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Persistent depressive symptomatology and inflammation: To what extent do health behaviours and weight control mediate this relationship? ☆

Mark Hamer *, Gerard J. Molloy, Cesar de Oliveira, Panayotes Demakakos

Department of Epidemiology and Public Health, 1-19 Torrington Place, University College London, London WC1E 6BT, UK

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ABSTRACT

We examined if persistent depressive symptoms are associated with markers of inflammation (C-Reactive Protein-CRP) and coagulation (fibrinogen), and if this association can be partly explained by weight control and behavioural risk factors (smoking, alcohol, physical activity). The study sample included 3609 men and women (aged 60.5 ± 9.2 years) from The English Longitudinal Study of Ageing, a prospective study of community dwelling older adults. Depressive symptoms (using the 8-item CES-D scale), health behaviours (smoking, alcohol, physical activity), body weight, and central adiposity were assessed at baseline and 2 years follow up. CRP and fibrinogen were assessed at follow up. At baseline 12.7% of the sample reported elevated depressive symptomatology, which persisted in 6.1% of participants at follow up. Baseline CES-D score was associated with CRP (β = .035, SE = .0066) and fibrinogen (β = .023, SE = .0060) measured 2 years later. Using simple mediation analysis we observed both a direct association of depressive symptoms on CRP (β = .013, SE = .0066) and indirect mediating effects through behavioural risk factors (β for total indirect effect β = .022, SE = .0023). For fibrinogen there were no direct effects of depression, and the association was entirely explained through indirect mediating effects of health behaviours. The presence of recurrent elevated depressive symptomatology at both time points was more strongly associated with CRP and fibrinogen. In summary, the association between depressive symptoms and low grade inflammation can be partly explained by behavioural risk factors. The presence of persistent depression appears to be associated with the greatest risk of elevated inflammation.

1. Introduction

Markers of low grade inflammation have been consistently associated with greater risk of cardiovascular disease (CVD) (Danesh et al., 2004). Inflammatory processes might also be an important psychobiological mechanism that links psychosocial stress with CVD (Steptoe et al., 2007; Vaccarino et al., 2007; Whooley et al., 2008; Hamer et al., 2008). In particular, there has been much interest in the association between depressive symptoms and inflammatory risk markers (Irwin and Miller, 2007). Several studies have reported elevated concentrations of various inflammatory markers in differing populations reporting depressive symptoms, including the medically healthy (e.g., Liukkonen et al., 2006; Panagiotakos et al., 2004), elderly (Kop et al., 2002; Penninx et al., 2003; Bremmer et al., 2008), and patients with acute coronary symptoms or existing CVD risk factors (Vaccarino et al., 2007; Empana et al., 2005; Pizzi et al., 2008). Other studies, however, have cast doubt on the association between depression and inflammation; for example, some have observed an inverse or null association (Whooley et al., 2007; Janszky et al., 2005), or suggested that the association is not causal but largely explained by common genes (Vaccarino et al., 2008). Generally, previous studies have employed cross-sectional designs that preclude any firm conclusions about the causality or directionality of a possible association. The few existing prospective studies that have examined the relationship between depressive symptoms and inflammation have produced conflicting findings regarding directionality (Milaneschi et al., 2008; Gimeno et al., 2008; Matthews et al., 2007). Another important issue has been the failure of most studies to assess depressive symptoms at multiple time points, which is important to establish if the inflammatory effects are related to persistent or transient symptoms. For example, in a recent study of healthy women, state but not trait levels of depressive symptoms were associated with changes in interleukin (IL)-6 (Rohleder and Miller, 2008).

In previous studies, little attention has focused on the factors that might explain the association between depressive symptoms and inflammation. In an effort to rigorously control for potential confounding (such as adiposity, alcohol, smoking) the associations between depression and inflammation are sometimes reduced to non-significance (Kop et al., 2002; Tiemeier et al., 2003), although in other studies may persist above and beyond the covariates. This approach might, however, be viewed as over-adjustment if some of

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* Corresponding author. Fax: +44 020 7916 8542.
E-mail address: m.hamer@ucl.ac.uk (M. Hamer).

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the covariates are in fact intermediate mechanisms, and previous studies have not specifically performed mediation analyses to resolve this issue. Behavioural changes, such as increased smoking or unsuccessful attempts at smoking cessation, reduced physical activity, modified dietary and alcohol intake, disturbed sleep, and weight change, may occur as an adaptation or coping response to depressive symptoms, thus are potentially important intermediate factors (Steptoe, 2007). These factors are also known to be associated with inflammation (Hamer and Stamatakis, 2008). For example, adiposity is an important production site of various pro-inflammatory cytokines (Pou et al., 2007). Physical activity and alcohol intake appear to have anti-inflammatory effects, whilst smoking is a potent risk factor for increased levels of low grade inflammation. We recently demonstrated that smoking, physical activity, hypertension, and C-reactive protein (CRP) partly explained the association between psychological distress and incident CVD in a community sample of Scottish adults (Hamer et al., 2008). However, the data on distress, behaviour, and inflammation were collected at the same point in time, thus it was difficult to precisely interpret the temporal associations between these variables. In the present study we therefore attempt to more precisely examine these associations using The English Longitudinal Study of Ageing (ELSA), a prospective study of community dwelling older adults (see Economic and Social Data Service, 2008, for study background). Specifically, the aims of this study were to examine if persistent depressive symptoms were associated with markers of inflammation (CRP) and coagulation (fibrinogen), and if these associations can be partly explained by adiposity and behavioural risk factors (smoking, alcohol, physical activity).

2. Methods

2.1. Design/setting and participants

ELSA is an ongoing cohort study that contains a nationally representative sample of the English population living in households. The original ELSA cohort consists of men and women born on or before 29 February 1952. The sample was drawn from households that have participated in Health Survey for England (HSE) in 1998, 1999, and 2001 (wave 0). HSE recruits participants using multistage stratified probability sampling with postcode sectors selected at the first stage and household addresses selected at the second stage. For the present analyses we report data from 2 years of follow up (wave 1 (baseline), 2002–2003 and wave 2, 2004–2005). There were 8323 participants with complete data at baseline of which 2917 were lost through follow up. A further 1797 participants were excluded because of incomplete bloods ($n = 992$) or anthropometric data ($n = 805$) at follow up, leaving a final sample size of 3609 individuals (46.5% men, aged 60.5 ± 9.2 years). Missing data at follow up was mostly because participants did not consent to a nurse visit or to give blood, and participants with clotting and bleeding disorders, or taking anti-coagulant medication were ineligible to give blood. In comparison with the overall sample, the sub-group used in the present analyses were slightly younger, more educated, had a lower prevalence of depressive symptoms, but were similar in health behaviours such as smoking and physical activity. In order to account for missing data all analyses were weighted for non-response. Participants gave full informed consent to participate in the study and ethical approval was obtained from the London Multi-centre Research Ethics Committee.

2.2. Measurements

At waves 1 and 2 interviewers collected demographic (e.g., age, social class, education) and health-related questions (smoking, alcohol intake, physical activity, and mental health). Baseline anthropometric data (weight, height, waist circumference) was used from wave 0 since it was not available at wave 1 of ELSA, but this data was collected at follow up (wave 2) in ELSA. Social–occupational class was defined using the National Statistics – Socio-Economic Classification (NS-SEC five-class version: managerial/professional occupations, intermediate occupations, small employers/own account workers, lower supervisory/technical occupations, and semi-routine and routine occupations) and education (categorised as: higher education, A-level or equivalent, O-level or equivalent, none). Presence of morbidity was recorded (including: doctor diagnosed heart disease, hypertension, diabetes, cancer, neuromuscular conditions, endocrine/metabolic conditions, epilepsy, bronchitis, asthma, and other respiratory disorders, and complaints related to the stomach, digestive system, and bowel). Depressive symptoms were assessed by an 8-item Centre of Epidemiological Studies Depression (CES-D) scale. We used a score of $\geqslant 4$ to define caseness of depression (Steffick, 2000). Physical activity interviews inquired about the frequency of participation in vigorous, moderate, and light physical activities (more than once per week, once per week, one to three times per month, hardly ever). The questions about physical activity were extracted from a validated physical activity interview that was employed in the HSE (Joint Health Surveys Unit, 2007).

At wave 2 blood samples were collected for the analysis of CRP and fibrinogen. The analysis of the blood data was carried out in the Royal Victoria Infirmary (Newcastle-upon-Tyne, UK). Detailed information on the technicalities of the blood analysis, the internal quality control, and the external quality assessment for the laboratory that carried it out can be retrieved from the 2004 HSE technical report (Graig et al., 2006) since both HSE and ELSA employed the same laboratory and the same guidelines and protocols for the blood analysis.

2.3. Statistical analyses

Weight gain or an increase in central adiposity between waves 0 and 2 was defined as an increase of at least 5% in body weight or waist circumference, respectively (Barzilay et al., 2006). The other behavioural risk factors were categorised as follows: physical activity (none/light activity only, moderate activity at least 1/wk, or vigorous activity at least 1/wk), smoking (none, current), alcoholic drinks (>4 per week, 1–4 per week, rarely, never). We calculated odds ratios (OR) and 95% confidence intervals (CI) for the association between depressive symptoms at wave 1 and behavioural risk factors at wave 2, adjusting for age, gender, social-occupational class, and morbidity. In addition we calculated ORs for the association between persistent depressive symptoms at both time points and behavioural risk factors. In order to examine associations between depression, behavioural risk factors, and CRP and fibrinogen we employed general linear models. We calculated adjusted beta regression coefficients and 95% CIs for participants with depressive symptoms only at baseline and those with persistent symptoms at both time points, in comparison with participants without any symptoms at baseline or follow up (reference). We also employed a bootstrapping technique (Preacher and Hayes, 2008) to examine mediation of the association of CES-D score at baseline on CRP and fibrinogen at follow up through weight change (wave 0 to wave 2), alcohol consumption, smoking, and physical activity at follow up. This multiple mediation model allowed us to test the total indirect effect of depression on inflammation and the extent to which specific variables mediate this association. Given the skewed distribution of CRP, the values were log transformed. All analyses were conducted using SPSS version 14.