

The Relationship of C-Reactive Protein to Obesity-Related Depressive Symptoms: A Longitudinal Study

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Objective: Obesity has been shown to produce a state of systematic low-grade inflammation that may have detrimental neuropsychiatric effects.

Design and Methods: Longitudinal associations between obesity, inflammation, and depressive symptoms amongst a cohort of older English adults over 4 years of follow-up were examined. Participants were 3,891 obese and nonobese people drawn from the English longitudinal study of ageing (ELSA) [aged 64.9 (SD = 8.8) years, 44.6% men]. Depressive symptoms were assessed at baseline and after 4 years of follow-up using the eight-item center for epidemiological studies—depression scale (CES-D).

Results: Approximately 26.3% ($N = 1,025$) of the sample were categorized as obese at baseline. Obesity at baseline was associated with elevated levels of depressive symptoms at follow-up ($P < 0.001$), in analyses that adjusted for depression levels at baseline and sociodemographic and background variables including the prevalence of permanent illness/disability, alcohol consumption, sedentary behavior, and smoking. In addition, C-reactive protein (CRP) concentrations at baseline were independently associated with CES-D depression scores at follow-up ($P = 0.008$) in fully adjusted analyses. Subsequent mediation analyses revealed that CRP levels explained ~20% of the obesity-related longitudinal change in depression scores.

Conclusion: These data suggest that chronic inflammation may be a key determinant of depressive symptoms in obesity.

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Introduction

Emerging evidence suggests that obesity can have marked psychological effects (1). In particular, the depressogenic effect of obesity is becoming increasingly apparent (2). However, the causal pathways that underlie the emergence of feelings of depression in obese people remain poorly understood. A central feature of obesity is chronic or low-grade systemic inflammation, characterized by elevated plasma levels of acute phase proteins, most notably C-reactive protein (CRP), and an increase in the pro-inflammatory cytokines interleukin-6 and tumor necrosis factor- α (3,4). In obesity adipocytes can promote inflammation by secreting acute phase reactants and inflammatory cytokines (4,5). In addition, obesity causes the enlargement of adipocytes which can impair the functioning of adipose tissue and increase the rate of adipocyte cell death and associated macrophage infiltration further contributing to low-grade nonresolving inflammation (5,6).

Numerous studies have documented an association between low-grade inflammation and depression (7,8). Studies examining the mental health effects of cytokine administration (especially inter-

feron- α) in both healthy individuals and cancer patients strongly suggest that inflammation can lead to depressive symptoms (6,9). Peripheral proinflammatory cytokine signals may access the brain through a set of humoral, neural, and cellular pathways and influence neuroendocrine functioning and mood-relevant neurotransmitters leading to symptoms of depression (6). Taken together the existing evidence suggests that the systematic inflammation originating in adipose tissue may account, at least in part, for the depressogenic effect of obesity. The present study aims to build on this research by testing the hypothesis that obesity is associated with an increase in depressive symptoms and that this increase may be explained by obesity-related elevations in the inflammatory marker CRP.

Methods

Participants

Data for this study came from waves 2 (2004-2005) and 4 (2008-2009) of the English longitudinal study of ageing (ELSA). ELSA is an ongoing longitudinal study that contains a population-based

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TABLE 1 Characteristics of participants with and without obesity

Variables	Obese	No obesity	P value
	(N = 1,025) M/% (SD)	(N = 2,866) M/% (SD)	
Core study variables			
Depressive symptoms baseline	1.55 (1.91)	1.27 (1.76)	<0.001
Depressive symptoms follow-up	1.5 (1.95)	1.14 (1.72)	<0.001
C-reactive protein (mg L ⁻¹)	3.42 (2.28)	2.06 (1.9)	<0.001
Demographic variables			
Age	64.1 (8.34)	65.12 (8.99)	= 0.001
Male	41%	46%	= 0.009
Single/never married	4.3%	4.6%	
Married	58.2%	58.3%	
Remarried	12.2%	11%	
Legally separated	1%	1.2%	
Divorced	9.1%	9.5%	
Widowed	15.2%	15.4%	
Retired	48.3%	50.7%	
Employed	30.2%	28.8%	
Selfemployed	6.2%	6.7%	
Unemployed	0.7%	0.8%	
Permanently sick/disabled	6%	2.6%	<0.001
Looking after home/family	8.8%	10.4%	
Education ^a	4.65 (2.24)	4.25 (2.24)	<0.001
Health behaviour			
Days consumed alcohol in last week	1.96 (2.33)	2.58 (2.49)	<0.001
Sedentary	2.8%	1.5%	= 0.01
Cigarette smoking	11%	13%	

^aEducation rated from 1 = Higher National Diploma/Certificate, Degree or equivalent to 7 = no qualification.

sample of older English adults. A total of 7,666 people underwent a clinical assessment as part of wave 2 in ELSA. Of these, 2,573 participants were excluded because of incomplete questionnaire, anthropometric or blood data, or elevated CRP levels (>10 mg L⁻¹) which may be indicative of acute infection (10). A further 1,202 did not participate in the wave 4 follow-up 4 years later. This left a final sample size of 3,891 people [aged 64.9 (SD = 8.8) years at baseline, 44.6% men]. All sample data were weighted for nonresponse to account for missing data in the regression models. Participants completed demographic and background health-related questions at baseline. Participants indicated their age, gender, level of education, marital status, main current activity, whether they smoke, sedentary behavior, and the frequency of their alcohol consumption, as shown in Table 1.

Measurements

This study uses anthropometric data and blood samples collected by nurses at baseline (wave 2 of ELSA) as part of a clinical assessment. Standing height was measured with a portable stadiometer, with participants standing in the center of the base plate looking straight ahead. Weight was gauged using the Tanita THD-305 portable electronic scales. Those with a body mass index of 30 kg m⁻²

or above were defined as obese. Blood samples were collected for the analysis of CRP, which was assessed using the N latex CRP mono immunoassay on the Dade Behring Nephelometer II Analyzer and conducted in line with the quality control guidelines specified in the Health Survey of England technical report (11).

A previously validated eight-item version of the center for epidemiological studies depression (CES-D) scale was administered at baseline and after 4 years of follow-up (12). The short form CES-D uses a yes/no response format, where yes = 1/no = 0 and scores range from 0 to 8, with scores ≥ 3 linked with clinically significant depression (13). The items assess sleep difficulties and feelings of loneliness, sadness, depression, lethargy, happiness, and enjoyment of life. The CES-D scores demonstrated levels of reliability at baseline (Cronbach's $\alpha = 0.78$) and follow-up sweeps ($\alpha = 0.79$) which were comparable to those identified in the original validation study ($\alpha = 0.78$).

Statistical analyses

Logistic and linear regression analyses were firstly used to identify if obese and nonobese participants differed in their demographic characteristics, health behaviors, and depression and CRP levels. Multivariate linear regression analyses were then used to test if the presence of obesity at baseline predicted levels of depressive symptoms at follow-up in analyses which controlled for baseline levels of depressive symptoms. All regression analyses conducted as part of the mediation analyses were adjusted for several known predictors of depression: age, gender, education, marital status, current main activity (e.g., permanently sick/disabled), smoking, sedentary behavior, and frequency of alcohol consumption. The mediation analyses applied the steps outlined in Baron and Kenny to statistically test the hypothesis that CRP levels act as a mediating variable in explaining the relationship between the predictor variable, obesity, and the outcome variable, depressive symptoms. The Sobel test was used to detect the statistical significance of the mediation (14).

Results

Participants

At baseline, 26.3% (N = 1,025) of participants were classified as obese. The obese group differed from the non-obese in that they were more likely to be younger, female, less educated, sedentary and permanently ill/disabled, as outlined in Table 1. Depression and CRP scores did not display marked levels of skewness or kurtosis. However, overall depressive symptoms were infrequently reported at baseline (M = 1.35, SD = 1.81, range = 0-8) and follow-up (M = 1.23, SD = 1.79). Those who were obese at baseline reported more depressive symptoms than others at both baseline (1.55 vs. 1.27) and follow-up (1.5 vs. 1.14). CRP levels were also significantly higher amongst obese participants (M = 3.42 mg L⁻¹ vs. M = 2.06 mg L⁻¹), as shown in Table 1.

Mediation analyses

The independent variable, obesity at baseline, predicted a longitudinal change in the dependent variable, depressive symptoms, over 4 years of follow-up ($b = 0.218$, SE = 0.058; $t = 3.78$, $P < 0.001$; $\beta = 0.052$). As anticipated, obesity accounted for a substantial portion of the variance in the proposed mediator, CRP concentrations ($b = 1.31$, SE = 0.073; $t = 17.97$, $P < 0.001$; $\beta = 0.276$). In line with

predictions CRP levels were associated with a longitudinal increase in depressive symptoms over 4 years ($b = 0.034$, $SE = 0.013$; $t = 2.67$, $P = 0.008$; $\beta = 0.038$), in analyses that included initial obesity levels at baseline. Finally, including CRP levels in a hierarchical regression model diminished the link between obesity and a change in depressive symptoms between baseline and follow-up ($b = 0.218$, $SE = 0.058$; $t = 3.78$, $P < 0.001$; $\beta = 0.052$, attenuated to $b = 0.174$, $SE = 0.06$; $t = 2.9$, $P = 0.004$; $\beta = 0.042$). The Sobel test confirmed that CRP levels partially mediated the longitudinal association between obesity and depressive symptoms ($Z = 2.64$, $P = 0.008$). Separate analyses replicated each step of the mediation analyses in regression models which were not weighted for non-response (Sobel $Z = 2.65$, $P = 0.008$). In both models CRP concentrations accounted for ~20% of the obesity-related longitudinal change in depressive symptoms.

Discussion

The present study showed that obesity was closely associated with raised levels of depressive symptoms over 4 years of follow-up in analyses that adjusted for initial levels of depression. At follow-up obese participants experienced 32% more depressive symptoms than nonobese participants, suggesting that obesity may have a clinically meaningful emotional impact. Similarly, inflammation levels, as gauged by the acute phase protein CRP, were markedly elevated in obese participants (66% higher than nonobese levels). Consistent with prior studies (7,8), the presence of chronic low grade inflammation, as indexed by raised CRP levels strongly predicted an increase in depressive symptoms at follow-up. Crucially, the mediation analysis supported the hypothesis that obesity, inflammation, and feelings of depression are interlinked. As anticipated, CRP concentrations partially accounted for the longitudinal association between obesity and depressive symptoms, explaining ~20% of variance in this relation. This finding is consistent with prior research that has shown CRP and interleukin-6 concentrations to explain part of the link between depression and the metabolic syndrome, a condition directly linked to abdominal obesity (15).

The current study was limited in several respects. First, it is not possible to infer that obesity preceded the presence of inflammation as both obesity and CRP were assessed at the same time-point. However, an established literature has documented numerous pathways through which adipose tissue gives rise to systemic inflammation (3-5). The current study is further limited in that it restricts the measurement of inflammation to a single biomarker, CRP. The media-

ting role of CRP could have been indicative of the causal effect of its primary inducer interleukin-6 which can stimulate afferent nerve fibers (e.g. the vagus nerve) and access the brain contributing to fatigue and the mood and cognitive symptoms of depression (6). Finally, depressive symptoms were not assessed using a structured clinical interview. These limitations noted, the current study is significant in that it extends prior research (15) by providing the first evidence from a national longitudinal study to suggest that inflammation may play a causal role in the development of depressive symptoms amongst obese individuals.

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