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Associations of C-reactive protein and interleukin-6 with cognitive symptoms of depression: 12-year follow-up of the Whitehall II study

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Abstract

Background—A lack of longitudinal studies has made it difficult to establish the direction of associations between circulating concentrations of low-grade chronic inflammatory markers, such as C-reactive protein and interleukin-6, and cognitive symptoms of depression. The present study sought to assess whether C-reactive protein and interleukin-6 predict cognitive symptoms of depression or whether these symptoms predict inflammatory markers.

Methods—A prospective occupational cohort study of British white-collar civil servants: Whitehall II. Serum C-reactive protein, interleukin-6 and cognitive symptoms of depression were measured at baseline in 1991-3 and at follow-up in 2002-4, an average follow-up of 11.8 years. Symptoms of depression were measured with 4 items describing cognitive symptoms of depression from the General Health Questionnaire. The number of participants varied between 3339 and 3070 (mean age 50 years, 30% women) depending on the analysis.

Results—Baseline C-reactive protein (β=0.046, p=0.004) and interleukin-6 (β=0.046, p=0.005) predicted cognitive symptoms of depression at follow-up, while baseline symptoms of depression did not predict inflammatory markers at follow-up. After full adjustment for sociodemographic, behavioural and biological risk factors, health conditions and medication use, baseline C-reactive protein (β=0.038, p=0.036) and interleukin-6 (β=0.041, p=0.018) remained predictive of cognitive symptoms of depression at follow-up.

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Conclusions—These findings suggest that inflammation precedes depression at least with regard to the cognitive symptoms of depression.

Background

A growing body of evidence suggests that elevated concentrations of inflammatory markers are associated with depression. Among the vast array of serologic markers of systemic inflammation, C-reactive protein (CRP) and interleukin-6 (IL-6), which regulates the synthesis of CRP, (Gabay, Kushner, 1999) have been the most thoroughly investigated.(Danesh *et al.*, 2004) Both experimental and epidemiological research have found that depressed people have higher plasma levels of inflammatory markers.(Dentino *et al.*, 1999; Penninx *et al.*, 2003; Tiemeier *et al.*, 2003; Ford, Erlinger, 2004; Liukkonen *et al.*, 2006; Cyranowski *et al.*, 2007; Dantzer, Kelley, 2007; Ranjit *et al.*, 2007; Bremmer *et al.*, 2008) However, experimental research is based on small clinical samples, and previous epidemiological research, despite large samples and thorough covariate assessment, is cross-sectional. Generally these studies have examined short-term associations between depression and inflammation, while examination of longer term associations is scarce. Furthermore, no prior study has directly evaluated the direction of the association, which remains controversial.(Kuo *et al.*, 2005; Frasure-Smith, Lesperance, 2006)

Plausible mechanisms exist for a bidirectional relationship between inflammation and depression. First, inflammation may lead to depression. Inflammation is associated with atherosclerotic changes (Ross, 1999) which may affect the frontal-subcortical circuits resulting in depression.(Maes *et al.*, 1995a; Maes *et al.*, 1995b) Also, inflammation is part of the immune system's adaptive reaction to infection which triggers a set of metabolic and behavioural adjustments.(Yaffe *et al.*, 2004) Animal studies have described the effect of the systemic inflammatory response on many of the common symptoms attributed to depression such as a reduction of locomotive and exploratory activity, lack of interest in social activities, and reduced food and water intake.(Dantzer, Kelley, 2007) Second, depression may lead to inflammation. Production of pro-inflammatory cytokines (e.g., IL-6) is increased by negative emotions and exposure to stressful experiences.(Kiecolt-Glaser *et al.*, 2002; Pace *et al.*, 2006) Depression also promotes and maintains inflammation by diminishing the sensitivity of the immune system to the glucocorticoid hormones responsible for ceasing the inflammatory response.(Carney *et al.*, 2002; Raison *et al.*, 2006)

Data from follow-up of the Whitehall II study of British civil servants, an ongoing large-scale occupational cohort study, (Marmot *et al.*, 1991) enable us to prospectively examine whether inflammation predicts cognitive symptoms of depression, or whether such symptoms predict inflammation. A strength of the study is an extended follow-up of CRP, IL-6 and cognitive symptoms of depression, as indicated by a subscale of General Health Questionnaire. (Stansfeld, Marmot, 1992)

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, from 20 London based Civil Service departments.(Marmot *et al.*, 1991) Since recruitment 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 gained from all participants. The University College London Medical School Committee on the Ethics of Human Research approved the protocol.

Our study included participants who responded to the items on cognitive symptoms of depression and for whom inflammation was measured at phase 3 (1991-1993) or phase 7 (2002-2004). Mean follow-up was 11.8 years (range 9.6 to 13.8). As inflammation was not measured earlier, Phase 3 is used as the baseline. The number of participants with data on both symptoms of depression and inflammation at baseline was 7474 for CRP and 7420 for IL-6. At baseline and follow-up, we excluded those with high CRP values (>10mg/L) and those who reported a cold or 'flu' in the last two weeks since these conditions are typically related to short-term large responses not representative of the individual.(Myers *et al.*, 2004) This left 5978 participants with CRP and 5907 with IL-6 data at baseline. Of these, 3339 (CRP) and 3298 (IL-6) also had measurements of cognitive symptoms at baseline and at follow-up. These participants were used to determine predictive associations between inflammation at baseline and symptoms of depression at follow-up. The corresponding numbers of participants with data on symptoms of depression at baseline and measurements of CRP and IL-6 at both phases were 3353 and 3070, respectively. These participants were used to examine associations between symptoms of depression at baseline and inflammation at follow-up. Participants lost to follow-up had higher levels of CRP (1.60 mg/L vs. 1.28 mg/L; $p<0.001$) and IL-6 (1.90 pg/mL vs. 1.71 pg/mL; $p<0.001$), and a higher cognitive symptom score (1.09 points vs. 0.97; $p=0.008$) at baseline than participants with follow-up data.

Inflammatory markers

Fasting serum was collected between 8AM and 1PM at phases 3 and 7 and stored at -70°C until analysis. Samples from both phases were analyzed at the same time. 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 lower than 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 at phase 3 (average elapse time between samples was 32 [SD=10.5] days), and 533 for CRP and 329 for IL-6 at phase 7 (average elapse time was 24 [SD=11.0] days). Intra- and inter-assay coefficients of variation were 4.7% and 8.3% for CRP, and 7.5% and 8.9% for IL-6 at phases 3 and 7, respectively. Reliability between samples was assessed with Pearson's r correlation coefficients: $r=0.77$ at phase 3 and $r=0.72$ at phase 7 for CRP, and $r=0.61$ and $r=0.63$, respectively, for IL-6.

Cognitive symptoms of depression

The General Health Questionnaire (GHQ) (Goldberg, 1972; Goldberg, Hillier, 1979) is used to detect minor psychiatric disorders in non-psychiatric populations.(Rasul *et al.*, 2007; Patel *et al.*, 2008; Watson *et al.*, 2008) To examine symptoms of depression a four-item scale (Cronbach $\alpha=0.88$) was derived from the GHQ-30. This has been validated within the Whitehall II study, (Stansfeld, Marmot, 1992) based on principal components factor analysis (Nicholson *et al.*, 2005) and compared with the seven-item severe depression subscale from the GHQ-28. (Stansfeld *et al.*, 2003) The items requested whether, compared to a usual state, the participant has recently: been thinking of yourself as a worthless person; felt that life is entirely hopeless; felt that life isn't worth living; and, found at times you couldn't do anything because nerves were too bad. These items assess cognitively-based symptoms of depression only. This was the only measure available since the GHQ does not include other aspects of depression (e.g., depressed mood or neurovegetative signs). Items were scored on a four-point scale (0="not at all", 1="no more than usual", 2="rather more than usual", and 3="much more than usual"), giving a range of 0 to 12. The test-retest reliability was $r=0.78$ in a sub-sample of 286 baseline participants who repeated the GHQ within a month.(Stansfeld *et al.*, 2003)

Covariates

Common correlates of inflammation and/or depression were included as covariates in the analysis and were obtained from phase 3 unless otherwise stated.(Woodward *et al.*, 1999; Woodward *et al.*, 2003; Elovainio *et al.*, 2006)

Sociodemographic data included age (in five-year categories), sex, observer-assigned ethnicity (White, South Asian, Black and other categories), and adult socioeconomic position based on participant's last known Civil Service employment grade categorised as high (administrators), middle (executives, professionals and technical staff) and low (clerical and office support staff). (Marmot, Brunner, 2005).

Health-related behaviours were categorized as follows: alcohol consumption over the recommended limits (>14 units for women and >21 units for men);(Royal College of Physicians *et al.*, 1995) good or poor diet based on bread, milk type, and fruit and vegetable consumption, (Kumari *et al.*, 2004) vigorous/moderate or none/mild leisure-time physical activity based on energy utilization, (Kumari *et al.*, 2004) and smoking (never, former and current). Biological measures were assessed according to standard guidelines: blood pressure (mmHg), total to high density lipoprotein (Total:HDL) cholesterol ratio, body mass index (BMI in kg/m^2) and waist-to-hip ratio.(Brunner *et al.*, 1999)

Health conditions assessed were: any coronary heart disease (CHD) up to and including Phase 3, as previously reported;(Kuper, Marmot, 2003) Type-2 diabetes mellitus based on self-reports and glucose tolerance tests;(Kumari *et al.*, 2004) and self-reported respiratory illness. Medication use included CHD, diabetes and Central Nervous System medication, antidepressants, non-CHD related analgesics, and female sex hormones (hormone replacement therapy and contraceptive pills).

Statistical analysis

CRP and IL-6 values were transformed by natural logarithm given their skewed distribution. To facilitate comparison across models, linear regression coefficients were calculated for one standard deviation increases in the standardized cognitive symptom score and inflammation levels. Models were always adjusted for age, sex and ethnicity since they influence the distribution of the inflammatory markers.(Wener *et al.*, 2000)

To explore the direction of the association between inflammation and cognitive symptoms of depression, two linear models were fitted. First, the effects of baseline inflammation on cognitive symptoms at follow-up were modelled, adjusting for cognitive symptoms at baseline. Second, the effects of baseline cognitive symptoms on inflammation at follow-up were modelled, adjusting for inflammation at baseline. Analyses were not constrained to participants with complete data on inflammation and cognitive symptoms at both phases. To ensure that sample differences did not account for differences in results, models were repeated using the same sample for all analyses. This had little effect on the pattern of associations, so results are presented using all the available data for each analysis.

The contribution of the covariates to the associations between inflammation and symptoms of depression was explored in linear regression models by including each of the following sets of factors in turn: socioeconomic factors, behavioural and biological risk factors, health conditions and medication use. Finally, the analysis was repeated with simultaneous adjustment for all the above covariates. Analyses were performed using STATA/SE v.9.2® [StataCorp, 2005].

Results

Table 1 presents the characteristics of the participants with data on cognitive symptoms of depression and either CRP or IL-6 at baseline. A similar covariate pattern was observed in the separate samples of CRP and IL-6 at baseline (data not shown). Levels of both the inflammatory markers and cognitive symptoms of depression were higher in women than men. Women were older, included a slightly higher proportion of participants from ethnic minorities, and were more likely to be from the lower employment grades. Except for exercise, women had a better profile of health-related behaviours. Women had higher BMI but smaller waist-to-hip-ratio, lower blood pressure and total to HDL cholesterol than men. However, women had a higher prevalence of any CHD, and, overall, women took more medication.

Cross-sectional associations between the inflammatory markers and cognitive symptoms of depression at phase 3 and at phase 7 are shown in Table 2. In the cross-sectional analyses at baseline, CRP (β=-0.067, p=0.011) was negatively associated with cognitive symptoms of depression among women, but not among men (p for sex interaction=0.025). In cross-sectional analyses at follow-up, the negative association between CRP and symptoms of depression was weaker (β=-0.046, p=0.126) in women and again no association was observed in men. For IL-6 no association was observed in women, while a positive association was observed in men (β=0.066, p<0.001). However, the sex interactions at follow-up were not significant.

Table 3 presents the longitudinal analyses of CRP and IL-6 as predictors of cognitive symptoms of depression. Among men these associations reached statistical significance both for CRP (β=0.058, p=0.002) and IL-6 (β=0.054, p=0.006). The effects were slightly weaker for women, but there was no statistical evidence of a sex interaction. Table 4 shows that cognitive symptoms of depression at baseline did not predict CRP (β=-0.013, p=0.341) or IL-6 (β=0.008, p=0.609) at follow-up in either sex.

As the longitudinal results did not differ overall by sex, the contribution of the five sets of covariates to associations between inflammation at baseline and cognitive symptoms of depression at follow-up are presented for both sexes combined (Table 5). For both CRP and IL6, adjustment for socioeconomic position produced the greatest attenuation of the association with depressive symptoms. For CRP additional attenuation was observed on adjustment for health conditions and medication for health conditions. However, none of the covariates, individually or in combination, accounted for more than a relatively small part of the association between inflammation at baseline and cognitive symptoms of depression at follow-up (19% for CRP and 11% for IL-6, all covariates combined). Covariate adjustment did not greatly alter the non-significant relationship between baseline symptoms of depression and inflammation at follow-up (data not shown).

Discussion

The present study is apparently the first to examine the direction of the association between two inflammatory markers (CRP and IL-6) and depression, specifically the cognitive symptoms of depression. Over a period of 12 years within a large sample of British civil servants, we found that higher levels of inflammation at baseline were associated with subsequent cognitive symptoms of depression in both sexes at follow-up. This association was independent of demographic characteristics, behavioural and biological risk factors, presence of health conditions, and medication use as well as baseline measures of inflammation and cognitive symptoms of depression. Although the effect appeared stronger in men than in women, formal tests of interaction did not confirm this sex difference. Cognitive symptoms of depression at baseline did not predict CRP or IL-6 at follow-up. Thus, our findings suggest

that the direction of the association is dominantly from inflammatory markers to cognitive symptoms of depression

Inflammation as a predictor of depressive symptoms

Our findings are in agreement with earlier cross-sectional studies demonstrating a correlation between inflammation and depression.(Dentino *et al*., 1999; Penninx *et al.*, 2003; Tiemeier *et al.*, 2003; Ford, Erlinger, 2004; Liukkonen *et al.*, 2006; Cyranowski *et al.*, 2007; Dantzer, Kelley, 2007; Ranjit *et al.*, 2007; Bremmer *et al.*, 2008) The cognitive symptoms of depression can be considered an indicator of early stages of clinically diagnosed depression.(Fogel *et al.*, 2006) Thus, our results suggest that inflammation plays a role as an initiator and contributor to the progression of depression rather than contributing to the later stages of depression development. However, the small size of the regression coefficients between baseline levels of inflammation and cognitive symptoms of depression at follow-up would indicate that the contribution of inflammation to cognitive symptoms is rather small.

In our data the associations between CRP and IL6 and depressive symptoms were not explained by a comprehensive set of covariates, suggesting that, other mechanisms not covered by this study may underlie the association. Unlike many prior studies, we were able to account for the effect of adult socioeconomic circumstances. Although these circumstances are unlikely to be true mediators, they precede behavioural and biological factors and so may be considered as markers of other stressful conditions, for example.(Brunner *et al.*, 1999) Thus, adjustment for socioeconomic factors may have controlled for the effect of some exposures we did not directly measure. Further, as we controlled for a wide range of covariates as well as baseline measures of inflammation and cognitive symptoms of depression it is unlikely that our models were biased due to incomplete adjustments.

Simultaneous adjustment for all these covariates attenuated the effect of inflammation on cognitive symptoms of depression slightly more for CRP than for IL-6. This minor differential effect is consistent with the possibility that interleukins, including IL-6, are functionally involved in the development of depression through direct effects on the central nervous system which promote depression, (Dantzer, Kelley, 2007) with CRP being only a general marker of inflammatory processes.(Dantzer *et al.*, 2006) Furthermore, it has been hypothesized that inflammatory cytokines may be linked to depression through the hypothalamic-pituitary-adrenal axis.(Wichers, Maes, 2002) Supporting this hypothesis, chronic activation of the immune system has been found to produce cytokine-induced depression, (Dantzer, Kelley, 2007), at least in persons who already have a medical condition. (Dantzer *et al.*, 2006)

One cause for concern was the possibility that our observed associations were merely the result of confounding by pre-existing illness at baseline. In addition to adjustments for three health conditions (CHD, respiratory illness and diabetes) analyses were adjusted for a wide range of medications and biological risk factors, indicators of current ill-health and pre-clinical disease. As expected, this adjustment produced some attenuation of the observed associations. However, a robust independent association remained after simultaneous adjustment for all the covariates. A further cause for concern was the possibility of confounding by new-onset co-morbid conditions that may have developed between our two measurement phases. CRP and IL-6 have been found to predict a number of health conditions, such as cardiovascular disease and diabetes.(Pradhan *et al.*, 2001; Danesh *et al.*, 2004) However, controlling simultaneously for the relevant covariates at follow-up as well as at baseline did not alter the main findings (results were as follows: β=0.035 for the CRP-depressive symptoms association, p=0.055 and β=0.037 for the IL-6-depressive symptoms association, p=0.034; this additional adjustment increased the percentage of attenuation only from 19% to 24% for CRP and from 11% to 20% for IL-6 in the fully-adjusted models). Adjustment for an even wider range of covariates may have explained a greater proportion of the association, but adding extra covariates may have

added degrees of freedom to the statistical tests, thus reducing the power to detect associations and potentially inflating Type I error.

Recently, Danese *et al.* (2007) found childhood maltreatment to predict elevated adult CRP levels independently of adult circumstances. The Whitehall II study does not have a measure of childhood maltreatment, but father's social class as a marker of early life circumstances has been shown to be inversely associated with adult fibrinogen levels in these data.(Brunner *et al.*, 1996) Repeating our analyses with additional adjustment for father's social class had little effect on our findings (β=0.035, p=0.058, n=3178 for CRP and β=0.038, p=0.026, n=3140 for IL-6). However, father's social class may have limited ability to capture childhood adversity. Childhood influences on the association between inflammation and depression merit further research.

Depressive symptoms as predictors of inflammation

Our results seem not to support the proposition that cognitive symptoms of depression promote low-grade inflammation. This finding is in line with studies on other outcomes. For instance, in a 7-year follow-up study the increased risk of future angina in men was attributable to anxiety and sleep disturbance rather than to cognitive symptoms of depression.(Nicholson *et al.*, 2005) Furthermore, in another 3-year study, somatic symptoms of depression were associated with carotid intima-media thickness, a measure of sub-clinical atherosclerosis, (Mancini *et al.*, 2004) while cognitive symptoms were not.(Stewart *et al.*, 2007) We exclusively examined cognitive symptoms of depression, thus, it is impossible to determine whether the observed relationships (and the lack of them) are specific to the cognitive symptoms. Extension of our research to other aspects of depression in relation to inflammation is needed to clarify this issue. A plausible alternative interpretation that would account for the lack of predictive association between baseline cognitive symptoms and follow-up inflammation in our study may be the narrow scope of the depression measure used and the long follow-up period. Had a broader measure of depression been available that included neurovegetative symptoms, which might more readily be expected to be associated with inflammation, it is possible that associations might have been observed in the cross-sectional analyses and those manifested longitudinally may have been greater.

Methodological considerations

In the present study, participants were middle-aged and mostly white workers in white-collar occupations, thus results may have limited applicability to other ethnic groups and occupations. Nonetheless, given the increased percentage of white-collar workers in affluent societies, (Office for National Statistics, 2005) our sample is largely representative, though observed associations are likely to be smaller than in the overall population because of the healthy worker effect.(Li, Sung, 1999)

As data on inflammation and depression at both baseline and follow-up were needed in the analysis, 20% to 55% of the participants were excluded due to missing data, depending on the analyses. This may have biased our results towards an underestimation of the association between inflammation and depression, since participants lost to follow-up had higher levels of CRP and IL-6 and a higher depression symptom score at baseline than participants with full data. Future research should confirm the generalizability of our findings.

In the Whitehall II study, data on depression and CPR and IL-6 have only been collected simultaneously at phases 3 and 7. Thus, further longitudinal research is needed to determine the long-term stability of the association and what trajectory it may take over time. Repeated data from more than two occasions and at shorter intervals will help to reduce some of the limitations discussed.

The depression scale used measured a specific aspect of depression only, the cognitive symptoms; it was not a measure of clinically recognized psychiatric disorder; and, does not indicate the chronicity of depression. Yet, the scale was reliable, it was factorially derived from a validated questionnaire within the Whitehall II study (Stansfeld, Marmot, 1992) and is composed of four of the seven items of a validated severe depression subscale, and has been used in previous publications.(Stansfeld *et al.*, 2003; Nicholson *et al.*, 2005) We did not find a consistent cross-sectional relationship between high levels of inflammation and depressive symptoms. It is possible that the cognitive symptoms of depression we measured are not associated in the same way with inflammation as measures of depression which include neurovegetative symptoms which might more readily be expected to be associated with inflammation. Further research is needed on this issue.

Measurement error, floor effects due to detection limits and ceiling effects might have also influenced our findings. Diurnal variations in circulating levels of inflammatory markers have been described.(Sothern *et al.*, 1995) However, given the reasonable reliability of both inflammatory markers and cognitive symptoms of depression, the impact of measurement error should be considered minor. Floor effects may also be negligible since only a few participants were below the detection limit. Ceiling effects mainly affected CRP levels for which the upper value was set to 10 mg/L, but upper limits are not defined for IL-6.(Myers *et al.*, 2004) Participants who reported recent colds or flu, or with high CRP levels, were excluded since a high value is considered to indicate acute inflammation and immune activation due to current illness potentially masking the relatively small elevations that may be associated with psychosocial factors or even chronic disease risk. Those acute, and typically large, responses are qualitatively different from the effects of chronic health conditions, such as the ones we adjusted for, and are short-term reactions not representative of the individual. An ongoing immune-related illness is another explanation for high CRP levels, but it is unlikely that such participants would have continued to participate in the study.

Regarding the skewness of the CRP and IL-6 data, most parametric statistical procedures are substantially unaffected if the assumption that data are normally distributed is not exactly satisfied. Further, the central limit theorem ensures that means will be normally distributed for large enough samples and are sufficient to produce valid results, even from highly skewed distributions.(Kingman, Zion, 1994) Repeating the analyses with CRP and IL-6 in tertiles, rather than with log-transformed continuous measures, essentially replicated the findings (regression coefficients for top vs. bottom tertiles were β=0.08; 95%CI: -0.001 to 0.159; p=0.052 for CRP and β=0.10; 95%CI: 0.02 to 0.17, p=0.012 for IL-6).

Conclusion

In summary, findings over a 12 year period from a large-scale prospective British occupational cohort show that inflammation predicts cognitive symptoms of depression, but that cognitive symptoms of depression do not predict inflammation. Extensive covariate adjustment had modest attenuation effects on the observed relationship. Our findings are consistent with an inflammatory mechanism in the generation of cognitive symptoms of depression, but provide no support for a pathway from these symptoms to inflammation.

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TABLE 1

Characteristics of the sample at baseline (1991-1993) by sex (n=5978).

Baseline characteristics	Percent or mean (standard deviation)		
	Men (n= 4175)	Women (n=1803)	p-value
Main variables			
C-reactive protein (mg/L) †	0.77 (3.0)	0.91 (3.2)	<0.001
Interleukin-6 (pg/mL) †	1.39 (1.7)	1.65 (1.9)	<0.001
Cognitive symptoms of depression score	0.95 (1.7)	1.17 (1.9)	<0.001
Sociodemographics			
Age (years)	49.3 (6.1)	50.4 (6.1)	<0.001
Ethnicity (White)	92.2%	85.8%	<0.001
Employment grade (Low)	6.4%	40.2%	<0.001
Health related behaviors			
Diet (Poor)	37.8%	32.2%	<0.001
Exercise (None/mild)	31.0%	50.4%	<0.001
Smoking (Current)	19.8%	16.7%	<0.001
Alcohol consumption (High consumption)	17.8%	9.5%	<0.001
Biological factors			
Waist-to-hip ratio	0.90 (0.06)	0.77 (0.07)	<0.001
Body Mass Index (kg/m^2)	25.0 (3.1)	25.5 (4.5)	<0.001
Systolic blood pressure (mmHg)	121.8 (13.4)	117.7 (14.0)	<0.001
Diastolic blood pressure (mmHg)	80.8 (9.1)	76.7 (9.1)	<0.001
Total:HDL Cholesterol	5.2 (1.6)	4.1 (1.3)	<0.001
Health conditions			
Coronary heart disease	7.4%	10.8%	<0.001
Respiratory illness	6.4%	5.8%	0.338
Diabetes	3.0%	2.9%	0.809
Medication use			
Coronary heart disease	8.0%	9.6%	0.037
Diabetes	0.6%	0.5%	0.779
Central Nervous System	2.5%	3.8%	0.003
Analgesics (Not for Coronary heart disease)	1.7%	3.6%	<0.001
Female sex hormones	-	18.4%	-
Antidepressants	1.3%	2.3%	0.007

*Sample with data on baseline cognitive symptoms of depression and either C-reactive protein or interleukin-6.

†Geometric mean and standard deviation.

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TABLE 2

Cross-sectional relationships* of C-reactive protein (CRP) and interleukin-6 (IL-6) levels with cognitive symptoms of depression at baseline (1991-1993) and at follow-up (2003-2004).

	Cognitive symptoms of depression									
	Baseline					Follow-up				
Inflammatory markers	**n**	**β**	**(SE)**	**p-value**	**p-value for sex interaction**	**n**	**β**	**(SE)**	**p-value**	**p-value for sex interaction**
CRP										
Men and Women	5978	-0.013	(0.014)	0.349	0.025	4625	-0.013	(0.016)	0.413	0.211
Men	4175	0.011	(0.016)	0.501		3239	0.0007	(0.019)	0.911	
Women	1803	-0.067	(0.026)	0.011		1336	-0.046	(0.030)	0.126	
IL-6										
Men and Women	5907	-0.004	(0.014)	0.794	0.069	4277	0.054	(0.016)	0.001	0.280
Men	4104	0.019	(0.017)	0.261		3074	0.066	(0.018)	<0.001	
Women	1803	-0.043	(0.025)	0.082		1203	0.030	(0.031)	0.323	

*Adjusted for age, sex and ethnicity. β = linear regression standardized coefficients expressing the change in standardized cognitive symptoms of depression per one standard deviation in the levels of the inflammatory markers.

TABLE 3

Longitudinal relationship* of C-reactive protein (CRP) and interleukin-6 (IL-6) levels at baseline (1991-1993) with cognitive symptoms of depression at follow-up (2003-2004).

	Depressive symptoms at follow-up †				
Inflammatory markers at baseline	**n**	**β**	**(SE)**	**p-value**	**p-value for sex interaction**
CRP					
Men and Women	3339	0.046	(0.016)	0.004	0.319
Men	2388	0.058	(0.019)	0.002	
Women	951	0.020	(0.030)	0.522	
IL-6					
Men and Women	3298	0.046	(0.016)	0.005	0.610
Men	2347	0.054	(0.020)	0.006	
Women	951	0.032	(0.028)	0.259	

*Adjusted for age, sex and ethnicity.

†Additional adjustment for cognitive symptoms of depression at baseline. β = linear regression standardized coefficients expressing the change in standardized cognitive symptoms of depression per one standard deviation in the levels of the inflammatory markers.

TABLE 4

Longitudinal relationship* of cognitive symptoms of depression at baseline (1991-1993) with C-reactive protein (CRP) and interleukin-6 (IL-6) levels at follow-up (2003-2004).

	Inflammatory markers at follow-up									
	CRP †					IL-6 ‡				
Depressive symptoms at baseline	**n**	**β**	**(SE)**	**p-value**	**p-value for sex interaction**	**n**	**β**	**(SE)**	**p-value**	**p-value for sex interaction**
Men and Women	3353	-0.013	(0.014)	0.341	0.731	3070	0.008	(0.015)	0.609	0.229
Men	2395	-0.016	(0.017)	0.332		2207	-0.005	(0.019)	0.781	
Women	958	-0.004	(0.023)	0.854		863	0.033	(0.027)	0.255	

*Adjusted for age, sex and ethnicity.

†Additional adjustment for C-reactive protein levels at baseline.

‡Additional adjustment for IL-6 levels at baseline. β = linear regression standardized coefficients expressing the change in the level of inflammatory markers per one standard deviation in cognitive symptoms of depression.

TABLE 5

Longitudinal relationship* of C-reactive protein (CRP) and interleukin-6 (IL-6) at baseline (1991-1993) with cognitive symptoms of depression at follow-up (2003-2004).

	Depressive symptoms at follow-up							
	For CRP at baseline				For IL-6 at baseline			
Adjustments †	**n**	**β**	**(SE)**	**p-value**	**n**	**β**	**(SE)**	**p-value**
Age, sex and ethnicity (model A)	3339	0.046	(0.016)	0.004	3298	0.046	(0.016)	0.005
A + Socioeconomic position	3339	0.042	(0.016)	0.009	3298	0.041	(0.016)	0.012
A + Health related behaviours	3332	0.043	(0.016)	0.007	3291	0.042	(0.016)	0.011
A + Biological factors	3264	0.047	(0.018)	0.008	3226	0.047	(0.017)	0.006
A + Health conditions	3320	0.044	(0.016)	0.006	3279	0.045	(0.016)	0.005
A + Medication use	3328	0.042	(0.016)	0.008	3287	0.046	(0.016)	0.005
Fully adjusted	3229	0.038	(0.018)	0.036	3191	0.041	(0.016)	0.018

† Additional adjustments for cognitive symptoms of depression at baseline. Health related behaviours included diet, exercise, smoking, and alcohol consumption; biological factors included: waist-to-hip ratio, body mass index, systolic and diastolic blood pressure, and total:HDL cholesterol; health conditions included: coronary heart disease, respiratory illness and diabetes; medication use included coronary heart disease, diabetes, central nervous system, analgesics (not for coronary heart disease), female sex hormones and antidepressants. β = linear regression standardized coefficients expressing the change in standardized depressive symptoms per one standard deviation in the levels of the inflammatory markers.