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Loneliness and stress-related inflammatory and neuroendocrine responses in older men and women

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Summary Loneliness is a predictor of mortality and increased cardiovascular morbidity. Inflammation is a potential pathway through which loneliness might impact health. The aim of the study was to investigate the relationship between loneliness and inflammatory interleukin-6 (IL-6), interleukin-1 receptor antagonist (IL-1Ra) and monocyte chemotactic protein-1 (MCP-1) responses to standardized mental stress. A secondary purpose was to evaluate whether individual variations in cortisol responses influenced the hypothesised relationship between loneliness and inflammation. Saliva samples and blood were taken from 524 healthy middle-aged men and women from the Whitehall II cohort at baseline, immediately after the stress tasks and 45 min later. Loneliness was measured using the revised UCLA loneliness scale. Greater loneliness was associated with larger IL-6 ($p = 0.044$) and IL-1Ra ($p = 0.006$) responses to psychological stress and higher MCP-1 ($p < 0.001$) levels in women, independently of age, grade of employment, body mass index and smoking status. No associations were observed in men. Cortisol responsivity was inversely related to loneliness in women, with the odds of being a cortisol responder decreasing with increased loneliness independently of covariates ($p = 0.008$). The impact of loneliness on health in women may be mediated in part through dysregulation of inflammatory and neuroendocrine systems.

1. Introduction

The impact of loneliness on health has become increasingly well recognised. Loneliness is independently predictive of mortality (Penninx et al., 1997; Patterson and Veenstra, 2010; Shiovitz-Ezra and Ayalon, 2010; Tilvis et al., 2011) and increases the risk of having a heart condition (Sorkin et al., 2002). There is some evidence that the effects of loneliness may be differentially experienced by men and women, although the literature on gender differences in loneliness levels is mixed (Pinquart and Sörensen, 2001; Theeke, 2009). For example, Thurston and Kubzansky (2009) showed that loneliness was prospectively linked with incident coronary heart disease (CHD) over a 19-year follow-up period, after controlling for standard risk factors. But effects were only found in women, and not in men.

Identification of the biological mechanisms through which loneliness might impact health would clarify the processes

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underlying these epidemiological observations. The biological concomitants of loneliness can be investigated using a number of different research strategies, including clinical assessments of variables such as blood pressure, naturalistic monitoring of biological function in everyday life, and mental stress testing (Steptoe and Poole, 2010). Mental stress testing involves the measurement of biological responses to acute challenges, and has the advantage that detailed dynamic responses can be studied under controlled conditions, reducing the impact of other factors that may confound associations. Loneliness has been linked with changes in cardiovascular processes such as elevated systolic blood pressure (Hawkley et al., 2006, 2010), greater diastolic blood pressure reactions to acute stress in women (Steptoe et al., 2004), elevated total peripheral resistance, lower heart rate variability and decreased cardiac output (Cacioppo et al., 2002; Hawkley et al., 2003). Ong et al. (2012) recently reported that loneliness was associated with greater blood pressure responses to social evaluative threat and with delayed post-stress recovery, and that this effect was accentuated by greater age. Elevated cortisol levels have been observed in both lonely students (Cacioppo et al., 2000; Pressman et al., 2005; Doane and Adam, 2010) and lonely adults (Steptoe et al., 2004; Adam et al., 2006). Cortisol is involved in regulating inflammation through activation of the glucocorticoid (GC) receptor mechanisms, leading to inhibition of pro-inflammatory signalling pathways (Raison and Miller, 2003; Rhen and Cidlowski, 2005). Previously we have shown that cortisol responders have significantly smaller cytokine responses compared with cortisol non-responders (Kunz-Ebrecht et al., 2003). Therefore, as loneliness has been linked with elevated cortisol levels, the heightened risk of diseases related to inflammation in the lonely may appear paradoxical.

One explanation is that loneliness may compromise the regulation by GCs of pro-inflammatory transcription pathways. Cole et al. (2007) analysed genome-wide transcriptional activity, and identified 209 transcriptions representing 144 genes that were differentially expressed in lonely compared to non-lonely individuals. Loneliness was associated with an over-expression of genes with elements for the pro-inflammatory NF-κB/Rel transcription pathway and impaired expression of anti-inflammatory GC response genes. Verifying the increased inflammatory signalling observed in the genomic analyses, lonely individuals had significantly greater circulating C-reactive protein (CRP) concentrations than non-lonely individuals.

Additionally, several studies have found a link between altered immunoregulation and stress responsivity in the lonely. For example, loneliness has been associated with reduced natural kill cell activity and less lymphocyte transformation by the Epstein Barr virus in response to examination stress (Kiecolt-Glaser et al., 1984a,b) and increased human herpes virus antibody titers following an environmental stressor (Dixon et al., 2001).

Overall, these data point towards an association between loneliness, stress responsivity and inflammation. Previously we observed an independent association between loneliness and heightened fibrinogen concentrations in response to psychological stress (Steptoe et al., 2004). By contrast, some studies involving samples taken at rest have not found a link between loneliness and inflammatory markers (O'Luanaigh et al., 2012; Shankar et al., 2011).

In the present study, we investigated the relationship of loneliness with inflammatory responses to standardized mental stress, assessing interleukin-6 (IL-6), interleukin-1 receptor antagonist (IL-1Ra), and the chemokine monocyte chemotactic protein-1 (MCP-1). Elevated IL-6 levels have been prospectively associated with coronary disease (Danesh et al., 2008) and heightened circulating IL-1Ra and certain polymorphisms of the IL-1Ra gene have been linked with coronary events (van Minkelen et al., 2009; Fragoso et al., 2010). MCP-1 is not as widely studied as IL-6 and IL-1Ra, but it is thought to play an important role in pathogenesis of vascular diseases by promoting recruitment of leukocytes to sites of inflammation in the vessel wall (Niu and Kolattukudy, 2009; Hansson and Hermansson, 2011). Elevated MCP-1 concentrations have been positively associated with subclinical arthrosclerosis and incident CHD (Herder et al., 2006; Tang et al., 2007). Gender differences in the relationship between loneliness and health have been reported (Thurston and Kubzansky, 2009) and gender may be a moderator both of inflammatory cytokine (Steptoe et al., 2002) and cortisol responses (Kudielka and Kirschbaum, 2005), with evidence of greater cortisol responses to acute stress in older women (Kudielka et al., 2004; Seeman et al., 1995). We tested for gender differences in association between loneliness and biological stress responses. We reasoned that that if inflammation mediates the influence of loneliness on disease risk, then loneliness would be positively associated with stress responses in IL-6, IL-1Ra and MCP-1. We were also interested in investigating whether individual variations in cortisol responses influenced the hypothesised relationship between loneliness and inflammation.

2. Method

2.1. Participants

Participants were recruited from the Whitehall II epidemiological cohort of British civil servants (Marmot et al., 1991) for psychophysiological stress testing between 2006 and 2008. The primary purpose of the study was to investigate biological responses to acute stress in relation to socioeconomic factors and subclinical coronary atherosclerosis and cardiovascular risk (e.g. Hamer et al., 2010; Steptoe et al., 2010; Hamer and Steptoe, 2012). Participants had no history or objective sign of CHD and no diagnosis or treatment for hypertension, diabetes, inflammatory diseases, allergies, anxiety or major depression. Civil service employment grade was used as an indicator of socioeconomic status, and recruitment was stratified to include a range of employment grades. 543 men and women age 53—76 years took part in stress testing, of whom 524 provided data on loneliness and at least one of the key biological measures (IL-6, IL-1Ra or MCP-1). People included and excluded from the statistical analyses did not differ in age, gender distribution, grade of employment, body mass index (BMI), smoking status or loneliness. In the seven days prior to testing, participants were prohibited from taking anti-inflammatory or anti-histamine medication and were rescheduled if they reported colds or other infections on the day of testing. Participants were also instructed