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The combined association of depressive symptoms and C-reactive protein for incident disease risk up to 12 years later. Findings from the English Longitudinal of Ageing (ELSA).

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Abstract

Background: Depression and inflammation are interrelated, and both are associated with the development of long-term conditions (LTCs). We investigated whether the combination of elevated depressive symptoms and elevated C-reactive protein (CRP) was associated with the rate of onset of a range of LTCs.

Methods: We analysed data from 5360 participants (65.77±9.46 years; 54.1% female) from the English Longitudinal Study of Ageing (ELSA). Depressive symptoms were indicated using the Centre for Epidemiological Studies Depression (CES-D) scale and scores were combined with high sensitivity (hs)-CRP values to reflect the additive interaction between low/high depressive symptoms (CES-D ≥4) and low/high CRP (>3mg/L). Participants were followed-up for up to 12 years to predict incident illness. Cox proportional hazard regression was used controlling for covariates.

Results: In fully adjusted models, the combination of elevated depressive symptoms and elevated CRP was an independent predictor of CHD (HR = 1.68, 95% C.I. = 1.01-2.78), stroke (HR = 2.02; 95% C.I. = 1.48-2.76), diabetes/high blood glucose (HR = 1.69; 95% C.I. = 1.11-2.57), and pulmonary disease (HR = 1.79; 95% C.I. = 1.02-3.15) relative to low depressive symptoms/low CRP, independently of age, sex, wealth, cohabitation, smoking status, body mass index and hypertension. Elevated depressive symptoms and low CRP was associated with arthritis incidence (HR = 1.49; 95% C.I. = 1.15-1.92). No association was found for cancer incidence.

Conclusion: A combination of depressive symptoms and CRP was implicated in the onset of CHD, stroke, diabetes/high blood glucose, and pulmonary disease up to 12 years later, reflecting the role of psychobiological processes across multiple disease states.

Key words: depression, C-reactive protein, coronary heart disease, stroke, arthritis, cancer, pulmonary disease, diabetes, long-term conditions.

1.0 Introduction

Depression is associated with a host of poor physical health outcomes (Moussavi et al., 2007), and has been shown to not only adversely affect prognosis in patients with known disease, but also act as a risk factor for incident disease in healthy populations. For example, depression has been associated with the onset of coronary heart disease (CHD) (Van der Kooy et al., 2007), stroke (Dong et al., 2012), arthritis (Patten et al., 2008), cancer (Jia et al., 2017), and type 2 diabetes (Mezuk et al., 2008). The reason for this association is not clear, though is likely to involve a biological component.

Depression is associated with an innate inflammatory response (Raison et al., 2006), and results from a recent meta-analysis have shown heightened levels of inflammatory markers, such as C-reactive protein (CRP), in depression (Haapakoski et al., 2015). Epidemiological evidence for the direction of the association between depression and inflammation has been mixed, with some studies suggesting that depression precedes inflammation (Stewart et al., 2009), while others have shown that inflammation precedes depression (Bell et al., 2017; Gimeno et al., 2008); still others have proposed a bidirectional association between depression and inflammation (Matthews et al., 2010). Irrespective of the temporal sequence, it has been suggested that an inflamed-depression subtype exists (Chamberlain et al., 2019; Pariante, 2017), which may have implications for treatment responsivity.

Given that high levels of inflammatory activity are indicative of an immune system response and have been associated with a variety of chronic illnesses, or so-called 'long-term conditions' (LTCs) (Choy and Panayi, 2001; Danesh et al., 2004; Gan et al., 2004; Wang et al., 2013), it is plausible that the interaction between depression and inflammation contributes to incident disease (Au et al., 2014). Using nationally representative data from the English Longitudinal Study of Ageing (ELSA), we aimed to test this hypothesis using 12 years of prospective data, across a variety of different LTC endpoints. Specifically, we hypothesised that a combination of elevated depressive symptoms and high levels of CRP would be more detrimental to future health than either factor on its own.

2.0 Methods

2.1 Participants and study design

Our sample was drawn from ELSA, a nationally representative general population study of adults aged 50 years and older living in England (Steptoe et al., 2013). The sample is followed up biennially; at every wave participants complete a computer-assisted personal interview plus a self-completion questionnaire. On alternate waves, a nurse visit enables the collection of blood samples and objective assessments of physical function. This current paper uses data collected across 12 years of study, from wave 2 (2004/5) through to wave 8 (2016/2017). Out of a total possible sample of 8780 core members participating at wave 2, 5360 were included in the analyses presented here, having complete data on all independent variables and covariates. Compared to those excluded, those included in the analytic sample were more likely to be female ($\chi^2 = 23.57$), non-smoking ($\chi^2 = 35.82$), of higher wealth ($\chi^2 = 132.53$), non-hypertensive ($\chi^2 = 223.24$), and of lower BMI ($t = 5.36$) (all $p < 0.001$); they were also more likely to be married or cohabiting ($\chi^2 = 12.01$, $p = 0.001$). Since different models were performed to predict each incident LTC, excluding those with the respective LTC at baseline, specific Ns are reported for the individual models.

2.2 Measures

2.2.1 Predictor variables: depressive symptoms and C-reactive protein

Depressive symptoms were measured at baseline using the eight-item Centre for Epidemiological Studies Depression scale (CES-D). Rather than being diagnostic, the CES-D measures symptoms that can be used to identify people at risk of depression (Radloff, 1977). The psychometric properties of the eight-item version have been shown to be comparable to the original twenty-item version (Steffick, 2000). The standard cut-off of ≥4 on the CES-D was used to split participants into low and high depressive symptoms (Hamer et al., 2009).

High sensitivity CRP (hs-CRP) was assessed from blood drawn by study nurses. Participants who had a clotting or bleeding disorder and those on anti-coagulant medication did not provide blood samples. Hs-CRP was measured using the N Latex CRP mono immunoassay on the Behring Nephelometer II analyser. All blood samples were analysed at the Royal Victoria Infirmary laboratory in Newcastle upon Tyne, UK (for a detailed description of blood analyses see Sproston and Mindell, 2004). Outliers above 20 mg/L were

removed from analyses since these may indicate the presence of an acute infection. A binary variable using a cut-off of >3 mg/L was used to indicate those with low and high values (He et al., 2010).

2.2.2 Outcome variables: incident LTCs

Participants were shown a list of illnesses and asked to self-report any doctor-diagnosed illnesses they had developed since the previous ELSA wave. Incident LTC was defined as a new positive report of CHD, stroke, diabetes/high blood glucose, pulmonary disease (e.g. chronic bronchitis, emphysema), arthritis, and cancer by participants at waves 3, 4 5, 6, 7 and 8, excluding participants who reported that same LTC at wave 2 baseline. These diseases were selected based on their consistency of reporting across waves and due to their prevalence in ELSA. For the purposes of our analyses, CHD was defined to include all cases of angina and myocardial infarction. To avoid self-reporting errors, arthritis was coded to include osteoarthritis, rheumatoid and arthritis type not specified.

2.2.3 Covariates

Covariates were all measured at baseline. Sociodemographic variables included in models were age, sex, and whether participants were cohabiting with a partner. Socioeconomic status was included in models as quintiles of net financial wealth, which refers to participants' gross financial wealth with financial debt subtracted. Height and weight were collected during the nurse visit and body mass index was derived using the standard formula (kg/m^2). Whether or not participants reported being a current smoker (no/yes) was also included. Doctor diagnosis of hypertension or use of anti-hypertensive medication was self-reported and these responses were combined with objective assessments taken at the nurse visit (hypertension defined as systolic blood pressure >140 and diastolic blood pressure >90) to generate a binary variable (no /yes).

2.3 Statistical analysis

The interaction between depression and CRP was calculated by combining the two binary variables into a categorical variable comprising low depressive symptoms/low CRP (reference group), low depressive symptoms/high CRP, elevated depressive symptoms/low CRP and elevated depressive symptoms/high CRP. Chi-square analyses were used to assess the association between depression and CRP. We performed

analyses to examine the association between the depressive symptoms/CRP interaction at baseline on individual incident LTCs over follow-up. Using fully adjusted Cox proportional hazard regression analyses, participants with each specific illness were excluded from the sample at baseline; therefore separate Ns are reported for these models. Results for all models are presented as age and sex adjusted and fully adjusted hazard ratios (HR) with 95% confidence intervals (C.I.). Fully adjusted models included the covariates: age, sex, wealth, cohabitation, smoking status, BMI and hypertension status. The supplementary file displays the results of sensitivity analyses removing all cases (those with and without incident disease) within the two years following baseline (Table 3), as a check for reverse causation. The assumption of proportional hazards was upheld in all the models. All analyses were conducted using SPSS version 24. Two-tailed tests were used throughout and the significance level was set at $p<0.05$, though exact significance levels are reported.

3.0 Results

Table 1 shows the characteristics of the sample. The average participant was (65.77 years old (± 9.46 years), and married or cohabiting. Few participants were smokers (13.7%), but the average BMI was above 25 kg/m^2 reflective of the high levels of obesity in the sample (BMI >30 kg/m^2 = 27.2%). Thirteen percent of participants scored positively for elevated depressive symptoms and a third of participants had heightened levels of CRP (>3 mg/l). Chi-square analyses revealed a significant association between elevated depressive symptoms and CRP (χ^2 = 15.03, p <0.001), with 38.6% of those with elevated depressive symptoms versus 31.3% of those with low depressive symptoms having elevated CRP >3 mg/l.

Table 2 displays the results of the individual Cox regression models performed for each incident illness. These analyses reveal significant effects of the depressive symptoms/CRP interaction for all LTC outcomes except cancer. Specifically, in fully adjusted models, participants with a combination of elevated depressive symptoms and elevated CRP (HR 1.68, 95% C.I. 1.01-2.78) had an increased hazard of developing incident CHD. The association with CHD appeared to be driven by elevated CRP (low depressive symptoms/high CRP: HR 1.37, 95% C.I. 1.03-1.82), as opposed to elevated depressive symptoms (elevated depressive symptoms/low CRP: HR 1.06, 95% C.I. 0.64-1.77). With regards to models predicting incident stroke, diabetes/high blood glucose and pulmonary disease all combinations of depressive symptoms and

CRP were associated with increased hazard of incident disease relative to those with low depressive symptoms and low CRP. Regarding incident arthritis, only the elevated depressive symptoms/low CRP predicted increased hazard of future disease, with those in this group being around 1.5 times more likely to develop arthritis over follow-up that those with low depressive symptoms/low CRP (HR 1.49, 95% C.I. 1.15-1.92). Sensitivity analyses are displayed in Table 3 in the supplementary file. In fully adjusted models, the results were upheld for CHD, cancer, pulmonary disease and arthritis. However, significant results were attenuated for diabetes/high blood glucose and removed for stroke.

4.0 Discussion

The results of this study reveal that depression and CRP were related cross-sectionally, and that the interaction between depression and CRP provides further evidence for one possible mechanism underlying the relationship between depression and LTC onset. Interestingly, we found different associations across illness outcomes, highlighting the complexity of the work in this field. Specifically, we found that a combination of depressive symptoms and CRP were predictive of incident CHD (myocardial infarction and angina), stroke, diabetes/high blood glucose, and pulmonary disease up to 12 years later, compared to those with low depressive symptoms and low CRP. Elevated depressive symptoms/low CRP predicted incident arthritis, while no associations were apparent for cancer incidence. Results were largely upheld in sensitivity analyses removing incident cases of disease within two years of baseline.

Depressive symptoms were overall low in ELSA, with approximately 13% of our sample showing elevated symptoms on the CES-D. This prevalence is slightly lower with work from other population studies; for example the National Health and Nutrition Examination Survey (NHANES) reported an elevated depressive symptoms population prevalence of 20% (Shim et al., 2011); the SHARE study reported prevalence of elevated depressive symptoms across European countries, with estimates ranging from 18.1% (Denmark) to 36.8% (Spain) (Castro-Costa et al., 2007). These differences may be accounted for by the use of different assessment tools across studies and different mean ages of participants. Our finding that not all those with elevated depressive symptoms have elevated CRP is in line with work to suggest inflammation is not

universally experienced in depression (Lynall et al., 2019), and may denote a specific phenotype (Chamberlain et al., 2019; Pariante, 2017).

Our results can be interpreted in light of earlier findings. Research has previously revealed depression to be implicated in the aetiology of a variety of different diseases, including CHD (Van der Kooy et al., 2007), stroke (Dong et al., 2012), arthritis (Patten et al., 2008), cancer (Jia et al., 2017), and type 2 diabetes (Mezuk et al., 2008). Moreover, high levels of inflammation, including CRP, have also been associated with diseases to include diabetes (Wang et al., 2013), CHD (Danesh et al., 2004), pulmonary disease (Gan et al., 2004) and rheumatoid arthritis (Choy and Panayi, 2001), to name but a few. However, mixed evidence exists for the association between CRP and cancer (Heikkilä et al., 2007). While there is some evidence for the interaction between depression and CRP for predicting incident diabetes (Au et al., 2014), to the best of our knowledge, our paper is the first to study the combined association of depression and CRP for disease onset across multiple LTC outcomes. Our findings for CHD suggest the association between depression and CRP for predicting future cardiac illness was largely accounted for by elevated CRP; the importance of CRP for future cardiac events has been demonstrated previously (He et al., 2010). Depression has been shown to be an independent risk factor for CHD, with evidence suggesting somatic symptoms to be particularly cardiotoxic (Carney and Freedland, 2012); in turn these somatic symptoms are thought by some to account for the association with inflammatory factors (Iob et al., 2019). Future work would benefit from studying these nuanced effects in detail. The results for arthritis were less congruent with previous literature since we showed that the combination of depression and low CRP was associated with increased risk of future arthritis, suggesting that depression but not CRP was important here. The fact our arthritis measure comprised both osteo and rheumatoid cases, both with distinct pathophysiology, may partly account for this discrepant finding. The null findings for cancer reflect the mixed results from meta-analyses regarding the role of depression in this literature (Ahn et al., 2016; Chida et al., 2008), perhaps attributable to the heterogeneity in disease pathology across different cancers.

Other variables important to the depression/inflammation and LTC relationship should also be considered. While we took into account key sociodemographic factors, smoking, obesity and hypertension,

other factors are also likely to fall on the causal pathway including physical activity and alcohol consumption (Hamer et al., 2012; Penninx, 2016). Moreover, the role of other inflammatory markers, including the interleukins, were not measured in ELSA and therefore not taken into account here, despite evidence for their association with depression (Haapakoski et al., 2015). While our study investigated the additive interaction between depression and inflammation, these two factors may or may not be causally related or indeed may both be caused by a third variable (Shimbo et al., 2005).

Our study has a number of strengths and limitations that must be borne in mind when interpreting the findings. Advantages of our study rest in the longitudinal nature of our data, allowing us to follow-up participants over 12 years to glean detailed information from this nationally representative cohort of older adults. Moreover, the large sample size, has allowed us to conduct well-controlled analyses taking a variety of confounders into consideration. However, depression relied on self-report assessment via the CES-D, which may be an imperfect indicator of depression status. Depressive symptoms and CRP are likely to fluctuate over time, which was not taken into account in these analyses. Moreover, our illness outcomes were also self-reported which may introduce measurement error to our results; though there is evidence of the reliability of self-reported physical illness in epidemiological cohort studies (Simpson et al., 2004).

In conclusion, we have reported evidence for a combined detrimental effect of depression and heightened CRP for future risk of incident CHD, stroke, diabetes/high blood glucose, and pulmonary disease, but not cancer. Our findings reflect the complexity of understanding the role of depression and inflammation across multiple disease outcomes, and represent the need for future work to further unpick the mechanisms of the association between mind and body.

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Table 1: Demographic, clinical and biological characteristics of the sample (N = 5360)

Characteristic	Mean ± SD or N(%)
Baseline sociodemographics	
Age (years)	65.77±9.46
Female	2900 (54.1)
Married/cohabiting	3822 (71.3)
Net financial wealth – quintiles	
1	903 (16.8)
2	910 (17.0)
3	1087 (20.3)
4	1194 (22.3)
5	1266 (23.6)
Baseline health variables	
Current smoker	734 (13.7)
Body mass index (kg/m^2)	27.75±4.71
Hypertension	2371 (44.2)
Baseline depression and CRP	
CES-D score	1.43±1.87
Elevated depressive symptoms (CES-D ≥4)	710 (13.2)
hs-CRP	3.07±3.34
hs-CRP (>3mg/l)	1729 (32.3)
Depressive symptoms/CRP interaction	
Low depressive symptoms/low CRP	3195 (59.6)
Low depressive symptoms/high CRP	1455 (27.1)
Elevated depressive symptoms/low CRP	436 (8.1)
Elevated depressive symptoms/high CRP	274 (5.1)
Incident disease at follow-up	
CHD (n = 4153)	259
Stroke (n = 4545)	626
Diabetes/high blood glucose (n = 4341)	366
Cancer (n = 3518)	413
Pulmonary disease (n = 3513)	197
Arthritis (n = 3031)	826

Table 2. Prospective associations between baseline CES-D/CRP interaction and individual incident LTCs over 12 years

Incident LTC outcome	N		Age and sex adjusted hazard ratio (95% C.I.)	*p*	Fully adjusted hazard ratio[a] (95% C.I.)	*p*
CHD	4153	↓depressive symptoms/↓CRP	Reference	-	Reference	-
		↓depressive symptoms/↑CRP	1.56 (1.19-2.04)	0.001	1.37 (1.03-1.82)	0.031
		↑depressive symptoms /↓CRP	1.17 (0.71-1.95)	0.535	1.06 (0.64-1.77)	0.823
		↑depressive symptoms /↑CRP	2.08 (1.28-3.39)	0.003	1.68 (1.01-2.78)	0.044
Stroke	4545	↓depressive symptoms/↓CRP	Reference	-	Reference	-
		↓depressive symptoms/↑CRP	1.54 (1.29-1.83)	<0.001	1.46 (1.21-1.76)	<0.001
		↑depressive symptoms /↓CRP	1.44 (1.08-1.91)	0.012	1.41 (1.06-1.88)	0.018
		↑depressive symptoms /↑CRP	2.17 (1.61-2.93)	<0.001	2.02 (1.48-2.76)	<0.001
Diabetes/ high blood glucose	4341	↓depressive symptoms/↓CRP	Reference	-	Reference	-
		↓depressive symptoms/↑CRP	2.29 (1.83-2.87)	<.0.001	1.41 (1.11-1.80)	0.005
		↑depressive symptoms /↓CRP	1.88 (1.27-2.76)	0.001	1.56 (1.06-2.31)	0.026
		↑depressive symptoms /↑CRP	2.97 (1.98-4.47)	<0.001	1.69 (1.11-2.57)	0.014
Cancer	3518	↓depressive symptoms/↓CRP	Reference	-	Reference	-
		↓depressive symptoms/↑CRP	1.12 (0.90-1.39)	0.329	1.04 (0.83-1.32)	0.725
		↑depressive symptoms /↓CRP	1.27 (0.89-1.83)	0.188	1.26 (0.88-1.82)	0.209
		↑depressive symptoms /↑CRP	0.73 (0.42-1.28)	0.270	0.66 (0.37-1.18)	0.161
Pulmonary disease	3513	↓depressive symptoms/↓CRP	Reference	-	Reference	-
		↓depressive symptoms/↑CRP	1.97 (1.44-2.70)	<0.001	1.56 (1.12-2.18)	0.009
		↑depressive symptoms /↓CRP	2.48 (1.55-3.96)	<0.001	1.98 (1.23-3.19)	0.005
		↑depressive symptoms /↑CRP	2.91 (1.70-4.99)	<0.001	1.79 (1.02-3.15)	0.043
Arthritis	3031	↓depressive symptoms/↓CRP	Reference	-	Reference	-
		↓depressive symptoms/↑CRP	1.14 (0.97-1.34)	0.115	0.96 (0.81-1.14)	0.623
		↑depressive symptoms /↓CRP	1.54 (1.19-1.98)	0.001	1.49 (1.15-1.92)	0.003
		↑depressive symptoms /↑CRP	1.42 (0.97-2.08)	0.071	1.20 (0.82-1.77)	0.352

[a] age, sex, cohabitation, wealth, smoking, BMI, and hypertension.

Highlights

- Participants aged 50 and over were followed for up to 12 years.
- Depressive symptoms plus raised C-reactive protein predicted incident diseases.
- Diseases predicted were heart disease, stroke, diabetes and pulmonary disease.
- All results were independent of a range of covariates.