Unhealthy lifestyle may increase later depression via inflammation in older women but not men

Sarah A. Hiles, PhD[1]; Amanda L. Baker, PhD[1]; Theo de Malmanche, MB.ChB[2]; Mark McEvoy, PhD[3,4]; Michael Boyle, FRACP, MD[5]; John Attia, MD, PhD[3,4]

---

[1] Priority Research Centre for Translational Neuroscience and Mental Health, Faculty of Health, University of Newcastle, New South Wales, Australia

[2] Immunology, Hunter Area Pathology Service, John Hunter Hospital, New South Wales, Australia

[3] Centre for Clinical Epidemiology and Biostatistics, Faculty of Health, University of Newcastle, New South Wales, Australia

[4] Hunter Medical Research Institute, John Hunter Hospital, New South Wales, Australia

[5] Department of Immunology and Infectious Diseases, Division of Medicine, John Hunter Hospital, New South Wales, Australia

Short Running Title: Inflammation, depression, and unhealthy behaviour

Corresponding Author: Sarah Hiles, Priority Research Centre for Translational Neuroscience and Mental Health, University of Newcastle, Callaghan, NSW, 2308, Australia.

Email: sarah.hiles@uon.edu.au

Abstract

Depression and inflammatory markers have a reliable cross-sectional association although less is known about the prospective relationship. The current study investigated whether pro-inflammatory markers are prospectively associated with depression, and whether indicators of unhealthy lifestyle, physical health and psychosocial functioning may drive this association. Participants were drawn from the Hunter Community Study, a community-dwelling cohort of individuals aged 55-85 years (N = 1410). Participants completed baseline physiological assessment, health-related questionnaires, and blood sampling for the analysis of inflammatory markers, C-reactive protein (CRP) and interleukin (IL)-6. Participants completed the same depressive symptom questionnaire again after 3.5 to 5.5 years. Depression outcomes at follow-up were analysed dichotomously using established scale cut-off scores and continuously as a "residual score", representing the variation in follow-up depressive symptoms not explained by baseline symptoms and age. Analyses were conducted on males and females separately. At baseline, indicators of unhealthy lifestyle, physical health and psychosocial functioning were associated with depressive symptoms and inflammatory markers. For males, there were no relationships between inflammatory markers and follow-up depression outcomes. In females, IL-6 was significantly associated with depression outcomes in univariate, but not multivariate analyses. However, IL-6 significantly mediated the association between the predictors of waist-to-hip ratio, smoking and psychological coping at baseline, and follow-up depression outcomes. The results support the inflammatory hypothesis of depression, although females may be more vulnerable to effects. The findings raise the possibility that unhealthy lifestyle and psychosocial stress may drive inflammation and subsequent depressive symptoms.

Keywords: Cohort; C-reactive protein; depression; inflammation; interleukin; prospective.

Introduction

The inflammatory hypothesis of depression posits that inflammation may have a causative role in depression. It is supported by observations of depressive-like behaviour following cytokine administration in animals and humans, and idiopathic major depressive disorder in patients treated with cytokines such as interferon-alpha or interleukin (IL)-2 (Anisman et al., 2005; Capuron et al., 2009; Dantzer et al., 2011; Miller et al., 2009; Myint et al., 2009; Reichenberg et al., 2001). Furthermore, inflammatory mediators, including IL-6, C-reactive protein (CRP), and tumor necrosis factor are consistently elevated in depression (Dowlati et al., 2010; Hiles et al., 2012; Howren et al., 2009). Emerging evidence from randomised controlled trials suggests that anti-inflammatory medications may improve depression outcomes (Akhondzadeh et al., 2009; Raison et al., 2013). Inflammatory mediators interact with key biological systems implicated in depression, including altering neuroendocrine stress activity, neural plasticity, cognitive functioning, reactive oxygen species, and neurotransmitter metabolism and activity (Irwin and Miller, 2007; Miller et al., 2009). Thus, a causal relationship is biologically plausible.

The source of the elevated inflammatory markers in depression remains unclear. Recent theories, such as the social signal transduction theory (Slavich and Irwin, 2014) and PATHOS-D (Raison and Miller, 2013), propose that real or imagined psychosocial stressors, represented cortically, activate autonomic and hormonal inflammatory pathways and upregulate inflammatory gene expression. This upregulation produces the elevated circulating inflammatory mediators that cause cognitive, emotional and behavioural symptoms of depression. However, the source of inflammation in people with depression may be broader than this, involving factors such as nascent or apparent physical illness, including obesity, and/or aspects of lifestyle (Berk et al., 2013). Aspects of physical illness and unhealthy lifestyle, including central adiposity, low physical activity, poor diet quality, smoking and

alcohol use, are frequently observed in people with depression and also have inflammatory consequences (Hamer et al., 2009a; Lopresti et al., 2013; Milaneschi et al., 2009; O'Connor et al., 2009). For instance, adipose tissue, particularly hypertrophic abdominal fat, produces inflammatory cytokines and mediators (Bastard et al., 2006; Maury and Brichard, 2010; Odegaard and Chawla, 2013) and it may be this abdominal, and not subcutaneous, fat that is associated with depression (Everson-Rose et al., 2009).

Little attention has been given to examining potential sources of inflammation in depression within longitudinal contexts. Indeed, few published studies address longitudinal evidence of whether elevations in inflammatory markers precede or follow depressive symptoms, and the evidence that is published is mixed. Meta-analysis of longitudinal studies indicate a small significant association between elevated CRP (eight studies) or IL-6 (three studies) and subsequent depressive symptoms, with moderate heterogeneity (Valkanova et al., 2013). There is also support for a bi-directional prospective relationship between inflammatory markers and depressive symptoms (Hamer et al., 2009a; b; Matthews et al., 2010). Given the limited and mixed evidence, further exploration of the prospective relationship is warranted, with close consideration of the influence of effect modifiers. For instance, although previous prospective studies have selectively examined women (Matthews et al., 2007; 2010) or men (Boyle et al., 2007), typically gender is considered as a control variable, rather than an effect modifier. There are well-established differences in the clinical presentation of depression in men and women (Marcus et al., 2005), likely due to both social factors and biological factors, including inflammatory markers and neuroendocrine stress hormones (Edwards et al., 2006; Kudielka and Kirschbaum, 2005; Larsson et al., 2009; Marriott and Huet-Hudson, 2006; McConnell et al., 2005). Therefore, examining the prospective relationship between depression and inflammatory markers by gender is pertinent.

To our knowledge, mediation analyses have not been completed to examine whether inflammatory markers mediate the relationship between baseline health and lifestyle factors, and later depression. This approach may highlight whether physical health and lifestyle could be a source of elevated inflammatory markers observed in people with depression. The current study explores the relationship between inflammatory markers, depressive symptoms and indicators of psychosocial functioning, physical health, and unhealthy lifestyle (central adiposity, low physical activity, poor diet quality, smoking and alcohol use). There are two discrete aims. The first aim is to explore a practical question from a biomarker perspective: whether baseline levels of inflammatory markers – IL-6 and CRP – are associated with levels of depressive symptoms at follow-up, and whether the effects remain after adjusting for confounding. The second aim is to examine lifestyle, physical health or psychosocial functioning as predictors of depressive symptom outcomes at follow-up, and explore whether inflammatory markers mediate this relationship, thereby providing evidence regarding potential sources of inflammatory markers in depression.

Material and Methods

Participants

Participants were drawn from the Hunter Community Study, a study of the health of older persons in the large regional centre of Newcastle, New South Wales, Australia (McEvoy et al., 2010). Participants gave informed consent to participate. All procedures were approved by the institutional ethics review board and conducted in accordance with the Declaration of Helsinki. Briefly, between December 2004 and December 2007, community-dwelling individuals from the Newcastle region were randomly selected from the Australian electoral roll and invited to participate in the study. 3318 individuals agreed (44.5% participation rate). The gender and marital status of these participants were similar to national

Australian profiles. Participants were re-contacted between January and December 2010 with an invitation to complete follow-up questionnaires. By follow-up, the study team was notified of 132 deaths (4%), 169 people actively withdrew (5%) and 767 (23%) were lost to follow-up with unknown reasons, leaving 2250 who completed follow-up questionnaires. Those who completed follow-up were significantly younger, were more likely to be married, had lower IL-6, and had lower depressive symptoms (all *p*'s < .05).

Procedures

At baseline, participants completed self-report questionnaires and a face-to-face clinical assessment to gather information regarding health status, functioning and health behaviours (for detail on measures see McEvoy et al., 2010). 78% of participants provided a serum blood sample for routine blood testing and for storage for future use, which included analysis of CRP and IL-6. At follow-up, participants completed self-report questionnaires with a focus on mental health.

Measures

Inflammatory markers: 12 hour fasting blood was collected (95% were collected in the morning). Samples were centrifuged at 4°C and 3000g for 10 minutes, and serum was stored at -80°C until analysis. High sensitivity CRP was analysed via CRP Flex System on Dimension Vista System immunonephelometry (Siemens Healthcare Diagnostics, Newark, DE, USA). The limit of detection was 0.16mg/L and coefficient of variation was 4.8%. High sensitivity IL-6 was analysed via Access IL-6 magnetic bead/chemiluminescent immunoassay (Beckman Coulter, Fullerton, CA, USA, ref A16369), performed on a Beckman DxI. The lower limit of detection was 0.5pg/mL and coefficient of variation was 12%.

Depressive symptoms: Depressive symptoms were measured at baseline and follow-up using the 20-item self-report Centre for Epidemiologic Studies Depression Scale (CES-D)

(Radloff, 1977). It provides a continuous score in the range of 0-60 based on the frequency of depressive symptoms in the past week. A cut-off score of 16 is used as a marker of at least mild and clinically relevant depressive symptomatology and possible depression (100% sensitivity and 88% specificity for major depression) (Beekman et al., 1997). The scale was designed for use in epidemiological studies and has been validated for use in older samples (Beekman et al., 1997). For participants missing five or fewer items on the scale, values were imputed based on the average of the items completed (in the final included sample, $N = 115$ [8.2%] were imputed at baseline; $N = 193$ [13.7%] were imputed at follow-up).

Lifestyle factors: Five factors were selected as indicators of unhealthy lifestyle: adiposity (body mass index or waist-to-hip ratio), steps per day, percentage of energy intake from saturated fat, smoking status, and alcohol misuse. Measures of adiposity were calculated from measurements taken by trained staff during the physical assessment. Average steps per day as an indicator of physical activity was obtained using measurements from a pedometer worn over a week. Diet quality, including assessment of saturated fat intake, was assessed using a previously validated semi-quantitative food frequency questionnaire (Smith et al., 1998), from which nutrient intakes were determined using a custom-made nutrient analysis programme based on the NUTTAB 2006 database (Food Standards Australia New Zealand, 2006). Saturated fat was selected as it is promoted as a key nutrient to reduce in public health guidelines (National Health and Medical Research Council and Department of Health and Ageing Australian Government, 2005; U.S. Department of Agriculture and U.S. Department of Health and Human Services, 2010; World Health Organization, 2013) and this particular aspect of diet is associated with elevated inflammatory markers (King et al., 2003). Smoking status was self-reported. Alcohol use was also self-reported using a modified timeline follow-back method (Cumming and Mitchell, 1997; Skinner, 1982; Sobell et al., 1979). Based on the number of days when alcohol was consumed and number of standard drinks consumed in the

last month, we determined whether the participant drank above contemporaneous Australian alcohol guidelines (>4 standard drinks per day for men, >2 standard drinks per day for women) (National Health and Medical Research Council, 2001).

Physical health and psychosocial functioning: The number of physical illnesses that a participant endorsed from a list of ten common illnesses was summed to create a proxy indicator of physical health (0-10; asthma, hypertension, angina, osteoarthritis, rheumatoid arthritis, heart attack, stroke, diabetes, atrial fibrillation, thyroid problems, osteoporosis, and bronchitis/emphysema). Additional indicators of physical functioning were dimensions of the Assessment of Quality of Life – 6D (AQoL-6D) (Richardson et al., 2012): Independent Living (needing help with household tasks, mobility, walking, self-care) and Pain (frequency of pain, discomfort, interference with activities). Indicators of psychosocial functioning were the AQoL-6D Relationships dimension (satisfaction with intimate relationships, health and family role, and health and community) and Coping dimension (energy, control of life, coping with problems).

Data analysis

Analyses were conducted using Stata SE/11 (StataCorp LP, USA). Participants who did not complete follow-up surveys (N = 1067), were without a blood sample (N = 734), or who reported lupus erythematosus or use of immunosuppressants (N = 1) were excluded. Furthermore, participants with high concentrations of inflammatory markers were also excluded from analysis as a conservative indicator of probable acute illness [CRP>10mg/L based on the guidelines of Clyne and Olshaker (1999) and IL-6>23pg/L which represented values more than 3 standard deviations above the mean in this sample; N = 106]. The 1908 participants excluded from the analyses were significantly older, and were more likely to be female and not married at baseline ($p < .05$).

As an alternative approach to using a clinical guideline of probable acute illness to exclude cases, a secondary sensitivity analysis was conducted where a statistical criterion was used to monitor outlying cases. To indicate influential data points, Cook's distance was calculated for key regression analyses between inflammatory markers and follow-up depression outcomes. Cook's distance values above $N/4$ were excluded (for females $N = 32$ for IL-6, $N = 30$ for CRP; for males $N = 22$ for IL-6, $N = 30$ for CRP).

All analyses were performed separately for females and males, as significant interactions between IL-6 and gender were observed in dummy coded regression analyses predicting baseline continuous CES-D score ($t(1301) = 1.96$, $p = .05$), follow-up continuous score ($t(1319) = 2.19$, $p = .03$) and dichotomous score ($Z = 1.94$, $p = .05$). We explored cross sectional associations between baseline inflammatory markers, depressive symptoms, lifestyle factors, physical health and psychosocial functioning using age-adjusted, lifestyle-adjusted and fully-adjusted multiple linear regression models with robust standard errors. Semi-partial correlations were calculated to demonstrate the unique relationship between the predictor and the outcome. Robust standard errors were used to account for observed heteroscedasticity and non-normality of residuals via inspection of plotted residuals and Breusch-Pagan/Cook-Weisberg tests.

To test the first study aim, we examined whether inflammatory markers, lifestyle factors, physical health and psychosocial functioning were associated with follow-up depressive symptoms. Baseline and follow-up measures of psychological symptoms were strongly correlated, so instead of using follow-up scores as the outcome variable we derived a residual score for each participant from a regression model of age and baseline CES-D score predicting follow-up CES-D score. Thus, the outcome for these analyses (henceforth referred to as "residual score") represents the variation in follow-up depressive symptoms not explained by baseline depressive symptoms and age. A high residual score indicates that the

participant had a higher than expected score at follow-up, relative to their baseline score and age. We also completed logistic regression on the outcome of dichotomised high vs. low depressive symptoms at follow-up, based on the established CES-D cut-off score of 16 (Beekman et al., 1997), excluding people with high depressive symptoms at baseline (CES-D ≥16).

To explore the second aim, mediation analysis was applied using a model of a lifestyle, health or psychosocial functioning indictor (based on a significant univariate direct effect, $p < .05$) predicting residual CES-D score, mediated via IL-6 or CRP. Sobel-Goodman mediation tests were completed and confidence intervals were derived based on Preacher and Hayes (2004) methods, using a bias-corrected bootstrapping approach with case resampling.

Results

Sample description

Table 1 describes the baseline characteristics of the 1410 participants included in these analyses. They were an average of 65.6 years old (*SD* = 7.1); 771 (50%) were females, 1074 (76%) were married or de facto/living with a partner, and all were living in the community. By follow-up, most were still living in the community, with less than 1% in retirement or hostel facilities.

Cross sectional associations

For females, most aspects of unhealthy lifestyle and all measures of physical health and psychosocial functioning were significantly associated with IL-6 (ranging in size from β = -0.01 to β = 0.37; Table 2; see also Supplementary Table 1). Only steps per day and current smoking remained significant after adjusting for other predictors (β = -0.20, β = 0.10, respectively). For males, similar patterns were observed (ranging from β = 0.01 to β = 0.37), although waist-to-hip ratio, number of health problems and AQoL-6D Independent Living

remained significant after full multivariate adjustment (β = 0.13; β = 0.10; β = 0.11, respectively). Similar patterns were observed for the association between CRP and other factors (ranging from β = 0 to β = 0.42; Table 2; Supplementary Table 2). For females, after full multivariate adjustment, once again steps per day and also safe use of alcohol remained significant predictors (β = -0.17; β = -0.09). For males, again waist-to-hip ratio and Independent Living scores remained significant predictors after multivariate adjustment (β = 0.16; β = 0.28, respectively).

Inflammatory markers, physical health, psychosocial functioning and many aspects of unhealthy lifestyle were cross-sectionally associated with baseline CES-D scores, which were largely similar for females and males (ranging from β = 0.02 to β = 0.62; Table 2; Supplementary Table 3). For females, IL-6 and waist-to-hip ratio remained significant after lifestyle adjustment, with similarly sized independent contributions according to semi-partial correlations of 0.12 and 0.10, respectively. After full adjustment, only the psychosocial indicators of Relationships and Coping were significant predictors (β = 0.24; β = 0.49, respectively). For males, after lifestyle adjustment, waist-to-hip ratio, steps per day and energy from saturated fat remained significant, contributing similarly according to semi-partial correlations (all $r\approx$0.08 or 0.09). After full adjustment, the significant predictors were AQoL-6D Relationships, Coping and Pain dimensions (β = 0.19, β = 0.40, β = 0.13, respectively).

Baseline inflammatory markers and follow-up depressive symptoms

Fewer factors were significantly associated with CES-D residual scores (i.e., variation in follow-up CES-D not explained by baseline CES-D and age; ranging from β = 0 to β = 0.14; Table 3). For females, IL-6 was no longer a significant predictor after lifestyle and full-adjustment. Significant predictors of residual score after full multivariate adjustment were waist-to-hip ratio, energy from saturated fat and AQoL-6D Pain (β = 0.09, β = 0.11, β = 0.16,

respectively). For males, inflammatory markers were not significant univariate predictors, whereas waist-to-hip ratio, Relationships, Coping and Pain were significant predictors (β between 0.07 and 0.12). However, the multivariate models for males were poor and no significant predictors were observed. Adding IL-6 to a multivariate regression model with lifestyle factors did not improve the model for females (R^2 change .002; $F(1,530) = 0.91$, $p = .34$) or males (R^2 change < .001; $F(1,542) = 0.001$, $p = .98$). We also examined whether inflammatory markers were associated with dichotomous depression at follow-up, excluding participants with high depressive symptoms at baseline (CES-D ≥ 16; Table 4). The only significant predictor after multivariate adjustment was AQoL6-D Coping (OR = 37.64, $p = .001$) in the model for females.

For the sensitivity analysis using a statistical criterion for outliers, the pattern of results remained the same as in the final analyses included in Table 3: for females, significant association between logIL-6 and depression residuals (b = 0.61, SE = 0.31, $t = 1.98$, $p = .048$) and not significant for logCRP and depression residuals; and for males, non-significant associations between logCRP/logIL-6 and depression residuals.

Inflammatory markers as mediators of the lifestyle to depression relationship

The univariate significant predictors of residual depression score were entered as predictors into a mediation analysis, with residual depression score as the outcome and IL-6 or CRP as mediator (Table 5). For females, IL-6 was as a significant mediator of the relationship between waist-to-hip ratio and depression outcomes, and current smoking and depression outcomes (indirect effects 0.01 and 0.25, respectively), with direct effect effects remaining significant (0.12 and 4.04, respectively). IL-6 also significantly mediated the relationship between AQoL-6D Coping and depression outcomes (0.56), rendering the direct effect non-significant (4.85). IL-6 was not a significant mediator for saturated fat intake or Pain. For males, IL-6 was not a significant mediator of relationships between any predictors

(waist-to-hip ratio, Relationships, Coping and Pain) and residual depression score. There were no significant indirect effects of CRP as a mediator between predictors and residual score for females or males.

Discussion

The current study sought to examine whether baseline levels of inflammatory markers predict later depression outcomes, and whether the effects are driven by aspects of physical health, unhealthy lifestyle and perceived psychosocial functioning. The strongest effects observed were that unhealthy lifestyle factors drive depression both directly and indirectly via inflammatory mediators. There was also evidence that the effect of psychological coping on depression outcomes is through inflammation. These effects were observed for females only, indicating evidence of a gender difference in the relationship between inflammatory markers, depression, and physical and psychological functioning.

Firstly, this study replicates the clear cross-sectional inter-relationship between inflammatory markers, depression, and health and lifestyle, while also highlighting gender differences. The cross-sectional relationship between IL-6 and depression remained after controlling for aspects of unhealthy lifestyle in females but not males. Estrogen is generally anti-inflammatory, and thus, one possibility is that low levels of estrogen in these post-menopausal women may make them more prone to depression via inflammatory states (Straub, 2007). The sex differences observed in neuroendocrine stress responses may also contribute (Kudielka and Kirschbaum, 2005). There is other evidence of sexual dimorphism in relationships between inflammatory markers and health and lifestyle, for instance women show a greater increase in IL-6 after a high fat meal than men (Payette et al., 2009), and women have a higher proportion of fat mass than men and a stronger association between adiposity and inflammatory markers (Thorand et al., 2006). Thus, gender seems to be an

important effect modifier in the depression-inflammation relationship, particularly considering the contribution of lifestyle.

The current study also sought to explore several unanswered questions regarding prospective evidence for the inflammatory hypothesis of depression: namely whether inflammatory markers have the potential to be useful biomarkers of later depression onset, and whether unhealthy lifestyle, physical health and psychosocial stress (as indicated by perceived quality of life) may be important potential sources of elevated inflammatory markers. In females, but not males, IL-6 was a significant predictor of follow-up depression outcomes. However, these effects were not significant after adjusting for lifestyle, which is consistent with previous findings indicating that unhealthy lifestyle confounds the relationship between depression and inflammatory markers (Duivis et al., 2011).

A noteworthy novel outcome in this study is that, for females, IL-6 mediates part of the association of baseline adiposity, smoking and psychosocial coping, with later depression outcomes. This highlights several potential sources of the inflammatory markers observed in depression. The finding that the relationship between an individual's perceived current ability to cope with stress and later onset of depressive symptoms is mediated by inflammation is consistent with contemporary depression theories which propose that perceived psychosocial stress is the trigger for inflammation (Raison and Miller, 2013; Slavich and Irwin, 2014). Although the variable of coping (consisting of an individual's sense of energy, control of life, and coping with problems) was used to infer psychosocial stress, the finding will be strengthened if future studies consider alternative measures of psychosocial stress, such as major life events scales, daily events or perceived stress scales.

The significant mediation effects of IL-6 for the association between adiposity and depression is particularly informative, given that waist-to-hip ratio endured as a significant predictor of residual CES-D scores after adjusting for other lifestyle factors. Inflammatory

mediators induced by hypertrophic, rather than lean, adipocytes (and excess nutrient intake) are already suggested to be involved in the pathogenesis of aspects of the metabolic syndrome, such as insulin resistance (Calay and Hotamisligil, 2013; Odegaard and Chawla, 2013), and may extend to depression. Other prospective studies also highlight the importance of lifestyle in the depression-inflammation relationship; including that CRP only partly explains the association between physical activity and risk of depression (Hamer et al., 2009a) and that a healthy diet may minimise the effect of depression on inflammatory markers (Milaneschi et al., 2009). The lack of association between physical activity and depression in the current study is surprising, given previous studies (Azevedo Da Silva et al., 2012; Hamer et al., 2009a; Song et al., 2012). Physical activity was measured via pedometer in the current study. This provides a good measure of walking compared with sedentary activity, which is a critical and effective indicator of physical health (Ewald et al., 2010), but not the intensity of physical activity, which may be more closely related to depression.

The current results indicate that aspects of unhealthy lifestyle may be another important source of the elevated inflammatory markers observed in depression, in addition to psychosocial stress. Consequently, contemporary causal theories of depression involving inflammation may need to consider unhealthy lifestyle and physical health alongside psychosocial stressors. For instance, PATHOS-D suggests that psychosocial stress activates a host defence response as part of an adaptive evolutionary process that primes the body, immunologically and behaviourally, to combat infection and avoid pathogen exposure in times of stress (Raison and Miller, 2013). The originally adaptive process is maladaptive in the modern social context, presenting as depression. PATHOS-D hypothesises that since other risk factors for depression that are largely non-social, such as aspects of unhealthy lifestyle, are also pro-inflammatory, they may be associated with the pathways evolved to fight infection. Further evidence as to whether unhealthy lifestyle and physical illness

precedes or follows psychosocial stress and changes in inflammatory mediators will inform modifications to theory.

This study must be viewed in light of several limitations. Firstly, we were limited in the possible causal models that we could test due to the data available. Alternative relationships, including whether baseline levels of depressive symptoms predict future levels of inflammation, could not be tested, since we did not measure inflammatory markers at follow-up. We also could not examine more complex, additive relationships or other possible potential sources of inflammatory markers, including chronic psychosocial stress, biological measures such as oxidative stress or hypothalamic-pituitary-adrenal axis activity. Future epidemiological studies that measure inflammatory markers, psychological functioning, and health and lifestyle indicators at multiple time-points are required to interpret the temporality and mediation between these factors. Depression was not defined through clinical interview, only through depressive symptom inventory, which may mean the effect sizes underestimate the true effect, as suggested by meta-analysis of cross sectional studies comparing effect sizes for diagnosed depression and elevated depressive symptoms (Hiles et al., 2012). Consequently, we also did not have the ability to examine subtypes of depression, although research indicates that melancholic vs. atypical depression are associated with differential inflammatory and immune profiles (Hickman et al., 2014; Kaestner et al., 2005; Rothermundt et al., 2001). There were also missing data and participants lost to follow-up. Blood was only collected from participants able to attend a clinic session within office hours, which may have led to a selective participant base. This was a community-dwelling older sample, and so does not represent young or institutionalised persons. Due to limitations in available data, we also do not know how changes in inflammatory or lifestyle indicators or incident pharmacological or psychosocial intervention between baseline and follow-up may have impacted results.

Our analyses have strengths over previous prospective studies of the depression-inflammatory marker relationship, particularly in the application of mediation analysis to identify objectively measured central adiposity as one important potential source of inflammatory mediators. Furthermore, these results highlight that future examination of the role of inflammation in depression need to consider that gender may act as an effect modifier, and that contemporary inflammatory theories of depression may need to account for gender differences and the role of unhealthy lifestyle. The findings that in females inflammatory markers precede depression and that adipose tissue may be one source of inflammation has consequences not only for theory, but also for the prevention and treatment of depression. It highlights unhealthy lifestyle as an important intervention target for the prevention and treatment for depression, through improvement of inflammatory pathways. These results may extend to other aspects of psychopathology, as elevations in inflammatory markers may be a feature of numerous psychopathologies, not simply depression, including anxiety (Copeland et al., 2012; Vogelzangs et al., 2013), bipolar disorder (Modabbernia et al., 2013), psychosis (Miller et al., 2011), and suicidal ideation (O'Donovan et al., 2013).

Acknowledgments

This research based was conducted as part of the Hunter Community Study, The University of Newcastle. We are grateful to the men and women of the Hunter region who provided the information recorded. We acknowledge funding from the University of Newcastle's Strategic Initiatives Fund, Gladys M Brawn Senior Research Fellowship scheme, Vincent Fairfax Family Foundation and the John Hunter Charitable Trust. We also acknowledge the Hunter Medical Research Institute who provided media support during the initial recruitment of participants and Dr Anne Crotty, Prof. Rodney Scott and Prof. Chris Levi who provided financial support towards freezing costs for the long-term storage of participant blood samples. For the follow-up survey, we acknowledge the xTEND investigators and funding from Xtrata and beyondblue.

Competing Interest Statement

The authors have no competing interests to report.

References

Akhondzadeh S, Jafari S, Raisi F, Nasehi AA, Ghoreishi A, Salehi B, et al. Clinical trial of adjunctive celecoxib treatment in patients with major depression: A double blind and placebo controlled trial. Depress Anxiety. 2009;26:607-11.

Anisman H, Merali Z, Poulter MO, Hayley S. Cytokines as a precipitant of depressive illness: Animal and human studies. Curr Pharm Des. 2005;11:963-72.

Azevedo Da Silva M, Singh-Manoux A, Brunner EJ, Kaffashian S, Shipley MJ, Kivimäki M, et al. Bidirectional association between physical activity and symptoms of anxiety and depression: The Whitehall II study. Eur J Epidemiol. 2012;27:537-46.

Bastard J-P, Maachi M, Lagathu C, Ji Kim M, Caron M, Vidal H, et al. Recent advances in the relationship between obesity, inflammation, and insulin resistance. Eur Cytokine Netw. 2006;17:4-12.

Beekman A, Deeg DJH, Van Limbeek J, Braam AW, De Vries MZ, Van Tilburg W. Criterion validity of the Center for Epidemiologic Studies Depression scale (CES-D): Results from a community-based sample of older subjects in The Netherlands. Psychol Med. 1997;27:231-5.

Berk M, Williams L, Jacka F, O'Neil A, Pasco J, Moylan S, et al. So depression is an inflammatory disease, but where does the inflammation come from? BMC Med. 2013;11:200.

Boyle SH, Jackson WG, Suarez EC. Hostility, anger, and depression predict increases in C3 over a 10 year period. Brain Behav Immun. 2007;21:816-23.

Calay ES, Hotamisligil GS. Turning off the inflammatory, but not the metabolic, flames. Nat Med. 2013;19:265-7.

Capuron L, Fornwalt FB, Knight BT, Harvey PD, Ninan PT, Miller AH. Does cytokine-induced depression differ from idiopathic major depression in medically healthy individuals? J Affect Disord. 2009;119:181-5.

Clyne B, Olshaker JS. The C-reactive protein. J Emerg Med. 1999;17:1019-25.

Copeland WE, Shanahan L, Worthman C, Angold A, Costello EJ. Generalized anxiety and C-reactive protein levels: A prospective, longitudinal analysis. Psychol Med. 2012;42:2641-50.

Cumming RG, Mitchell P. Alcohol, smoking and cataracts: The Blue Mountains Eye Study. Arch Ophthalmol. 1997;115:1296-303.

Dantzer R, O'Connor JC, Lawson MA, Kelley KW. Inflammation-associated depression: From serotonin to kynurenine. Psychoneuroendocrinology. 2011;36:426-36.

Dowlati Y, Herrmann N, Swardfager W, Liu H, Sham L, Reim EK, et al. A meta-analysis of cytokines in major depression. Biol Psychiatry. 2010;67:446-57.

Duivis HE, de Jonge P, Penninx BW, Na BYC, B E, Whooley MA. Depressive symptoms, health behaviors, and subsequent inflammation in patients with coronary heart disease: Prospective findings from the Heart and Soul Study. Am J Psychiatry. 2011;168:913-20.

Edwards KM, Burns VE, Ring C, Carroll D. Sex differences in the interleukin-6 response to acute psychological stress. Biol Psychol. 2006;71:236-9.

Everson-Rose SA, Lewis TT, Karavolos K, Dugan SA, Wesley D, Powell LH. Depressive symptoms and increased visceral fat in middle-aged women. Psychosom Med. 2009;71:410-6.

Ewald B, McEvoy M, Attia J. Pedometer counts superior to physical activity scale for identifying health markers in older adults. Br J Sports Med. 2010;44:756-61.

Food Standards Australia New Zealand. NUTTAB 2006 Australian Food Composition Tables. Canberra, ACT, Australia: Department of Health and Ageing; 2006.

Hamer M, Molloy GJ, de Oliveira C, Demakakos P. Leisure time physical activity, risk of depressive symptoms, and inflammatory mediators: The English Longitudinal Study of Ageing. Psychoneuroendocrinology. 2009a;34:1050-5.

Hamer M, Molloy GJ, de Oliveira C, Demakakos P. Persistent depressive symptomatology and inflammation: To what extent do health behaviours and weight control mediate this relationship? Brain Behav Immun. 2009b;23:413-8.

Hickman RJ, Khambaty T, Stewart JC. C-reactive protein is elevated in atypical but not nonatypical depression: Data from the National Health and Nutrition Examination Survey (NHANES) 1999–2004. J Behav Med. 2014;37:621-9.

Hiles SA, Baker AL, de Malmanche T, Attia J. A meta-analysis of differences in IL-6 and IL-10 between people with and without depression: Exploring the causes of heterogeneity. Brain Behav Immun. 2012;26:1180-8.

Howren MB, Lamkin DM, Suls J. Associations of depression with C-reactive protein, IL-1, and IL-6: A meta-analysis. Psychosom Med. 2009;71:171-86.

Irwin MR, Miller AH. Depressive disorders and immunity: 20 years of progress and discovery. Brain Behav Immun. 2007;21:374-83.

Kaestner F, Hettich M, Peters M, Sibrowski W, Hetzel G, Ponath G, et al. Different activation patterns of proinflammatory cytokines in melancholic and non-melancholic major depression are associated with HPA axis activity. J Affect Disord. 2005;87:305-11.

King DE, Egan BM, Geesey ME. Relation of dietary fat and fiber to elevation of C-reactive protein. Am J Cardiol. 2003;92:1335-9.

Kudielka BM, Kirschbaum C. Sex differences in HPA axis responses to stress: A review. Biol Psychiatry. 2005;69:113-32.

Larsson C, Gullberg B, Rastam L, Lindblad U. Salivary cortisol differs with age and sex and shows inverse associations with WHR in Swedish women: A cross-sectional study. BMC Endocrine Disorders. 2009;9:16.

Lopresti AL, Hood SD, Drummond PD. A review of lifestyle factors that contribute to important pathways associated with major depression: Diet, sleep and exercise. J Affect Disord. 2013;148:12-27.

Marcus SM, Young EA, Kerber KB, Kornstein S, Farabaugh AH, Mitchell J, et al. Gender differences in depression: Findings from the STAR* D study B. J Affect Disord. 2005;87:141-50.

Marriott I, Huet-Hudson Y. Sexual dimorphism in innate immune responses to infectious organisms. Immunol Res. 2006;34:177-92.

Matthews KA, Schott LL, Bromberger JT, Cyranowski JM, Everson-Rose SA, Sowers M. Associations between depressive symptoms and inflammatory/hemostatic markers in women during the menopausal transition. Psychosom Med. 2007;69:124-30.

Matthews KA, Schott LL, Bromberger JT, Cyranowski JM, Everson-Rose SA, Sowers M. Are there bi-directional associations between depressive symptoms and C-reactive protein in mid-life women? Brain Behav Immun. 2010;24:96-101.

Maury E, Brichard SM. Adipokine dysregulation, adipose tissue inflammation and metabolic syndrome. Mol Cell Endocrinol. 2010;314:1-16.

McConnell JP, Branum EL, Ballman KV, Lagerstedt SA, Katzmann JA, Jaffe AS. Gender differences in C-reactive protein concentrations-confirmation with two sensitive methods. Clin Chem Lab Med. 2005;40:56-9.

McEvoy M, Smith W, D'Este C, Duke J, Peel R, Schofield P, et al. Cohort profile: The Hunter Community Study. Int J Epidemiol. 2010;39:1452-63.

Milaneschi Y, Corsi AM, Penninx BW, Bandinelli S, Guralnik JM, Ferrucci L. Interleukin-1 receptor antagonist and incident depressive symptoms over 6 years in older persons: The InCHIANTI study. Biol Psychiatry. 2009;65:973-8.

Miller AH, Maletic V, Raison CL. Inflammation and its discontents: The role of cytokines in the pathophysiology of major depression. Biol Psychiatry. 2009;65:732-41.

Miller BJ, Buckley P, Seabolt W, Mellor A, Kirkpatrick B. Meta-analysis of cytokine alterations in schizophrenia: Clinical status and antipsychotic effects. Biol Psychiatry. 2011;70:663-71.

Modabbernia A, Taslimi S, Brietzke E, Ashrafi M. Cytokine alterations in bipolar disorder: A meta-analysis of 30 studies. Biol Psychiatry. 2013;74:15-25.

Myint AM, Schwarz MJ, Steinbusch HWM, Leonard BE. Neuropsychiatric disorders related to interferon and interleukins treatment. Metab Brain Dis. 2009;24:55-68.

National Health and Medical Research Council. Australian Alcohol Guidelines: Health Risks and Benefits. Canberra, Australia: Australian Government Publishing Service; 2001.

National Health and Medical Research Council and Department of Health and Ageing Australian Government. Dietary Guidelines for Australians: A Guide to Healthy Eating. Canberra: Australian Government; 2005.

O'Connor M-F, Bower JE, Cho HJ, Creswell JD, Dimitrov S, Hamby ME, et al. To assess, to control, to exclude: Effects of biobehavioral factors on circulating inflammatory markers. Brain Behav Immun. 2009;23:887-97.

O'Donovan A, Rush G, Hoatam G, Hughes BM, McCrohan A, Kelleher C, et al. Suicidal ideation is associated with elevated inflammation in patients with major depressive disorder. Depress Anxiety. 2013;30:307-14.

Odegaard JI, Chawla A. Pleiotropic actions of insulin resistance and inflammation in metabolic homeostasis. Science. 2013;339:172-7.

Payette C, Blackburn P, Lamarche B, Tremblay A, Bergeron J, Lemieux I, et al. Sex differences in postprandial plasma tumor necrosis factor–α, interleukin-6, and C-reactive protein concentrations. Metabolism. 2009;58:1593-601.

Preacher KJ, Hayes AF. SPSS and SAS procedures for estimating indirect effects in simple mediation models. Behavior Research Methods, Instruments, & Computers. 2004;36:717-31.

Radloff LS. The CES-D Scale. Applied Psychological Measurement. 1977;1:385-401.

Raison CL, Miller AH. The evolutionary significance of depression in Pathogen Host Defense (PATHOS-D). Mol Psychiatry. 2013;18:15-37.

Raison CL, Rutherford RE, Woolwine BJ, Shuo C, Schettler P, Drake DF, et al. A randomized controlled trial of the tumor necrosis factor antagonist infliximab for treatment-resistant depression: The role of baseline inflammatory biomarkers. JAMA Psychiatry. 2013;70:31-41.

Reichenberg A, Yirmiya R, Schuld A, Kraus T, Haack M, Morag A, et al. Cytokine-associated emotional and cognitive disturbances in humans. Arch Gen Psychiatry. 2001;58:445-52.

Richardson J, Peacock S, Hawthorne G, Iezzi A, Elsworth G, Day N. Construction of the descriptive system for the assessment of quality of life AQoL-6D utility instrument. Health Qual Life Outcomes. 2012;10:38.

Rothermundt M, Arolt V, Fenker J, Gutbrodt H, Peters M, Kirchner H. Different immune patterns in melancholic and non-melancholic major depression. Eur Arch Psychiatry Clin Neurosci. 2001;251:90-7.

Skinner HA. Development and validation of a lifetime alcohol consumption assessment procedure. Toronto, ON, Canada: Addiction Research Foundation; 1982.

Slavich GM, Irwin MR. From stress to inflammation and major depressive disorder: A social signal transduction theory of depression. Psychol Bull. 2014;140:774-815.

Smith W, Mitchell P, Reay EM, Webb K, Harvey PWJ. Validity and reproducibility of a self-administered food frequency questionnaire in older people. Aust N Z J Public Health. 1998;22:456-63.

Sobell MB, Maisto SA, Sobell LC, Cooper AM, Cooper T, Sanders B. Developing a prototype for evaluating alcohol treatment effectiveness. In: Sobell LC, Sobell MB, Ward E, editors. Evaluating Alcohol and Drug Abuse Treatment Effectiveness: Recent Advances. New York: Pergamon Press; 1979.

Song MR, Lee Y-S, Baek J-D, Miller M. Physical activity status in adults with depression in the National Health and Nutrition Examination Survey, 2005–2006. Public Health Nurs. 2012;29:208-17.

Straub RH. The complex role of estrogens in inflammation. Endocr Rev. 2007;28:521-74.

Thorand B, Baumert J, Döring A, Herder C, Kolb H, Rathmann W, et al. Sex differences in the relation of body composition to markers of inflammation. Atherosclerosis. 2006;184:216-24.

U.S. Department of Agriculture and U.S. Department of Health and Human Services. Dietary Guidelines for Americans, 2010, 7th ed. Washington, DC: U.S. Government Printing Office; 2010.

Valkanova V, Ebmeier KP, Allan CL. CRP, IL-6 and depression: A systematic review and meta-analysis of longitudinal studies. J Affect Disord. 2013;150:736-44.

Vogelzangs N, Beekman ATF, de Jonge P, Penninx BWJH. Anxiety disorders and inflammation in a large adult cohort. Translational Psychiatry. 2013;3:e249.

World Health Organization. Draft Comprehensive Global Monitoring Framework and Targets for the Prevention and Control of Noncommunicable Diseases. World Health Organization; 2013.

Table 1. Baseline characteristics of included participants (*N* = 1410).

		Total	Males	Females	
Characteristic		**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	***p*** [a]
Age (years)		65.6 (7.1)	66.0 (7.4)	65.1 (6.8)	.02
Centre for Epidemiologic Studies Depression Scale (CES-D)		6.8 (7.7)	6.2 (7.8)	7.2 (7.5)	.02
IL-6 (pg/mL) [b]		2.4 (2.0)	2.5 (1.9)	2.3 (2.0)	<.01
CRP (mg/L) [b]		2.6 (2.1)	2.4 (1.9)	2.8 (2.2)	.01
Waist-to-hip ratio (as %)		89.4 (8.8)	95.5 (5.8)	83.4 (6.8)	<.01
Body mass index		28.5 (4.6)	28.7 (4.0)	28.3 (5.2)	.08
Steps per day (in thousands)		7.2 (3.1)	7.0 (3.3)	7.3 (3.0)	.16
% energy from saturated fat		11.5 (3.1)	11.6 (3.1)	11.4 (3.1)	.24
Number of self-reported physical health problems (0-10)		1.4 (1.4)	1.3 (1.3)	1.6 (1.4)	<.01
Assessment of Quality of Life (standardised scores; 0-1)					
Independent living		0.14 (0.17)	0.14 (0.17)	0.14 (0.17)	.70
Relationships		0.12 (0.17)	0.12 (0.18)	0.12 (0.17)	.90
Coping		0.17 (0.16)	0.16 (0.15)	0.18 (0.16)	.04
Pain		0.28 (0.27)	0.27 (0.26)	0.29 (0.27)	.29
Characteristic		***N* (%)**	***N* (%)**	***N* (%)**	***p***
Gender	Male	699 (50.0)			
	Female	711 (50.0)			
Marital status	Married	1048 (76.0)	572 (83.6)	476 (68.6)	
	De facto/living with partner	26 (1.9)	13 (1.9)	13 (1.9)	
	Widowed	132 (9.6)	29 (4.2)	103 (14.8)	
	Divorced or separated	135 (9.8)	50 (7.3)	85 (12.3)	
	Never married	37 (2.7)	20 (2.9)	17 (2.9)	<.01
CES-D category	Scores ≥ 16	160 (12.3)	67 (10.3)	93 (14.2)	
	Scores < 16	1145 (87.7)	585 (89.7)	560 (85.8)	.03
Current smoking	No	1299 (94.8)	645 (94.9)	654 (94.8)	
	Yes	71 (5.2)	35 (5.2)	36 (5.2)	<.01
Alcohol use	No use	236 (17.1)	90 (13.1)	146 (21.0)	
	Safe use	888 (64.2)	426 (62.0)	462 (66.3)	
	Hazardous use	139 (10.0)	117 (17.0)	22 (3.2)	
	Use at unknown quantity	121 (8.7)	54 (7.9)	67 (9.6)	<.01

[a] *p* values refer to differences between males and females.

[b] Descriptive statistics report raw values, inferential statistics were conducted on log-transformed values to correct for non-normality.

efficients between baseline lifestyle factors, interleukin (IL)-6, C-reactive protein (CRP), and Centre for Scale (CES-D), adjusted (adj.) for age, age and lifestyle, and all predictors. Significant results using α = .05 k. Further details including unstandardised coefficients and exact *p* values are included in supplementary ry tables 1, 2, 3).

	Outcomes								
	logIL-6			**logCRP**			**CES-D**		
	Age adj. β	Lifestyle adj. β	Fully adj. β	Age adj. β	Lifestyle adj. β	Fully adj. β	Age adj. β	Lifestyle adj. β	Fully adj. β
	-	-	-	**0.39***	-	-	**0.14***	**0.13***	0.04
	0.37*	-	-	-	-	-	**0.13***	-	-
	0.14*	-	-	**0.13***	-	-	-	-	-
	0.11*	0.06	0.04	**0.15***	**0.10***	0.08	**0.13***	**0.11***	0.05
	0.27*	-	-	**0.40***	-	-	**0.14***	-	-
ds)	**-0.24***	**-0.22***	**-0.20***	**-0.21***	**-0.19***	**-0.17***	-0.03	0.01	0.05
fat	**0.08***	0.07	0.06	**0.08***	0.04	0.03	**0.10***	0.07	0.02
	0.13*	**0.10***	**0.10***	0.07	0.05	0.04	**0.10***	0.07	0.06
o use)									
	-0.09*	-0.06	-0.04	**-0.11***	**-0.11***	**-0.09***	-0.09	-0.03	-0.02
	-0.01	-0.01	-0.01	0.003	0.02	0.02	0.02	0.01	0.02
ity	-0.03	-0.03	-0.01	**-0.09***	**-0.11***	-0.07	-0.06	-0.03	-0.04
(0-10)	**0.09***	-	-0.01	0.04	-	-0.05	**0.18***	-	0.07
Life									
	0.18*	-	0.02	**0.14***	-	0.02	**0.29***	-	-0.09
	0.14*	-	0.03	**0.13***	-	0.07	**0.47***	-	**0.24***
	0.13*	-	0.07	**0.11***	-	-0.001	**0.62***	-	**0.49***
	0.16*	-	0.09	**0.13***	-	0.10	**0.30***	-	0.08
	-	-	-	**0.42***	-	-	0.04	-0.004	-0.07
	0.37*	-	-	-	-	-	**0.09***	-	-
	0.03	-	-	0.09	-	-	-	-	-
	0.18*	**0.16***	**0.13***	**0.21***	**0.19***	**0.16***	**0.13***	**0.10***	0.04
	0.19*	-	-	**0.33***	-		**0.18***	-	
ds)	**-0.11***	-0.07	-0.04	**-0.12***	-0.06	-0.03	**-0.12***	**-0.09***	0.03
fat	-0.02	-0.02	-0.01	0.05	0.05	0.05	**0.09***	**0.09***	0.04
	0.06	0.01	0.0001	**0.08***	0.06	0.02	0.04	0.04	0.0004
o use)									
	-0.02	-0.03	-0.02	**-0.11***	-0.11	-0.10	-0.01	-0.004	0.02
	0.04	-0.02	-0.03	-0.01	-0.06	-0.09	0.04	0.03	0.02
ity	0.01	-0.02	-0.02	0.68	0.01	0.004	**0.13***	0.10	0.06
(0-10)	**0.12***	-	**0.10***	0.07	-	-0.03	**0.24***	-	0.05
Life									
	0.16*	-	**0.11***	**0.28***	-	**0.28***	**0.47***	-	0.06
	0.10*	-	0.04	**0.11***	-	-0.03	**0.51***	-	**0.19***
	0.09*	-	-0.03	**0.10***	-	-0.08	**0.59***	-	**0.40***
	0.11*	-	-0.01	**0.17***	-	-0.004	**0.38***	-	**0.13**

Table 3. Association of baseline inflamatory markers, lifestyle factors, physical health and quality of life measures, v
scores, which represent the variation in follow-up Centre for Epidemiologic Studies Depression Scale (CES-D) score
and age.

		Unadjusted				**Lifestyle adjusted**[a]				
Gender	**Predictor variable**	**b**	**SE**	**β**	***p***	**b**	**SE**	**β**	***p***	**Semi-partial *r***
Female	logIL-6	**1.18**	**0.52**	**0.09**	**.024**	0.57	0.58	0.04	.330	0.04
	logCRP	-0.31	0.42	-0.03	.469	-	-	-	-	-
	Waist-to-hip ratio (as %)	**0.13**	**0.05**	**0.10**	**.009**	**0.12**	**0.05**	**0.09**	**.028**	**0.09**
	Body mass index	0.03	0.06	0.02	.609	-	-	-	-	-
	Steps per day (in thousands)	-0.04	0.12	-0.01	.739	0.09	0.13	0.03	.510	0.03
	% energy from saturated fat	**0.33**	**0.11**	**0.12**	**.002**	**0.29**	**0.11**	**0.11**	**.012**	**0.10**
	Smoke now (0 no, 1 yes)	**4.29**	**2.16**	**0.11**	**.048**	3.53	2.17	0.10	.104	0.10
	Alcohol use (reference: no use)									
	Safe use	-1.09	0.89	-0.06	.224	-1.63	0.99	-0.09	.101	-0.08
	Hazardous use	1.06	2.77	0.02	.703	-0.83	2.77	-0.02	.764	-0.02
	Use at unknown quantity	1.93	1.65	0.06	.241	0.30	1.81	0.01	.870	0.01
	Number of self-reported physical health problems (0-10)	-0.09	0.22	-0.02	.657	-	-	-	-	-
	Assessment of Quality of Life									
	Independent living	3.82	2.40	0.08	.111	-	-	-	-	-
	Relationships	3.65	2.47	0.07	.140	-	-	-	-	-
	Coping	**5.41**	**2.57**	**0.10**	**.036**	-	-	-	-	-
	Pain	**4.46**	**1.40**	**0.14**	**.002**	-	-	-	-	-
Male	logIL-6	0.18	0.42	0.01	.675	0.01	0.45	0.001	.979	0.001
	logCRP	0.59	0.41	0.06	.144	-	-	-	-	-
	Waist-to-hip ratio (as %)	**0.09**	**0.04**	**0.07**	**.026**	0.09	0.05	0.07	.077	0.06
	Body mass index	0.14	0.08	0.07	.070	-	-	-	-	-
	Steps per day (in thousands)	-0.04	0.08	-0.02	.631	-0.03	0.09	-0.01	.729	-0.01
	% energy from saturated fat	-0.04	0.08	-0.02	.660	-0.01	0.09	-0.01	.892	-0.01
	Smoke now (0 no, 1 yes)	0.77	1.18	0.02	.515	0.79	1.29	0.02	.541	0.02
	Alcohol use (reference: no use)									
	Safe use	-0.02	0.85	-0.002	.978	0.64	0.65	0.04	.327	0.03
	Hazardous use	-0.12	1.02	-0.006	.910	-0.10	0.89	-0.01	.907	0.004
	Use at unknown quantity	0.11	1.18	0.004	.924	0.36	1.11	0.01	.748	0.01

Number of self-reported physical health problems (0-10)	-0.09	0.29	-0.02	.680	-	-	-	-	-
Assessment of Quality of Life					-	-	-	-	-
Independent living	2.21	2.18	0.05	.309	-	-	-	-	-
Relationships	**5.20**	**1.84**	**0.12**	**.005**	-	-	-	-	-
Coping	**5.48**	**2.02**	**0.11**	**.007**	-	-	-	-	-
Pain	**5.48**	**2.02**	**0.11**	**.007**	-	-	-	-	-

[a] Lifestyle adjusted multivariate Females: $F(9,539) = 2.57$, $p = .009$; $R^2 = .0458$; Males $F(8,542) = 0.72$, $p = .674$, $R^2 = .0068$. Excluding CRP and body mass index, as they are measuring similar latent variable as IL-6 and waist-to-hip ratio, respectively. For females, results were the same pattern when CRP ($p = .207$) was used instead of IL-6, although when body mass index was used, body mass index was not a significant predictor ($p = .577$), while energy from saturated fat remained significant ($p = .011$). For males, using CRP ($p = .370$) instead of IL-6, or body mass index ($p = .195$) instead of waist-to-hip ratio, did not change the pattern of results.

[b] Fully adjusted multivariate Females: $F(14,515) = 2.10$, $p = .010$; $R^2 = .0683$; Males : $F(14, 524) = 0.91$, $p = .548$, $R^2 = .0204$. Excluding CRP and body mass index, as they are measuring similar latent variable as IL-6 and waist-to-hip ratio, respectively. For females, results were the same patten when CRP ($p = .060$) was used instead of IL-6, and when body mass index was used, body mass index was not a significant predictor ($p = .796$), while energy from saturated fat ($p = .013$) and pain ($p = .011$) remained significant. For males, results were the same pattern when CRP ($p = .191$) was used instead of IL-6 and when BMI ($p = .174$) was used instead of waist-to-hip ratio.

Table 4. Association of baseline inflamatory markers, lifestyle factors, physical health and quality of life measures, no depression (Centre for Epidemiologic Studies Depression Scale [CES-D] scores ≥16 and <16, respectively), excl

		Age adjusted				Lifestyle ad	
Gender	**Predictor variable**	**OR**	**95% CI**		***p***	**OR**	**95% C**
Female	logIL-6	**1.87**	**1.24**	**2.81**	**.003**	1.57	0.98
	logCRP	0.96	0.69	1.32	.793	-	-
	Waist-to-hip ratio (as %)	1.03	1.00	1.07	.075	1.02	0.98
	Body mass index	1.03	0.98	1.09	.186	-	-
	Steps per day (in thousands)	0.99	0.89	1.09	.798	1.03	0.92
	% energy from saturated fat	1.07	0.98	1.16	.135	1.07	0.98
	Smoke now (0 no, 1 yes)	**2.88**	**1.09**	**7.60**	**.033**	2.11	0.71
	Alcohol use (reference: no use)						
	Safe use	0.70	0.37	1.32	.271	0.58	0.29
	Hazardous use	1.03	0.21	5.09	.974	0.44	0.05
	Use at unknown quantity	1.50	0.63	3.61	.362	1.10	0.39
	Number of self-reported physical health problems (0-10)	**1.20**	**1.01**	**1.42**	**.043**	-	-
	Assessment of Quality of Life					-	-
	Independent living	**13.64**	**3.39**	**54.98**	**<.001**	-	-
	Relationships	**12.99**	**2.70**	**62.50**	**.001**	-	-
	Coping	**77.55**	**14.65**	**410.61**	**<.001**	-	-
	Pain	**5.84**	**2.36**	**14.41**	**<.001**	-	-
Male	logIL-6	0.82	0.48	1.38	.452	0.76	0.41
	logCRP	1.38	0.94	2.03	.098	-	-
	Waist-to-hip ratio (as %)	1.04	0.99	1.10	.106	1.06	0.99
	Body mass index	1.05	0.98	1.13	.194	-	-
	Steps per day (in thousands)	0.98	0.88	1.09	.732	0.99	0.89
	% energy from saturated fat	0.98	0.89	1.08	.720	1.00	0.90
	Smoke now (0 no, 1 yes)	2.29	0.74	7.05	.149	2.34	0.63
	Alcohol use (reference: no use)						
	Safe use	0.92	0.40	2.10	.842	1.28	0.46
	Hazardous use	0.88	0.30	2.62	.824	0.77	0.20
	Use at unknown quantity	0.54	0.11	2.68	.449	0.84	0.15
	Number of self-reported physical health problems (0-10)	1.08	0.87	1.35	.475	-	-
	Assessment of Quality of Life						
	Independent living	**37.59**	**6.65**	**212.46**	**<.001**	-	-
	Relationships	**39.82**	**9.03**	**175.60**	**<.001**	-	-
	Coping	**95.00**	**14.76**	**611.65**	**<.001**	-	-
	Pain	**4.17**	**1.36**	**12.80**	**.013**	-	-

[a] Lifestyle adjusted multivariate Females: $\chi^2(10) = 13.96$, $p = .124$; pseudo $R^2 = .041$, area under ROC curve = .63; Males $\chi^2(10) = 8.18$, $p = .52$, pseudo $R^2 = .030$, area under ROC curve = .62. Excluding CRP and body mass index, as they are measuring similar latent variable as IL-6 and waist-to-hip ratio, respectively. For females, when CRP was used instead of IL-6, CRP was not a significant predictor ($p = .409$). When body mass index was used instead of waist-to-hip ratio, body mass index was not a significant predictor ($p = .457$) and IL-6 was marginally associated with depression ($p = .087$). For males, the pattern of results did not change when using CRP ($p = .215$) instead of IL-6 or body mass index ($p = .146$) instead of waist-to-hip ratio.

b Fully adjusted multivariate Females: $\chi^2(14) = 33.94$, $p = .002$; pseudo $R^2 = .103$, area under ROC curve = .73; Males $\chi^2(14) = 28.29$, $p = .01$, pseudo $R^2 = .103$, area under ROC curve = .76. Excluding CRP and body mass index, as they are measuring similar latent variable as IL-6 and waist-to-hip ratio, respectively. For females, CRP was not a significant predictor ($p = .213$) when used instead of IL-6, and BMI was not a significant predictor ($p = .714$) when used instead of waist-to-hip ratio. Similar results were observed for males ($p = .249$ for CRP; $p = .641$ for BMI).

Table 6. Mediation results examining either interleukin (IL)-6 or C-reactive protein (CRP) as a mediator of the relationship between lifestyle factors or psychosocial functioning and the residual score predicting follow-up depressive symptoms**.** Predictor variables were selected from those that were significant predictors in univariate analysis.

Gender	Mediator	Predictor variable	Direct effect coefficient	Boostrapped 95% CI (bias corrected)		Indirect effect coefficient	Boostrapped 95% CI (bias corrected)		Ratio of effect (indirect: direct)
Females	IL-6	Waist-to-hip ratio	**0.1163**	**0.0087**	**0.2185**	**0.0124**	**0.0007**	**0.0320**	**0.1066**
		% energy from saturated fat	**0.3193**	**0.1158**	**0.5488**	0.0117	-0.0006	0.0450	0.0366
		Smoke now (0 no, 1 yes)	**4.0399**	**0.3173**	**9.1437**	**0.2492**	**0.0014**	**0.7612**	**0.0617**
		Assessment of Quality of Life							
		Coping	4.8471	-0.4854	10.1120	**0.5580**	**0.0602**	**1.3406**	**0.1151**
		Pain	**4.1087**	**1.2191**	**7.1070**	0.3482	-0.0488	0.9029	0.0847
	CRP	Waist-to-hip ratio	**0.1374**	**0.0379**	**0.2465**	-0.0087	-0.0281	0.0053	0.0633
		% energy from saturated fat	**0.3334**	**0.1195**	**0.5471**	-0.0024	-0.0261	0.0075	0.0072
		Smoke now (0 no, 1 yes)	**4.3750**	**0.8317**	**9.2473**	-0.0858	-0.5190	0.0608	0.0196
		Assessment of Quality of Life							
		Coping	**5.6286**	**0.8686**	**11.2331**	-0.2235	-0.9473	0.1052	-0.0397
		Pain	**4.6695**	**2.0089**	**7.6164**	-0.2125	-0.7193	0.0927	-0.0455
Males	IL-6	Waist-to-hip ratio	**0.0940**	**0.0028**	**0.1789**	0.0005	-0.0195	0.0181	0.0053
		Assessment of Quality of Life							
		Relationships	**5.1542**	**1.7553**	**9.2803**	0.0488	-0.2513	0.4800	0.0095

	Coping	**5.4587**	**1.5081**	**9.1726**	0.0207	-0.3131	0.4021	0.0038
	Pain	1.8032	-0.3246	4.1159	0.0329	-0.0922	0.2939	0.0182
CRP		0.0813	-0.0027	0.1627	0.0131	-0.0072	0.0406	0.1611
	Waist-to-hip ratio							
	Assessment of Quality of Life							
	Relationships	**4.9092**	**1.4376**	**8.5099**	0.2937	-0.0033	1.0072	0.0598
	Coping	**5.2157**	**1.4299**	**9.0902**	0.2637	-0.0477	1.1067	0.0506
	Pain	1.5825	-0.7076	3.7793	0.2535	-0.0153	0.8073	0.1602

Supplementary tables

Supplementary table 1. Association of lifestyle factors, physical illness and quality of life, with interleukin (IL)-6; adjusted for age only, age and lifestyle, and fully adjusted with all predictors.

Supplementary table 2. Association of lifestyle factors, physical illness and quality of life, with C-reactive protein (CRP); adjusted for age only, age and lifestyle, and fully adjusted with all predictors.

Supplementary table 3. Association of baseline inflammatory markers and lifestyle factors, physical illness and quality of life, with baseline depressive symptoms (Centre for Epidemiologic Studies Depression Scale; CES-D); adjusted for age only, age and lifestyle, and fully adjusted with all predictors.

Supplementary table 1. Association of lifestyle factors, physical illness and quality of life, with interleukin (IL)-6; adjusted for age only, age and lifestyle, and fully adjusted with all predictors.

		Adjusted for age				***Lifestyle adjusted*** [a]					***Fully adjusted*** [b]				
Gender	**Predictor variable**	**b**	**Robust SE**	**β**	***p***	**b**	**Robust SE**	**β**	***p***	**Semi-partial *r***	**b**	**Robust SE**	**β**	***p***	**Semi-partial *r***
Female	CES-D	**0.011**	**0.003**	**0.135**	**<.001**	-	-	-	-	-	-	-	-	-	-
	CRP	**0.287**	**0.027**	**0.374**	**<.001**	-	-	-	-	-	-	-	-	-	-
	Waist-to-hip ratio (as %)	**0.011**	**0.004**	**0.113**	**.003**	0.006	0.004	0.061	.110	0.059	0.003	0.004	0.037	.345	0.035
	Body mass index	**0.033**	**0.004**	**0.271**	**<.001**	-	-	-	-	-	-	-	-	-	-
	Steps per day (in thousands)	**-0.049**	**0.008**	**-0.240**	**<.001**	**-0.046**	**0.009**	**-0.222**	**<.001**	**-0.205**	**-0.042**	**0.009**	**-0.204**	**<.001**	**-0.185**
	% energy from saturated fat	**0.015**	**0.007**	**0.076**	**.040**	0.014	0.008	0.072	.063	0.071	0.012	0.008	0.060	.119	0.059
	Smoke now (0 no, 1 yes)	**0.351**	**0.117**	**0.125**	**.003**	**0.285**	**0.120**	**0.104**	**.018**	**0.102**	**0.275**	**0.125**	**0.103**	**.028**	**0.100**
	Alcohol use (reference: no use)														
	Safe use	**-0.118**	**0.060**	**-0.089**	**.049**	-0.082	0.062	-0.061	.184	-0.051	-0.048	0.061	-0.036	.428	-0.030
	Hazardous use	-0.034	0.122	-0.010	.779	-0.026	0.127	-0.007	.838	-0.007	-0.016	0.130	-0.005	.901	-0.004
	Use at unknown quantity	-0.072	0.092	-0.034	.433	-0.065	0.099	-0.028	.515	-0.025	-0.014	0.102	-0.005	.911	-0.004
	Number of self-reported physical health problems (0-10)	**0.042**	**0.017**	**0.094**	**.016**	-	-	-	-	-	-0.002	0.021	-0.005	.917	-0.004
	Assessment of Quality of Life														
	Independent living	**0.652**	**0.144**	**0.180**	**<.001**	-	-	-	-	-	0.078	0.201	0.021	.700	0.015
	Relationships	**0.540**	**0.150**	**0.144**	**<.001**	-	-	-	-	-	0.112	0.190	0.029	.555	0.023
	Coping	**0.492**	**0.128**	**0.128**	**<.001**	-	-	-	-	-	0.281	0.172	0.070	.103	0.059
	Pain	**0.371**	**0.089**	**0.161**	**<.001**	-	-	-	-	-	0.206	0.123	0.089	.094	0.066
Male	CES-D	0.003	0.003	0.031	.393	-	-	-	-	-	-	-	-	-	-
	CRP	**0.293**	**0.027**	**0.369**	**<.001**	-	-	-	-	-	-	-	-	-	-
	Waist-to-hip ratio (as %)	**0.019**	**0.004**	**0.180**	**<.001**	**0.018**	**0.004**	**0.164**	**<.001**	**0.160**	**0.014**	**0.004**	**0.130**	**.001**	**0.121**
	Body mass index	**0.029**	**0.005**	**0.188**	**<.001**										
	Steps per day (in thousands)	**-0.021**	**0.007**	**-0.113**	**.003**	-0.013	0.008	-0.072	.079	-0.066	-0.008	0.008	-0.043	.308	-0.038
	% energy from saturated fat	-0.005	0.007	-0.024	.506	-0.004	0.008	-0.019	.612	-0.019	-0.003	0.008	-0.013	.720	-0.013

Smoke now (0 no, 1 yes)	0.157	0.095	0.055	.098	0.036	0.097	0.013	.708	0.012	0.0002	0.102	0.0001	.998	0.0001
Alcohol use (reference: no use)														
Safe use	-0.023	0.064	-0.018	.726	-0.037	0.070	-0.029	.598	-0.019	-0.019	0.073	-0.015	.797	-0.010
Hazardous use	0.071	0.080	0.043	.374	-0.039	0.084	-0.024	.643	-0.017	-0.050	0.086	-0.031	.566	-0.021
Use at unknown quantity	0.025	0.100	0.011	.806	-0.052	0.107	-0.022	.628	-0.018	-0.036	0.108	-0.015	.741	-0.012
Number of self-reported physical health problems (0-10)	**0.057**	**0.016**	**0.123**	**<.001**	-	-	-	-	-	**0.045**	**0.020**	**0.096**	**.026**	**0.084**
Assessment of Quality of Life														
Independent living	**0.617**	**0.122**	**0.164**	**<.001**	-	-	-	-	-	**0.407**	**0.206**	**0.105**	**.049**	**0.072**
Relationships	**0.361**	**0.137**	**0.102**	**.009**	-	-	-	-	-	0.136	0.219	0.038	.535	0.029
Coping	**0.355**	**0.145**	**0.086**	**.014**	-	-	-	-	-	-0.131	0.227	-0.031	.564	-0.025
Pain	**0.267**	**0.086**	**0.111**	**.002**	-	-	-	-	-	-0.020	0.126	-0.008	.873	-0.007

[a] Lifestyle adjusted multivariate, females: $F(8,603) = 9.67$, $p < .001$, $R^2 = .125$; males: $F(8, 597) = 13.27$, $p < .001$, $R^2 = .133$. Excluding CRP and body mass index, as they are measuring similar latent variables as IL-6 and waist-to-hip ratio, respectively. For both females and males, using body mass index instead of waist-to-hip ratio did not change the pattern of results, except that body mass index was a significant predictor ($p < .001$).

[b] Fully adjusted multivariate, females: $F(13,576)=6.82$, $p < .001$, $R^2 = .145$; males $F(13,573) = 9.28$, $p < .001$, $R^2 = .156$. Excluding CRP and body mass index, as they are measuring similar latent variables as IL-6 and waist-to-hip ratio, respectively. Using body masss index instead of waist-to-hip ratio did not change the pattern of results, except that body mass index was a significant predictor ($p < .001$) for females, and for males body mass index was a significant predictor ($p = .004$) and Independent Living was no longer significant ($p = .102$).

Supplementary table 2. Association of lifestyle factors, physical illness and quality of life, with C-reactive protein (CRP); adjusted for age only, age and lifestyle, and fully adjusted with all predictors.

		Adjusted for age				***Lifestyle adjusted*** [a]					***Fully adjusted*** [b]				
Gender	**Predictor variable**	**b**	**Robust SE**	**β**	***p***	**b**	**Robust SE**	**β**	***P***	**Semi-partial *r***	**b**	**Robust SE**	**β**	***p***	**Semi-partial *r***
Female	CES-D	**0.014**	**0.004**	**0.130**	**.001**	-	-	-	-	-	-	-	-	-	-
	IL-6	**0.508**	**0.051**	**0.390**	**<.001**	-	-	-	-	-	-	-	-	-	-
	Waist-to-hip ratio (as %)	**0.018**	**0.006**	**0.147**	**.002**	**0.012**	**0.006**	**0.097**	**.044**	**0.096**	0.010	0.006	0.084	.088	0.080
	Body mass index	**0.063**	**0.006**	**0.398**	**<.001**	-	-	-	-	-	-	-	-	-	-
	Steps per day (in thousands)	**-0.057**	**0.011**	**-0.211**	**<.001**	**-0.051**	**0.012**	**-0.189**	**<.001**	**-0.190**	**-0.047**	**0.013**	**-0.174**	**<.001**	**-0.158**
	% energy from saturated fat	**0.020**	**0.010**	**0.079**	**.034**	0.011	0.010	0.044	.249	0.047	0.009	0.010	0.033	.399	0.032
	Smoke now (0 no, 1 yes)	0.242	0.137	0.066	.078	0.175	0.012	0.049	.219	0.048	0.149	0.144	0.042	.301	0.041
	Alcohol use (reference: no use)														
	Safe use	**-0.192**	**0.076**	**-0.112**	**.012**	**-0.189**	**0.079**	**-0.108**	**.017**	**-0.089**	**-0.164**	**0.080**	**-0.093**	**.040**	**-0.077**
	Hazardous use	0.016	0.157	0.003	.918	0.070	0.163	0.015	.666	0.014	0.075	0.163	0.016	.646	0.015
	Use at unknown quantity	**-0.254**	**0.112**	**-0.092**	**.024**	**-0.294**	**0.131**	**-0.110**	**.024**	**-0.096**	-0.227	0.138	-0.074	.101	-0.064
	Number of self-reported physical health problems (0-10)	0.025	0.023	0.043	.281	-	-	-	-	-	-0.028	0.028	-0.049	.317	-0.042
	Assessment of Quality of Life														
	Independent living	**0.637**	**0.195**	**0.135**	**.001**	-	-	-	-	-	0.081	0.299	0.016	.787	0.012
	Relationships	**0.637**	**0.196**	**0.130**	**.001**	-	-	-	-	-	0.329	0.260	0.065	.206	0.050
	Coping	**0.558**	**0.193**	**0.112**	**.004**	-	-	-	-	-	-0.005	0.246	-0.001	.985	-0.001
	Pain	**0.399**	**0.116**	**0.132**	**.001**	-	-	-	-	-	0.296	0.166	0.097	.074	0.072
Male	CES-D	0.009	0.004	0.085	.059	-	-	-	-	-	-	-	-	-	-
	IL-6	**0.534**	**0.054**	**0.424**	**<.001**	-	-	-	-	-	-	-	-	-	-
	Waist-to-hip ratio (as %)	**0.029**	**0.005**	**0.213**	**<.001**	**0.026**	**0.005**	**0.192**	**<.001**	**0.185**	**0.022**	**0.006**	**0.158**	**<.001**	**0.147**
	Body mass index	**0.065**	**0.007**	**0.334**	**<.001**										

Steps per day (in thousands)	**-0.028**	**0.010**	**-0.117**	**.006**	-0.015	0.010	-0.064	.141	-0.060	-0.008	0.010	-0.033	.434	-0.029
% energy from saturated fat	0.012	0.010	0.049	.208	0.010	0.010	0.049	.220	0.050	0.013	0.010	0.049	.208	0.048
Smoke now (0 no, 1 yes)	**0.266**	**0.132**	**0.076**	**.045**	0.215	0.145	0.058	.139	0.059	0.087	0.143	0.023	.540	0.022
Alcohol use (reference: no use)														
Safe use	**-0.173**	**0.085**	**-0.108**	**.042**	-0.173	0.091	-0.107	.058	-0.073	-0.166	0.095	-0.102	.080	-0.067
Hazardous use	-0.023	0.109	-0.011	.830	-0.122	0.117	-0.060	.295	-0.042	-0.189	0.119	-0.092	.112	-0.062
Use at unknown quantity	0.053	0.129	0.018	.681	0.035	0.141	0.011	.805	0.010	0.013	0.145	0.004	.929	0.004
Number of self-reported physical health problems (0-10)	0.038	0.022	0.065	.085	-	-	-	-	-	-0.019	0.026	-0.032	.461	-0.028
Assessment of Quality of Life														
Independent living	**1.295**	**0.191**	**0.275**	**<.001**	-	-	-	-	-	**1.389**	**0.302**	**0.284**	**<.001**	**0.195**
Relationships	**0.469**	**0.176**	**0.106**	**.008**	-	-	-	-	-	-0.155	0.245	-0.034	.528	-0.026
Coping	**0.499**	**0.201**	**0.097**	**.013**	-	-	-	-	-	-0.439	0.254	-0.083	.085	-0.067
Pain	**0.507**	**0.122**	**0.168**	**<.001**	-	-	-	-	-	-0.012	0.163	-0.004	.943	-0.003

[a] Lifestyle adjusted multivariate females, $F(8,612) = 5.81$, $p < .001$, $R^2 = .072$; males $F(8,597) = 5.06$, $p < .001$, $R^2 = .063$. Excluding IL-6 and body mass index, as they are measuring similar latent variables as IL-6 and waist-to-hip ratio, respectively. For females, using body mass index instead of waist-to-hip ratio lead to a different pattern of results, where only body mass index ($p < .001$) and alcohol use at an unknown quantity ($p = .023$) were significant predictors. For males, adding body mass index instead of waist-to-hip ratio, body mass index was significant ($p < .001$), with no other significant predictors.

[b] Fully adjusted multivariate females, $F(13, 576) = 4.22$, $p < .001$, $R^2 = .086$; males $F(13,573) = 5.28$, $p < .001$, $R^2 = .109$. Excluding IL-6 and body mass index, as they are measuring similar latent variables as IL-6 and waist-to-hip ratio, respectively. For females, using body mass index instead of waist-to-hip ratio resulted in different significant predictors: body mass index ($p < .001$), Independent Living ($p = .030$) and Pain ($p = .016$). For males, the pattern of results remained the same when body mass index was used instead of waist-to-hip ratio (body mass index $p < .001$).

Supplementary table 3. Association of baseline inflammatory markers and lifestyle factors, physical illness and quality of life, with baseline depressive symptoms (Centre for Epidemiologic Studies Depression Scale; CES-D); adjusted for age only, age and lifestyle, and fully adjusted with all predictors.

		Adjusted for age				***Fully adjusted*** [a]					***Fully adjusted*** [b]				
Gender	**Predictor variable**	**b**	**Robust SE**	**β**	***p***	**b**	**Robust SE**	**β**	***p***	**Semi-partial *r***	**b**	**Robust SE**	**β**	***p***	**Semi-partial *r***
Female	logIL-6	**1.712**	**0.480**	**0.143**	**<.001**	**1.523**	**0.517**	**0.129**	**.003**	**0.120**	0.445	0.421	0.038	.295	0.035
	logCRP	**1.199**	**0.396**	**0.130**	**.003**	-	-	-	-	-	-	-	-	-	-
	Waist-to-hip ratio (as %)	**0.148**	**0.052**	**0.129**	**.005**	**0.119**	**0.058**	**0.105**	**.039**	**0.101**	0.054	0.039	0.048	.172	0.045
	Body mass index	**0.193**	**0.071**	**0.135**	**.007**	-	-	-	-	-	-	-	-	-	-
	Steps per day (in thousands)	-0.084	0.114	-0.034	.463	0.025	0.118	0.010	.831	0.009	0.118	0.088	0.048	.184	0.043
	% energy from saturated fat	**0.231**	**0.113**	**0.097**	**.041**	0.165	0.115	0.070	.152	0.069	0.064	0.083	0.027	.441	0.027
	Smoke now (0 no, 1 yes)	**3.280**	**1.500**	**0.101**	**.029**	2.243	1.569	0.071	.153	0.069	1.887	1.234	0.060	.127	0.059
	Alcohol use (reference: no use)														
	Safe use	-1.071	0.771	-0.068	.165	-0.496	0.787	-0.031	.529	-0.026	-0.284	0.630	-0.018	.652	-0.015
	Hazardous use	0.896	1.555	0.020	.565	0.566	1.552	0.013	.716	0.012	0.741	1.538	0.017	.630	0.016

	Use at unknown quantity	-1.446	1.092	-0.056	.186	-0.760	1.361	-0.027	.577	-0.024	-1.066	1.170	-0.038	.362	-0.033
	Number of self-reported physical health problems (0-10)	**0.976**	**0.233**	**0.183**	**<.001**	-	-	-	-	-	0.379	0.205	0.072	.065	0.062
	Assessment of Quality of Life														
	Independent living	**12.693**	**1.967**	**0.289**	**<.001**	-	-	-	-	-	-3.837	2.371	-0.086	.106	-0.061
	Relationships	**21.583**	**1.994**	**0.474**	**<.001**	-	-	-	-	-	**10.906**	**2.217**	**0.237**	**<.001**	**0.185**
	Coping	**28.819**	**2.024**	**0.615**	**<.001**	-	-	-	-	-	**23.210**	**2.530**	**0.485**	**<.001**	**0.413**
	Pain	**8.450**	**1.214**	**0.302**	**<.001**	-	-	-	-	-	2.264	1.266	0.082	.074	0.060
Male	logIL-6	0.448	0.525	0.036	.393	-0.052	0.528	-0.004	.922	-0.004	-0.860	0.436	-0.070	.050	-0.064
	logCRP	**0.843**	**0.428**	**0.085**	**.049**	-	-	-	-	-	-	-	-	-	-
	Waist-to-hip ratio (as %)	**0.182**	**0.057**	**0.134**	**.001**	**0.133**	**0.063**	**0.097**	**.034**	**0.092**	0.051	0.051	0.038	.323	0.035
	Body mass index	**0.352**	**0.087**	**0.178**	**.000**	-	-	-	-	-	-	-	-	-	-
	Steps per day (in thousands)	**-0.293**	**0.100**	**-0.123**	**.003**	**-0.212**	**0.099**	**-0.090**	**.033**	**-0.082**	0.063	0.071	0.027	.371	0.024
	% energy from saturated fat	**0.208**	**0.095**	**0.085**	**.029**	**0.219**	**0.103**	**0.086**	**.033**	**0.085**	0.102	0.080	0.041	.202	0.040
	Smoke now (0 no, 1 yes)	1.294	1.357	0.036	.341	1.279	1.574	0.035	.417	0.034	0.018	1.059	0.0004	.987	0.001

Alcohol use (reference: no use)														
Safe use	-0.234	0.838	-0.014	.780	-0.072	0.889	-0.004	.935	0.003	0.325	0.675	0.020	.630	0.014
Hazardous use	0.728	1.091	0.035	.505	0.064	1.200	0.031	.594	0.021	0.298	0.968	0.015	.759	0.010
Use at unknown quantity	**3.969**	**1.750**	**0.126**	**.024**	3.242	1.800	0.102	.072	0.086	2.019	1.346	0.064	.134	0.053
Number of self-reported physical health problems (0-10)	**1.379**	**0.289**	**0.238**	**<.001**	-	-	-	-	-	0.310	0.237	0.053	.191	0.046
Assessment of Quality of Life														
Independent living	**22.724**	**2.581**	**0.474**	**<.001**	-	-	-	-	-	2.768	2.956	0.057	.349	0.039
Relationships	**22.342**	**2.503**	**0.508**	**<.001**	-	-	-	-	-	**8.673**	**2.902**	**0.193**	**.003**	**0.150**
Coping	**30.658**	**2.378**	**0.585**	**<.001**	-	-	-	-	-	**20.575**	**2.896**	**0.398**	**<.001**	**0.319**
Pain	**11.318**	**1.553**	**0.379**	**<.001**	-	-	-	-	-	**3.858**	**1.411**	**0.127**	**<.001**	**0.099**

[a] Lifestyle adjusted multivariate females: $F(9,558) = 2.69$, $p = .005$, $R^2 = .049$; males: $F(9,574) = 2.82$, $p = .002$, $R^2 = .044$. Excluding CRP and body mass index, as they are measuring similar latent variables as IL-6 and waist-to-hip ratio, respectively. For females,using body mass index instead of waist-to-hip ratio, body mass index was not significant ($p = .118$), but the pattern for other predictors remained the same. Using CRP ($p = .030$) instead of IL-6 also did not change the pattern of results. For males, using body mass index instead of waist-to-hip ratio, body mass index ($p = .003$) and energy from saturated fat ($p = .043$) were significant, and steps per day ($p = .073$) trended to significance. Using CRP ($p = .584$) instead of IL-6 did not change the pattern of results.

[b] Fully adjusted multivariate females: $F(14, 541) = 17.66$, $p < .001$, $R^2 = .045$; males: $F(14,545) = 14.72$, $p < .001$, $R^2 = .423$. Excluding CRP and body mass index, as they are measuring similar latent variables as IL-6 and waist-to-hip ratio, respectively. For females, using body mass index instead of waist-to-hip ratio or CRP instead of IL-6 did not change the patterns of results, except neither were significant predictors (body mass index $p = .628$; CRP $p = .201$). For

males, using body mass index instead of waist-to-hip ratio, body mass index was not a significant predictor (p = .988), IL-6 was no longer a signficiant predictor (p = .072), and other predictors remained the same. Using CRP instead of IL-6, the pattern of results remained the same, although CRP was not significant (p = .443).