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

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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 3.5–5.5 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.

1. 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.

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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.

2. Material and methods

2.1. 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 < 0.05).

2.2. 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.

2.3. Measures

2.3.1. Inflammatory markers

12 h fasting blood was collected (95% were collected in the morning). Samples were centrifuged at 4 °C and 3000 g for 10 min, 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 0.16 mg/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 0.5 pg/mL and coefficient of variation was 12%.

2.3.2. 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