also more likely to be in the lowest cognitive performance group in all cognitive tests, but numbers were too small to conduct detailed analysis. Those reporting a recent cold/flu were excluded since under those circumstances, concentrations of inflammatory markers are likely to be elevated due to infection not reflecting people's usual levels of inflammation. In our data, concentrations of inflammatory markers among those reporting a flu were higher (1.25 mg/L vs. 0.84 mg/L for CRP, and 1.70 pg/mL vs. 1.49 pg/mL for IL-6; both p<0.00001). Finally, those with high CRP values (i.e., >10 mg/L), indicating acute inflammation and immune activation due to current illness, were also excluded since these are likely to reflect short-term responses not representative of the individual's current circulating concentrations of low-grade chronic inflammatory markers (Myers et al., 2004). On the whole, excluded participants had higher concentrations of inflammatory markers and were more likely to be in the lowest cognitive performance group in all tests.

Thus, the number of participants for whom data on inflammatory markers at Phase 3 and cognitive tests, either at Phase 5, or at both Phases 5 and 7, were available for analysis varied by inflammatory marker, sex, type of cognitive measure and phase of measurement as follows: CRP in men (3029–3047) and in women (1205–1220) and IL-6 in men (3018–3036) and women (1247–1255) who completed any of the five cognitive function measures at Phase 5; CRP in men (2649–2664) and in women (1014–1028) and IL-6 in men (2636–2654) and women (1044–1059) who completed any of the five cognitive function measures at both Phases 5 and 7 (see Tables 2 to 4 for detailed samples).

Inflammatory markers

Fasting serum was collected between 8AM and 1PM in Phase 3 and stored at −70°C until analysis in Phase 7. CRP was measured using a high-sensitivity immunonephelometric assay in a BN ProSpec nephelometer (Dade Behring, Milton Keynes, UK). IL-6 was measured using a high-sensitivity ELISA assay (R & D Systems, Oxford, UK). Values below the detection limit (0.154 mg/L for CRP and 0.08 pg/mL for IL-6) were assigned a value equal to half the detection limit. To measure short-term biological variation and laboratory error, a repeated sample was taken from a subset of 150 participants for CRP and 241 for IL-6 (average elapsed time between samples was 32 [SD=10.5] days). Intra- and inter-assay coefficients of variation were 4.7% for CRP and 7.5% for IL-6. Test-retest reliability between samples was assessed with Pearson's r correlation: r=0.77 and r=0.61 for IL-6.

Tests of cognitive function

Five standard tasks were chosen to comprehensively evaluate cognitive functioning in middle-aged adults. The first was a test of **short-term verbal memory** where participants were presented a list of 20 one- or two-syllable words, randomly selected from a list of common English words (Marzano et al., 2005), at 2-second intervals and asked to write down immediately afterwards as many words as they could remember in any order that they wished (i.e., immediate free recall, a standard procedure for testing short-term memory) (Lezak et al., 2004). The Alice Heim 4-I (**AH4-I**) is composed of a series of 65 verbal and mathematical reasoning items of increasing difficulty (Heim, 1970). This test of inductive reasoning is a test of fluid general mental abilities measuring the ability to identify patterns and infer principles and rules. Participants had 10 minutes to complete this section. The **Mill Hill** vocabulary test measures crystallized verbal intelligence, assesses knowledge of verbal meaning and encompasses the ability to recognize and comprehend words (Raven, 1965). The test was used in its multiple format, a list of 33 stimulus words ordered by increasing difficulty and six response choices. Finally, two measures of verbal fluency were used: phonemic fluency was assessed via “s” words and semantic fluency via “animal” words (Borkowski et al., 1967). Subjects were asked to recall in writing as many words beginning with “s” and as many animal names as they could. One minute was allowed for each test.

High scores on all tests denote better performance and the tests chosen are appropriate for this age-group and allow discrimination between good and poor performance. Global cognitive tests like the Mini Mental State Examination (Folstein et al., 1975) are widely used in older age groups but have problems with ceiling effects in middle aged populations. The interval between Phases 5 and 7 (mean 5.4 years; range 3.2 to 7.2) was not equal for everybody, so we computed an estimated 5-year change score derived from the available data on the observed change, as in previous analysis with these data (Sabia et al., 2008). Given that there are no universally agreed criteria for judging poor cognitive performance in order to assign it clinical significance, distributional cut-points appear a useful option (Anstey et al., 2001; Weaver et al., 2002). Some researchers have used tertiles (Weaver et al., 2002), but the use of tertiles would have resulted in one-third of our high functioning cohort to be classified as having a “poor” performance. In line with some other researchers (Anstey et al., 2001) we used performance or decline in the worst “quintile” to identify poor cognitive status. Thus, the worst quintile identifies the lowest cognitive performance and the largest, and perhaps most functionally important, decline and is compared with those showing either no change or improvements. Considering that sex differences in cognitive performance are often reported, we used sex-specific cut points (Thilers et al., 2007). The worst quintile of change corresponded to losses of 2 words (out of 20) for memory, 6 points (out of 65) on the AH4-I, 2 words (out of 33) on the Mill Hill and 3 words (out of 35) on the fluency tests.

Covariates

Common correlates of inflammation and/or cognitive function were included as covariates in the analysis and were obtained from phase 3 unless otherwise stated (Albert et al., 1995; Woodward et al., 1999; Woodward et al., 2003). Sociodemographic data included age, sex, marital status (i.e., married/cohabiting, single, divorced or widowed) and adult socioeconomic position (SEP) based on participant's last known Civil Service employment grade, categorized as high (administrators), intermediate (executives, professionals and technical staff) and low (clerical and office support staff) (Marmot, Brunner, 2005).

Health-related behaviors included smoking (never, former and current smokers); alcohol consumption (in number of units of alcohol based on questions on the number of alcoholic drinks - “measures” of spirits, “glasses” of wine, and “pints” of beer - consumed in the last week); leisure-time physical activity (vigorous/moderate or none/mild based on energy utilization) (Kumari et al., 2004); and, frequency of food and vegetable consumption (i.e., from less seldom/less than a month to at least once each day).

Health conditions included Type-2 diabetes based on self-reports and glucose tolerance tests. Only participants not known to be diabetic were invited to fast in order to take the glucose tolerance test (Kumari et al., 2004); minor psychiatric disorders (GHQ caseness, score ≥4, on the 30-item General Health Questionnaire [GHQ]) (Goldberg, 1972); and prevalent coronary heart disease (CHD) up to and including Phase 3 assessed based on all available data (from questionnaires, study ECGs, hospital acute ECGs, cardiac enzymes, and clinical records) as previously reported (Kuper, Marmot, 2003). Blood pressure (in mmHg) was the average of two measures taken in the sitting position after five minutes rest with an automated devise. We used continuous measures of blood pressure rather than cut-offs to indicate hypertension as our prior work suggests adverse effects of elevated blood pressure not to be restricted to the hypertension category (Singh-Manoux, Marmot, 2005). Finally, we also used the total to high density lipoprotein (Total:HDL) cholesterol ratio as a covariate. Lipids were extracted from serum refrigerated at −4°C and assayed within 72 hours using enzymatic colorimetric methods. We chose to use Total:HDL cholesterol ratio rather than other cholesterol measure since it has been shown to be a powerful predictor of CHD risk (National Heart Lung and Blood Institute (US), 2002).

Statistical analysis

Given the skewed distributions of CRP and IL-6, the association between inflammation and cognitive function were examined using sex-specific inflammation tertiles. Sample characteristics, as a function of tertiles of the inflammatory markers, are described by their

percentage or mean and standard deviation as appropriate. The distribution of units of alcohol consumed was skewed, with 20% of participants reporting having consumed zero units. After substituting all zeros by 0.1 (Elston et al., 1996) the variable was transformed by natural logarithm and the geometric mean and standard deviation were used.

In preliminary analysis we used multiple analysis of covariance (MANCOVA), an extension of the analysis of covariance method for cases where there is more than one dependent variable, in order to examine two questions. One, to explore whether there was an overall relationship between inflammatory markers (in tertiles) and the five measures of cognition (continuous measures) after taking into account the interrelation between the cognitive measures. MANCOVA results inform whether there is an overall statistically significant effect of inflammation on cognitive function. If so, further analyses are needed to identify the specific measures of cognitive function that are associated with inflammatory markers. Two, to examine whether the association between inflammation and cognition was similar in men and women. MANCOVA analyses showed, one, an overall effect ($p<0.0001$) of both CRP and IL6 on the cognitive measures both at Phases 5 and 7; two, an indication of an interaction with sex for CRP ($p=0.064$ at Phase 5 and $p=0.063$ at Phase 7) and IL6 ($p=0.0002$ at Phase 5 and $p<0.0001$ at Phase 7). Thus, subsequent testing was conducted separately for each inflammatory marker, for each measure of cognitive function and for men and women. Testing of the relationship between inflammatory markers and low cognitive performance (based on scores at Phase 5) and decline (for change between phases 5 and 7) was carried out using logistic regression with both low cognitive performance and decline identified as performance in the worst quintile. The lowest tertile of CRP and IL-6 was the reference category and the odds ratio (OR) and 95% confidence intervals (95% CI) were calculated to estimate the risk of low cognitive performance and decline in the other tertiles. Following others (Glymour et al., 2005) baseline-unadjusted results for cognitive change are presented. Logistic regression models were computed separately for each inflammatory marker, for each measure of cognitive function and for men and women.

RESULTS

Table 1 presents the characteristics of the participants. A similar association with covariates was observed among participants who completed cognitive function measures at Phase 7 or at both Phases 5 and 7 (data not shown). Overall, sample characteristics were graded as a function of tertiles of inflammation. However, neither CRP nor IL-6 were associated with married/cohabiting status, alcohol consumption (in men alone), GHQ caseness, and diabetes (in women alone). Fruit and vegetables consumption was not related to CRP in men and smoking was not related to IL-6 in women. Both sexes had similar average age and diabetes prevalence. The following were more prevalent among women: low SEP, none or only mild leisure-time physical activity, frequent fruit and vegetable consumption, CHD and GHQ caseness. Women were less frequently married/cohabiting and current smokers, drank less alcohol, and had a lower Total:HDL cholesterol ratio and blood pressure.

Results of the association of CRP with each of the five cognitive function tests in men are presented in Table 2. In the highest tertile of CRP, age-adjusted analyses showed increased likelihood of low cognitive performance at Phase 5 for all five measures. The test for linear trend across the CRP categories was robust for all five measures at Phase 5. In fully-adjusted models, an association remained with the AH4-I (OR=1.38; 95% CI: 1.05–1.82) and the Mill Hill (OR=1.52; 95% CI: 1.14–2.03). The longitudinal analysis showed an association of the highest CRP tertile with decline in the Mill Hill in both age- and fully-adjusted analysis (OR=1.36; 95%CI: 1.05–1.76). In women (Table 3), associations with AH4-I, Mill Hill, phonemic fluency and, marginally, memory were observed in the age-adjusted analyses, but not in the fully adjusted models. In women, the age-adjusted association of high CRP with decline in the Mill Hill persisted in the fully-adjusted analysis (OR=1.56; 95% CI: 1.04–2.32).

Corresponding associations for IL-6 among men (Table 4) in age-adjusted analyses showed that higher levels of IL-6 were associated with low cognitive performance in the five cognitive tests at Phase 5. Linear trend tests showed the same pattern. In fully-adjusted analyses, high IL-6 was associated with lower semantic fluency (OR=1.27; 95%CI: 1.14–2.03) and, even though marginally, with decline in the Mill Hill test (OR=1.26; 95% CI: 0.99–1.61). In women (Table 5), the age-adjusted analyses showed that, compared to the lowest tertile, there was a greater likelihood of lower cognitive performance for all tests at Phase 5, except for the memory test. In fully-adjusted analyses, medium levels of IL-6 remained associated with Mill Hill (OR=1.93; 95% CI: 1.22–3.07) and phonemic fluency (OR=1.51; 95% CI: 1.01–2.26). The results for decline between phases showed no robust association of IL-6 in women.

DISCUSSION

The present study demonstrates associations between higher systemic inflammation, indicated by both CRP and IL-6 levels, and specific cognitive function domains in a large prospective cohort of middle-aged (age 49 on average) women and men over a 6 year follow-up period. In general, the associations were more evident in men than in women. Overall, our results provide moderate evidence of an association between raised levels of inflammatory markers in midlife and lower cognitive status, but little evidence of an association with cognitive decline in this age-group.

We found prospective associations of CRP with inductive reasoning (i.e., AH4-I test) and vocabulary (i.e., Mill Hill test), of IL-6 with fluency, and no association with short-term memory. The differential impact on specific domains is plausible since different cognitive functions activate different brain locations (e.g., inductive reasoning activates the prefrontal cortex (Goel, Dolan, 2004), tasks of verbal fluency involve the frontal (Alvarez, Emory, 2006) and the temporal lobe (Ostberg et al., 2007), and verbal ability is known to activate the left frontal lobe) which inflammation may affect. However, although likely, it is not entirely proven that inflammatory process in the brain and in the circulatory system are linked (Eikelenboom et al., 1992). Inflammation may also influence cognitive outcomes either directly through effects on the neurodegenerative process or indirectly via vascular factors (Dziedzic, 2006). Some evidence suggests that vascular disease does not always affect memory (Phillips, Mate-Kole, 1997; Bowler, 2000) and if inflammation works primarily via vascular pathways then the lack of association with short-term memory is understandable. Unfortunately, data to elucidate the potential pathways through which inflammation may differentially affect separate brain locations was unavailable in our study.

There was evidence of an association between high levels of inflammatory markers and decline in the Mill Hill test (except for IL-6 in women) between 6 and 12 years after the assessment of the inflammatory markers, but little evidence of associations with decline in other tests. Perhaps the short time interval between the two assessments has affected our ability to observe associations. The results for the Mill Hill test are somewhat puzzling. The Mill Hill test measures accumulated information and vocabulary generally thought not to be subject to age-related decline or change in non-demented population (Rabbitt et al., 2003), but it may be affected by ageing more than initially suspected (Stuart-Hamilton, 2006). Recent evidence (Krabbe et al., 2007) supports the hypothesis that inflammation (especially cytokine-related) is a risk factor in age-related neurodegeneration. However, it also shows that the effects of inflammatory markers are very complex, differentially affecting diverse aspects of cognitive function, including verbal crystallized intelligence such as the one measured by the Mill Hill test, and having differing impacts at different stages of neurodegeneration. Further research is needed to confirm and fully understand our findings.

Prior evidence is mixed since some earlier research examining the association between inflammation and specific cognitive function domains found CRP related to low performance in word learning tasks (Teunissen et al., 2003), and IL-6 related to declines in non-verbal reasoning and information processing speed (Rafnsson et al., 2007), orientation (Alley et al., 2008), and memory (Schram et al., 2007; Alley et al., 2008); whereas some research did not find associations with specific domains (Dik et al., 2005; Weuve et al., 2006; Alley et al., 2008). All prior large studies have been conducted in older samples (i.e., aged 60 or older) than ours (Dik et al., 2005; Weuve et al., 2006; Rafnsson et al., 2007; Schram et al., 2007; Alley et al., 2008). The disparity of results may be due to methodological differences (e.g., the use of different test to assess the diverse aspects of cognitive function and a varied covariate adjustment strategy), which makes it difficult to compare study findings. Further research will need to corroborate our findings and confirm whether or not inflammation is independently involved in the pathogenesis of cognitive deficit as some of our results suggest.

Our study must be interpreted considering the following methodological issues. The associations between inflammation and cognitive function were prospectively examined in a large and well-characterized British occupational middle-aged cohort. Participants were mainly white women and men working in white-collar occupations, thus results may have limited applicability. Nonetheless, given the increase of the percentage of workers in affluent societies employed in white-collar jobs (Office for National Statistics), our sample is largely representative, although observed associations are likely to be smaller than in the overall population due to the healthy worker effect (Li, Sung, 1999). Withdrawal from the cohort and mortality may have masked the impact of inflammatory markers on cognitive decline, especially since both higher concentrations levels of inflammatory markers and higher rates of cognitive function decline predict mortality (Tilvis et al., 2004; Schupf et al., 2005).

Of the 10,308 original participants of the Whitehall II study, 80.0% of the men and 68.4% of the women had inflammation measures at Phase 3 and, of those, 73.9% and 68.2% had completed at least one of the five cognitive tests at Phase 5. From this eligible study sample, 78.8% and 79.8% were respectively included in the final analytic sample after excluding some of these participants based on previous known stroke, a recent cold or flu, high CRP values or having incomplete covariate data. Thus, depending on the analyses, 40% to 55% of the initial sample was excluded. This may have biased our results towards an underestimation of the association between inflammation and cognitive performance, since excluded participants had higher levels of CRP and IL-6 and lower cognitive performance scores than participants with full data. Future research should confirm the generalizability of our findings.

The exclusion of participants due to recent or current infection deserves further comment. Nearly 20% of the sample was excluded due to infection. This exclusion was based on current CDC/AHA guidelines (Myers et al., 2004), which indicate that acute inflammation and immune activation due to current illness reflects short-term responses not representative of the individual's current circulating concentrations of low-grade chronic inflammation. As a result, inclusion of those participants in our analyses would have mixed participants having low-grade chronic inflammation with those participants having temporally elevated concentrations of inflammatory makers. The best option would have been to repeat the measurement of inflammatory markers after infection, but unfortunately this was not possible at the time the data was collected. As previously mentioned, the inclusion of those participants would have most likely inflated the reported associations. There is also evidence that long-term factors such as obesity and socioeconomic status may play a role

in the modulation of the immune system via persistent infections (Dowd et al., 2008). However, relatively little is known about the potential effects of inflammation in this fairly common group (i.e., participants with infection), and further research will be needed to address this matter.

Inflammation was assessed only once, which may be an inaccurate marker of ongoing exposure over time. It is widely established that protein levels may be reduced during storage as a result of proteolysis and aggregation, although much less in known about what specifically happens to CRP or IL-6. Thus, levels of CRP and IL-6 values analyzed from stored samples may have been inaccurate and erroneously low, which may have resulted in underestimation of the associations with cognitive function. However, that would have mostly mattered if the level of deterioration of the samples differed by level of cognitive performance. Nevertheless, although the long-term stability of CRP and IL-6 is unknown, CRP frozen at −20°C has been shown to remain remarkably stable over a 5-year storage period (Juonala et al., 2006) and serum levels of both CRP and IL-6 have reported to be fairly reliable over extended periods in time (Rao et al., 1994; Macy et al., 1997; Ockene et al., 2001; Gimeno et al., 2007).

Analyses of change with only two points in time are affected by regression towards the mean, floor effects set by the detection limits and ceiling effects. Our cognitive data are appropriate as there are few floor and ceiling effects with the tests chosen. However, our analysis is prone to the common problems when analysing change using only two waves of data. Adjusting for baseline levels of the outcome when modelling change is usually done to control for these biases, but recent research criticizes this approach as it does not satisfactorily control for these biases and it is likely to overestimate the associations (Glymour et al., 2005). Collecting data more than twice will help to overcome these problems as well as allow estimation the shape of the change over time through multiple occasions of measurement (Sacker et al., 2005).

Finally, CRP and IL-6 predict future symptoms of depression (Gimeno et al., 2008) and depression is associated with cognitive impairment (Thomas, O'Brien, 2008). In order to control for the potential confounding effect of depression we included in our analyses the GHQ30 (Goldberg, 1972). Although not specifically a measure of clinically diagnosed depression, nor of its chronicity, the GHQ30 assesses symptoms of anxiety, insomnia, social dysfunction and depression, and therefore can be considered a global indicator of psychological distress. Since the final fully-adjusted models included this measure, as well as an extensive list of sociodemographics, health behaviours and health conditions, it is unlikely that our models were biased due to incomplete adjustments. All these covariates have been shown to be associated with cognitive function in our work.

In summary, our prospective analyses suggest that systemic low-grade inflammation in midlife is moderately associated with low cognitive performance status in specific cognitive domains, but we found little evidence of an association with cognitive decline. Given these findings, and that causality cannot be firmly established from our study, it may be premature to heavily promote the development of intervention therapies to defer the onset of the impairment already in midlife. Nevertheless, it appears important to continue the study of the association of inflammation with low cognitive performance and decline in middle- and early old age in order to understand normative and pathological cognitive ageing.

Ackowledgements:

FUNDING

AS-M is supported by a “European Young Investigator Award” from the European Science Foundation. MGM is supported by an MRC research professorship. DG is supported by the National Institute on Aging (AG13196), US NIH. The Whitehall II study was supported by grants from the Medical Research Council; Economic and Social Research Council; British Heart Foundation; Health and Safety Executive; Department of Health; National Heart Lung and Blood Institute (HL36310), US NIH; National Institute on Aging (AG13196), US NIH; Agency for Health Care Policy Research (HS06516); and the John D & Catherine T MacArthur Foundation Research Network on Successful Midlife Development and Socioeconomic Status and Health. The funders had no further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

The authors thank all participating civil service departments and their welfare, personnel, and establishment officers; the Occupational Health and Safety Agency; the Council of Civil Service Unions; all participating civil servants in the Whitehall II study; and all members of the Whitehall II study team. Inflammatory markers were analyzed in the laboratory of Professor Lowe and Dr Rumley, Division of Cardiovascular and Medical Sciences, University of Glasgow, Royal Infirmary, Glasgow, Scotland, UK. Dr Gimeno would like to thank Dr Á dám G. Tabák from the Whitehall II study for his clinical advice, and Dr. Dritana Marko from the Institute of Health Policy at the University of Texas School of Public Health in Houston, Texas, USA for her help in editing the revised version of the manuscript.

Footnotes:

CONTRIBUTORS

Dr Gimeno and Dr Singh-Manoux conceptualized the original idea. Dr Gimeno prepared the first draft and did all the analyses. All the authors contributed to manuscript revision. Dr Gimeno is the guarantor. Professor Marmot directs the Whitehall II study. All authors meet the criteria for authorship stated in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals.

COMPETING INTERESTS

None of the authors has any competing interest to declare.

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Figure 1

Sample selection. †Includes sociodemograhic characteristics, health behaviours and health conditions (see table 1 for details). ‡Maximum number of participants with available measures of inflammatory markers, either CRP or IL-6, at Phase 3 who completed at least one of the five tests of cognitive function either at Phase 5 or at both Phases 5 and 7 (see Tables 2 to 4 for detailed samples of the number of participants available for specific analyses).

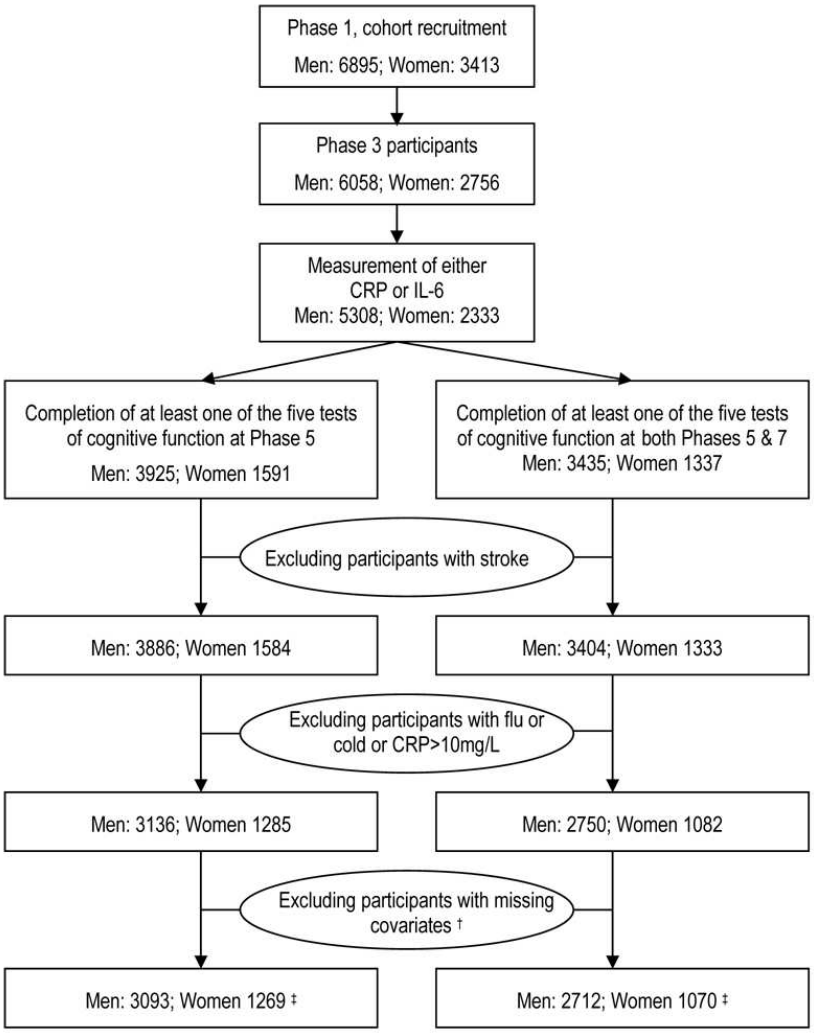

Table 1

Characteristics of the sample completing cognitive function testing Phase 5 * by tertiles of C-reactive protein (CRP) and interleukin-6 (IL-6) at Phase 3.

		CRP (in tertiles)				IL-6 (in tertiles)				
Characteristics		**Lower**	**Middle**	**Higher**	**p trend†**	**Lower**	**Middle**	**Higher**	**p trend†**	**Total‡**
Cut-points for tertiles (CRP in mg/L and IL-6 in pg/mL)	Men	<0.51	0.51–1.19	>1.19		<1.09	1.09–1.62	>1.62		
	Women	<0.57	0.57–1.44	>1.44		<1.23	1.23–2.00	>2.00		
N	Men	1,045	1,074	933		1,052	1,027	962		3,093
	Women	443	405	376		447	425	397		1,269
Age (mean (SD))	Men	48.3 (5.8)	49.5 (6.2)	50.2 (6.2)	<0.001	47.8 (5.7)	49.7 (6.2)	50.6 (6.1)	<0.001	49.3 (6.1)
	Women	48.3 (5.7)	49.9 (6.0)	51.5 (6.1)	<0.001	48.3 (5.8)	50.0 (6.0)	51.3 (6.0)	<0.001	49.8 (6.0)
Married/cohabiting (%)	Men	81.6	84.3	83.6	0.225	82.7	83.4	82.6	0.989	83.0
	Women	64.6	65.2	58.5	0.080	64.7	61.9	61.7	0.369	62.8
Low SEP (%)	Men	3.7	4.3	7.4	<0.001	3.2	4.6	7.7	<0.001	5.1
	Women	30.0	37.8	40.7	<0.001	26.6	39.3	42.8	<0.001	35.9
Current smoker (%)	Men	12.4	17.3	24.7	<0.001	14.3	16.4	24.2	<0.001	17.9
	Women	9.5	14.1	20.0	<0.001	12.3	14.1	17.4	0.061	14.5
Alcohol units in a week (G-mean (GSD))	Men	4.5 (5.9)	5.4 (5.5)	4.9 (6.6)	0.327	4.9 (5.7)	5.1 (5.7)	4.8 (6.7)	0.847	4.9 (6.0)
	Women	2.3 (6.4)	1.7 (6.7)	1.4 (7.5)	<0.001	2.5 (6.2)	1.7 (7.0)	1.2 (7.3)	<0.001	1.7 (7.0)
None/mild physical activity (%)	Men	28.5	29.1	34.0	<0.001	27.7	30.6	33.2	<0.001	30.5
	Women	44.8	50.6	54.5	0.001	43.9	51.5	54.9	<0.001	49.9
Fruit and vegetables consumption More than once a day (%)	Men	66.6	60.7	56.1	<0.001	65.5	62.1	56.0	<0.001	61.2
	Women	70.7	70.9	65.4	0.112	71.8	72.0	63.5	0.010	69.3
CHD (%)	Men	5.1	5.6	9.1	<0.001	5.1	6.4	8.0	0.009	6.5
	Women	6.8	8.8	15.2	<0.001	7.2	8.9	14.1	0.001	9.9
Diabetes (%)	Men	1.1	2.5	4.5	<0.001	0.5	3.7	3.6	<0.001	2.6
	Women	2.0	1.7	3.5	0.200	2.2	2.1	3.0	0.473	2.4
GHQ caseness (%)	Men	11.5	10.9	12.5	0.483	12.4	11.7	10.9	0.314	11.7
	Women	15.8	14.1	13.8	0.424	15.7	14.8	12.9	0.250	14.5

Total to HDL cholesterol ratio (mean (SD))	Men	4.6 (1.3)	5.2 (1.5)	5.7 (1.8)	<0.001	4.7 (1.4)	5.2 (1.6)	5.5 (1.7)	<0.001	5.2 (1.6)
	Women	3.6 (1.0)	4.0 (1.2)	4.4 (1.4)	<0.001	3.7 (1.1)	4.0 (1.2)	4.4 (1.4)	<0.001	4.0 (1.3)
Systolic blood pressure (mmHg) (mean (SD))	Men	118.7 (12.3)	121.2 (13.0)	123.5 (13.3)	<0.001	119.2 (12.2)	121.3 (13.0)	122.9 (13.6)	<0.001	121.1 (13.0)
	Women	113.6 (12.4)	117.4 (13.5)	120.1 (14.2)	<0.001	113.9 (12.5)	117.1 (13.7)	120.1 (14.2)	<0.001	116.9 (13.7)
Diastolic blood pressure (mmHg) (mean (SD))	Men	78.5 (8.3)	80.7 (8.7)	82.2 (9.5)	<0.001	78.9 (8.1)	80.6 (8.9)	81.9 (9.7)	<0.001	80.4 (9.0)
	Women	74.4 (8.5)	76.8 (9.3)	78.2 (8.6)	<0.001	74.3 (8.3)	76.9 (8.7)	78.2 (9.5)	<0.001	76.4 (9.0)

* Sample completing any of the five cognitive function measures used at phase 5.

† P trend = p for linear trend across the tertiles of CRP or IL-6 as appropriate.

‡ Sample completing any of the five cognitive function measures used at phase 5 and with either CRP or IL-6 data available. SD=standard deviation; G-mean=geometric mean; GSD=geometric standard deviation; SEP=socioeconomic position; CHD= Coronary heart disease; GHQ=General Health Questionnaire; HDL= High-density lipoprotein.

TABLE 2

Relationships between tertiles of C-reactive protein (CRP) at phase 3 (1991–93) and low cognitive performance at Phase 5 (1997–99) and cognitive decline between phases 5 and 7 (2002–04) in MEN†.

	Memory	**AH4-I**	**Mill Hill**	**Phonemic fluency**	**Semantic fluency**
CRP tertiles	**OR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**
Low cognitive performance Phase 5	(n=3036)	(n=3032)	(n=3047)	(n=3030)	(n=3029)
Age-adjusted					
Low (<0.51 mg/L)	1	1	1	1	1
Medium (0.51–1.19 mg/L)	1.05 (0.81–1.36)	1.45 (1.16–1.82)	1.12 (0.87–1.44)	1.29 (1.00–1.67)	1.00 (0.74–1.29)
High (>1.19 mg/L)	1.45 (1.13–1.87)	1.73 (1.37–2.18)	2.02 (1.59–2.58)	1.50 (1.16–1.94)	1.34 (1.04–1.74)
p for linear trend	0.003	<0.001	<0.001	0.002	0.021
Fully-adjusted ‡					
Low (<0.51 mg/L)	1	1	1	1	1
Medium (0.51–1.19 mg/L)	0.95 (0.73–1.25)	1.42 (1.09–1.84)	0.92 (0.69–1.22)	1.21 (0.92–1.59)	0.87 (0.66–1.16)
High (>1.19 mg/L)	1.21 (0.92–1.60)	1.38 (1.05–1.82)	1.52 (1.14–2.03)	1.18 (0.89–1.58)	1.00 (0.75–1.34)
p for linear trend	0.153	0.026	0.003	0.272	0.959
Cognitive decline between phases 5 & 7 †	(n=2657)	(n=2664)	(n=2667)	(n=2649)	(n=2655)
Age-adjusted					
Low (<0.51 mg/L)	1	1	1	1	1
Medium (0.51–1.19 mg/L)	0.93 (0.74–1.18)	0.78 (0.62–0.98)	1.14 (0.90–1.44)	1.08 (0.86–1.36)	1.15 (0.92–1.44)
High (>1.19 mg/L)	1.08 (0.85–1.37)	0.89 (0.70–1.13)	1.38 (1.09–1.75)	1.09 (0.86–1.38)	0.98 (0.77–1.25)
p for linear trend	0.560	0.320	0.008	0.469	0.914
Fully-adjusted ‡					
Low (<0.51 mg/L)	1	1	1	1	1
Medium (0.51–1.19 mg/L)	0.74 (0.74–1.19)	0.76 (0.60–0.97)	1.14 (0.89–1.45)	1.11 (0.88–1.40)	1.11 (0.88–1.40)
High (>1.19 mg/L)	1.09 (0.84–1.40)	0.84 (0.65–1.09)	1.36 (1.05–1.76)	1.13 (0.88–1.46)	0.90 (0.69–1.16)
p for linear trend	0.533	0.176	0.018	0.323	0.439

† Estimates reflect change over five years.

‡ Adjusted for sociodemograhic characteristics, health behaviours and health conditions.

TABLE 3

Relationships between tertiles of C-reactive protein (CRP) at phase 3 (1991–93) and low cognitive performance at Phase 5 (1997–99) and cognitive decline between phases 5 and 7 (2002–04) in WOMEN†.

	Memory	AH4-I	Mill Hill	Phonemic fluency	Semantic fluency
CRP tertiles	**OR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**
Low cognitive performance Phase 5	(n=1214)	(n=1212)	(n=1220)	(n=1209)	(n=1205)
Age-adjusted					
Low (<0.57 mg/L)	1	1	1	1	1
Medium (0.57–1.44 mg/L)	1.41 (0.97–2.05)	1.33 (0.91–1.95)	1.49 (1.02–2.18)	1.57 (1.09–2.27)	1.11 (0.76–1.63)
High (>1.44 mg/L)	1.45 (0.99–2.12)	1.61 (1.11–2.35)	1.33 (0.90–1.97)	1.12 (0.76–1.64)	1.07 (0.73–1.58)
p for linear trend	0.057	0.013	0.159	0.602	0.723
Fully-adjusted ‡					
Low (<0.57 mg/L)	1	1	1	1	1
Medium (0.57–1.44 mg/L)	1.29 (0.87–1.92)	0.93 (0.59–1.48)	1.26 (0.80–1.98)	1.42 (0.95–2.12)	0.88 (0.57–1.34)
High (>1.44 mg/L)	1.25 (0.82–1.89)	1.09 (0.68–1.75)	0.98 (0.61–1.58)	0.89 (0.58–1.38)	0.76 (0.49–1.19)
p for linear trend	0.314	0.688	0.866	0.533	0.237
Cognitive decline between phases 5 & 7 †	(n=1026)	(n=1025)	(n=1028)	(n=1014)	(n=1014)
Age-adjusted					
Low (<0.57 mg/L)	1	1	1	1	1
Medium (0.57–1.44 mg/L)	0.67 (0.46–0.97)	0.78 (0.53–1.14)	1.19 (0.82–1.74)	1.13 (0.78–1.64)	0.80 (0.55–1.17)
High (>1.44 mg/L)	0.74 (0.50–1.09)	1.07 (0.73–1.56)	1.57 (1.08–2.30)	1.00 (0.67–1.49)	0.98 (0.70–1.44)
p for linear trend	0.106	0.760	0.019	0.976	0.896
Fully-adjusted ‡					
Low (<0.57 mg/L)	1	1	1	1	1
Medium (0.57–1.44 mg/L)	0.65 (0.44–0.96)	0.77 (0.52–1.14)	1.16 (0.78–1.70)	1.22 (0.83–1.80)	0.89 (0.61–1.32)
High (>1.44 mg/L)	0.70 (0.46–1.05)	1.02 (0.68–1.53)	1.56 (1.04–2.32)	1.07 (0.70–1.63)	1.13 (0.75–1.69)
p for linear trend	0.071	0.927	0.031	0.724	0.590

† Estimates reflect change over five years.

‡ Adjusted for sociodemograhic characteristics, health behaviours and health conditions.

TABLE 4

Relationships between tertiles of interleukin-6 (IL-6) at phase 3 (1991–93) and ow cognitive performance at Phase 5 (1997–99) and cognitive decline between phases 5 and 7 (2002–04) in MEN[†].

	Memory	AH4-I	Mill Hill	Phonemic fluency	Semantic fluency
IL-6 tertiles	**OR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**
Low cognitive performance Phase 5	(n=3025)	(n=3021)	(n=3036)	(n=3019)	(n=3018)
Age-adjusted					
Low (<1.09 pg/mL)	1	1	1	1	1
Medium (1.09–1.62 pg/mL)	0.96 (0.74–1.26)	1.28 (1.01–1.62)	1.43 (1.11–1.84)	1.15 (0.88–1.50)	1.06 (0.84–1.08)
High (>1.62 pg/mL)	1.36 (1.06–1.75)	1.74 (1.38–2.18)	1.82 (1.42–2.33)	1.63 (1.26–2.11)	2.03 (1.56–2.64)
p for linear trend	0.013	<0.001	<0.001	<0.001	<0.001
Fully-adjusted [‡]					
Low (<1.09 pg/mL)	1	1	1	1	1
Medium (1.09–1.62 pg/mL)	0.87 (0.66–1.14)	1.09 (0.84–1.42)	1.16 (0.88–1.54)	1.01 (0.76–1.33)	0.96 (0.71–1.29)
High (>1.62 pg/mL)	1.07 (0.81–1.40)	1.23 (0.94–1.61)	1.22 (0.91–1.63)	1.20 (0.91–1.59)	1.52 (1.14–2.03)
p for linear trend	0.568	0.128	0.184	0.184	0.002
Cognitive decline between phases 5 & 7 [†]	(n=2645)	(n=2650)	(n=2654)	(n=2636)	(n=2641)
Age-adjusted					
Low (<1.09 pg/mL)	1	1	1	1	1
Medium (1.09–1.62 pg/mL)	0.73 (0.73–1.17)	0.93 (0.73–1.17)	1.02 (0.80–1.29)	1.03 (0.82–1.30)	1.06 (0.84–1.33)
High (>1.62 pg/mL)	1.05 (0.82–1.33)	1.01 (0.80–1.29)	1.32 (1.04–1.67)	1.02 (0.81–1.30)	1.08 (0.83–1.37)
p for linear trend	0.739	0.916	0.022	0.834	0.516
Fully-adjusted [‡]					
Low (<1.09 pg/mL)	1	1	1	1	1
Medium (1.09–1.62 pg/mL)	0.91 (0.72–1.16)	0.92 (0.73–1.17)	0.99 (0.78–1.26)	1.06 (0.84–1.35)	1.02 (0.80–1.29)
High (>1.62 pg/mL)	1.03 (0.81–1.32)	1.01 (0.79–1.29)	1.26 (0.99–1.61)	1.07 (0.83–1.37)	1.03 (0.81–1.33)
p for linear trend	0.809	0.953	0.065	0.610	0.796

[†] Estimates reflect change over five years.

[‡] Adjusted for sociodemograhic characteristics, health behaviours and health conditions.

TABLE 5

Relationships between tertiles of interleukin-6 (IL-6) at phase 3 (1991–93) and low cognitive performance at Phase 5 (1997–99) and cognitive decline between phases 5 and 7 (2002–04) in WOMEN[†].

IL-6 tertiles	Memory	AH4-I	Mill Hill	Phonemic fluency	Semantic fluency
	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
Low cognitive performance Phase 5	(n=1255)	(n=1255)	(n=1263)	(n=1251)	(n=1247)
Age-adjusted					
Low (<1.23 pg/mL)	1	1	1	1	1
Medium (1.23–2.00 pg/mL)	0.88 (0.61–1.27)	1.54 (1.05–2.25)	2.15 (1.44–3.20)	1.77 (1.22–2.57)	1.35 (0.92–1.99)
High (>2.00 pg/mL)	1.25 (0.88–1.79)	2.05 (1.41–2.98)	2.16 (1.44–3.23)	1.52 (1.04–2.23)	1.74 (1.19–2.55)
p for linear trend	0.200	<0.001	<0.001	0.042	0.004
Fully-adjusted [‡]					
Low (<1.23 pg/mL)	1	1	1	1	1
Medium (1.23–2.00 pg/mL)	0.77 (0.52–1.13)	1.12 (0.71–1.76)	1.93 (1.22–3.07)	1.51 (1.01–2.26)	1.06 (0.69–1.62)
High (>2.00 pg/mL)	0.98 (0.66–1.43)	1.32 (0.84–2.07)	1.44 (0.90–2.32)	1.16 (0.76–1.77)	1.23 (0.80–1.87)
p for linear trend	0.941	0.216	0.211	0.581	0.334
Cognitive decline between phases 5 & 7 [†]	(n=1056)	(n=1057)	(n=1059)	(n=1044)	(n=1044)
Age-adjusted					
Low (<1.23 pg/mL)	1	1	1	1	1
Medium (1.23–2.00 pg/mL)	0.81 (0.56–1.17)	1.10 (0.76–1.60)	1.19 (0.83–1.71)	0.60 (0.41–0.87)	0.93 (0.65–1.35)
High (>2.00 pg/mL)	0.83 (0.57–1.22)	1.23 (0.84–1.80)	1.24 (0.85–1.80)	0.64 (0.43–0.94)	1.15 (0.79–1.68)
p for linear trend	0.326	0.296	0.266	0.015	0.475
Fully-adjusted [‡]					
Low (<1.23 pg/mL)	1	1	1	1	1
Medium (1.23–2.00 pg/mL)	0.81 (0.55–1.18)	1.12 (0.77–1.64)	1.11 (0.76–1.61)	0.63 (0.43–0.92)	1.06 (0.72–1.56)
High (>2.00 pg/mL)	0.82 (0.54–1.22)	1.20 (0.80–1.81)	1.10 (0.74–1.64)	0.64 (0.42–0.97)	1.43 (0.95–2.14)
p for linear trend	0.292	0.367	0.637	0.025	0.091

[†] Estimates reflect change over five years.

[‡] Adjusted for sociodemograhic characteristics, health behaviours and health conditions.