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Anxiety, C-reactive protein, and obesity in NHANES 1999–2004

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ABSTRACT

The inflammatory marker C-reactive protein has been linked to anxiety across a number of studies. This paper uses data for 1,439 participants of the National Health and Nutrition Examination Survey (NHANES) 1999–2004 to examine the association between anxiety and C-reactive protein (CRP), and the potential for moderation by body mass index. No association was found between anxiety or depression and CRP in unadjusted or multivariable-adjusted logistic regression analyses, nor was there evidence of moderation by continuous BMI, BMI class, or obesity. Future studies on the relationship between anxiety and CRP should utilize larger general population samples or populations with a high prevalence of anxiety. There is also a need for prospective studies in this area to better discern the temporal relationships between anxiety and inflammation.

1. Introduction

Inflammation has been suggested to play a role in the pathophysiology of anxiety. In particular, the inflammatory marker C-reactive protein (CRP) has been linked to anxiety across a number of studies [1, 2, 3, 4, 5, 6, 7, 8, 9]. In addition, both anxiety and CRP have been separately linked to obesity [10, 11]. A 2010 meta-analysis by Gariepy et al. demonstrated an overall increased odds of anxiety among adult men and women with obesity across 16 studies (pooled odds ratio 1.4, 95% confidence interval 1.2–1.6), and a 2013 meta-analysis by Choi et al. demonstrated an overall positive correlation between CRP protein and body mass index (BMI) across 51 studies (pooled Pearson correlation 0.36, 95% confidence interval 0.30–0.42) [10, 11]. These studies raise the question as to what role obesity plays in the relationship between anxiety and CRP. Pierce et al. (2017) investigated this relationship in a cohort of 100 adult men and women with obesity and demonstrated a positive correlation between anxiety and CRP, which remained robust after adjusting for BMI [9]. This association between anxiety and elevated CRP independent of BMI suggests that there may be a direct effect of inflammation in the pathogenesis of anxiety, which has been noted across a small number of other studies as well [4, 8, 9].

For this reason, this current study seeks to investigate the role of BMI in the association between anxiety and CRP in a nationally representative general US population cohort. The primary aim of this study was to examine the association between anxiety and CRP and determine whether this association is moderated by BMI.

Previous studies have also noted an association between elevated CRP and depression [12, 13, 14, 15, 16, 17]. In addition, studies by Tayefi et al. and Duivis et al. suggest that this relationship may also be influenced by BMI [3, 4]. For this reason, we secondarily sought to examine the association between depression and CRP and determine whether this association is moderated by BMI.

2. Methods

2.1. Participant sample

This cross-sectional analysis uses existing data from the National Health and Nutrition Examination Survey (NHANES) public use data files for 1999–2004. NHANES 1999–2004 was selected for analysis because

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anxiety was only captured in cycles including and subsequent to NHANES 1999–2000. Additionally, public use files for mental health data are only available through NHANES 2003–2004.

NHANES is a rigorous, large-scale, long-running, general population research initiative by the Centers for Disease Control and Prevention (CDC) to collect data about the US general population for vital and health statistics via anthropometric measurement, blood samples, interview, and self-report questionnaire. While NHANES has been in operation for more than 60 years, beginning with the 1959–1962 National Health Examination Survey (NHES I), mental health was first captured as a component of NHANES beginning with NHANES III (1988–1999) and continuing on through current iterations. The NHANES III mental health survey evaluated symptoms of depression and mania only, using the 1981 Diagnostic Interview Schedule (DIS). Following the end of NHANES III in 1999, NHANES began running continuously in two-year cycles [18]. Beginning in 1999 and continuing through the current cycle, mental health began to be captured via the Composite International Diagnostic Interview (CIDI) instead, with the reasoning that the CIDI is more suitable than the DIS in large epidemiologic studies like NHANES because it can be administered by lay personnel. The mental health survey for NHANES 1999 onward captures depression, generalized anxiety disorder, and panic disorder only.

2.2. Anxiety

Our primary exposure of interest was anxiety. Anxiety data were collected as a component of NHANES via the CIDI, a questionnaire developed based on ICD-10 and DSM-IV criteria to capture 12-month prevalence of generalized anxiety disorder (GAD) and panic disorder. For the purposes of this study, and in accordance with previous work conducted by Hickman et al. [19], the primary exposure of anxiety was defined as the presence of GAD and/or panic disorder (combined as 'anxiety disorder') as captured by the CIDI.

The secondary exposure of interest was major depression. Depression data were collected as a component of NHANES via the CIDI, which captured 12-month prevalence of major depression.

2.3. C-reactive protein

The outcome measure CRP was collected via blood draw as a component of NHANES and was reported in mg/dL. CRP was modeled as a continuous log-transformed variable, with values below the lower detection limit imputed by NHANES as the lower detection limit divided by $\sqrt{2}$. As a sensitivity analysis, CRP was dichotomized above or below the detection limit of 0.22 mg/dL, in keeping with the methods of Ford et al. [12] CRP concentrations at or above 0.22 mg/dL were present in 698 participants (48.5%).

2.4. Statistical analysis

Regression analyses were modeled with anxiety as the independent (predictor) variable and CRP as the dependent (response) variable. CRP was modeled first as a continuous variable and next as a dichotomous variable with a cutpoint of 0.22 mg/dL, using linear and logistic regression models respectively. Statistical analyses were conducted first with unadjusted models, followed by multivariable-adjusted models that adjusted for the effects of age, race, sex, smoking status, education, physical activity level, stroke, myocardial infarction, diabetes, hyperlipidemia, and hypertension. Moderation by obesity (defined as BMI $\geq$30 kg/m^2) was assessed through the inclusion of an anxiety*obesity interaction term, followed by stratified analyses to follow-up on any significant or marginally significant interaction. We also modeled continuous BMI and weight classes (underweight <18.5, normal weight 18.5–24.9, overweight 25.0–29.9, class I obesity 30.0–34.9, class II obesity 35.0–39.9, class III obesity 40.0–49.9, class IV obesity 50.0–59.9, class V obesity >60.0) and to assess for potential non-linear influences of obesity on the anxiety-CRP relationship. All statistical analyses were conducted using SAS 9.4.

3. Results

3.1. Descriptive analysis

A total of 1,439 NHANES participants ages 20–39 with non-missing CRP, anxiety, and depression data were available for this analysis. Of these, there were a total of 59 participants with anxiety (4.1%) as captured by the CIDI. Participants with anxiety were more likely than those without anxiety to be tobacco users and have a history of stroke (Table 1).

Secondary analysis revealed 105 participants with depression (7.3%). Participants with depression were more likely than those without depression to be white, be tobacco users, and have a history of hypertension (Table 1).

3.2. Anxiety and C-reactive protein

Linear regression failed to reveal any association between anxiety and CRP in unadjusted (β = -0.11, se = 0.18, p = 0.56) or multivariable-adjusted analysis (β = -0.22, se = 0.17, p = 0.19), nor was there evidence of moderation by obesity (p = 0.48), categorical BMI (p = 0.97), or continuous BMI (p = 0.96) (Table 2). In sensitivity analysis, multivariable-adjusted logistic regression failed to reveal any association between anxiety and elevated CRP (>0.22 mg/dL) (p = 0.30).

3.3. Depression and C-reactive protein

In secondary analysis, linear regression failed to reveal any association between depression and CRP in unadjusted (β = 0.20, se = 0.14, p = 0.16) or multivariable-adjusted analysis (β = 0.12, se = 0.13, p = 0.38), nor was there evidence of moderation by obesity (p = 0.26), categorical BMI (p = 0.59), or continuous BMI (p = 0.99) (Table 2). In sensitivity analysis, multivariable-adjusted logistic regression failed to reveal any association between depression and elevated CRP (>0.22 mg/dL) (p = 0.67).

3.4. Post-hoc power calculation

Our analyses were adequately powered to detect small to medium main effects. Under the assumptions of an independent samples t-test, at an alpha of 0.05, *post hoc* power calculations suggest 80% power to detect an effect size of 0.37 SD for CRP in anxiety and an effect size of 0.28 SD for CRP in depression.

4. Discussion

This study examined the association between anxiety and CRP and its relation to obesity in 1,439 members of the NHANES 1999–2004, a large-scale general population US cohort. This study revealed no association between anxiety and CRP, which lies in contrast to the existing body of literature [4, 5, 6, 7, 8, 9, 16]. This may be because previous studies were conducted among larger cohorts [5, 6] and special populations [7, 8, 9], which may have greater statistical power and larger effect sizes, respectively.

This study also failed to detect an association between depression and CRP. Our sensitivity analysis findings contrast those reported Ford et al., who found major depression to be associated with higher CRP [12]. This difference may due to the use of different NHANES cohorts. Ford et al. selected from NHANES III which ran from 1988 to 1994, whereas the current study selected from a combined cohort of NHANES 1999–2000, NHANES 2001–2002, and NHANES 2003–2004, impacting total eligible sample size – NHANES III included 8,435 participants with complete data, whereas the 1999–2004 combined cohort included 1,439

Table 1
Descriptive analysis by anxiety and depression.

Categorical Variables	Total (n = 1439)	Anxiety (n = 59)	No Anxiety (n = 1380)	p-value	Depression (n = 105)	No Depression (n = 1334)	p-value
		N (%)	*N* (%)		*N* (%)	*N* (%)	
Sex				0.66			0.27
Male	650 (45.2%)	25 (42.4%)	625 (45.3%)		42 (40.0%)	608 (45.6%)	
Female	789 (54.8%)	34 (57.6%)	755 (54.7%)		63 (60.0%)	726 (54.4%)	
Race				0.069			**0.013**
Hispanic	426 (29.6%)	14 (23.7%)	412 (29.9%)		19 (18.1%)	407 (30.5%)	
White	667 (46.3%)	31 (52.5%)	636 (46.1%)		63 (60.0%)	604 (45.3%)	
Black	283 (19.7%)	8 (13.6%)	275 (19.9%)		17 (16.2%)	266 (19.9%)	
Other	63 (4.4%)	6 (10.2%)	57 (4.13%)		6 (5.7%)	57 (4.3%)	
Education				0.17			0.81
Some High School	338 (23.5%)	19 (32.2%)	319 (23.2%)		27 (25.7%)	311 (23.4%)	
High School Diploma	797 (55.5%)	32 (52.2%)	765 (55.6%)		58 (55.2%)	739 (55.5%)	
College Graduate	301 (21.0%)	8 (13.5%)	293 (21.3%)		20 (19.1%)	281 (21.1%)	
Physical Activity				0.85			0.080
Sedentary	285 (19.8%)	12 (20.3%)	273 (19.8%)		30 (28.6%)	255 (19.1%)	
Light Activity	728 (50.6%)	27 (45.8%)	701 (50.8%)		52 (49.5%)	676 (50.7%)	
Moderate Activity	285 (19.8%)	14 (23.7%)	271 (19.6%)		16 (15.2%)	269 (20.2%)	
Heavy Activity	141 (9.8%)	6 (10.2%)	135 (9.8%)		7 (6.7%)	134 (10.0%)	
Tobacco User	404 (28.1%)	25 (42.4%)	379 (27.5%)	**0.013**	42 (40.0%)	362 (27.1%)	**0.0047**
Diabetes	27 (1.9%)	3 (5.1%)	24 (1.7%)	0.064	1 (1.0%)	26 (2.0%)	0.47
Hypercholesterolemia	135 (9.4%)	6 (10.2%)	129 (9.3%)	0.83	11 (10.5%)	124 (9.3%)	0.69
Hypertension	186 (12.9%)	12 (20.3%)	174 (12.6%)	0.083	21 (20.0%)	165 (12.4%)	**0.025**
Myocardial Infarction	3 (0.21%)	0 (0%)	3 (0.22%)	0.72	0 (0.0%)	3 (0.2%)	0.63
Stroke	3 (0.21%)	1 (1.7%)	2 (0.14%)	**0.011**	1 (1.0%)	2 (0.2%)	0.083
Obesity	465 (32.3%)	17 (28.8%)	448 (32.5%)	0.56	37 (35.2%)	428 (32.1%)	0.51
Continuous Variables		Mean (sd)	Mean (sd)		Mean (sd)	Mean (sd)	
Age (years)	29.13 (5.63)	30.51 (6.02)	29.07 (5.61)	0.061	30.04 (5.98)	29.06 (5.60)	0.093
BMI (kg/m^2)	28.17 (6.83)	27.38 (7.87)	28.20 (6.78)	0.071	28.49 (8.24)	28.14 (6.71)	0.62
CRP (mg/L)	0.45 (0.82)	0.42 (0.57)	0.45 (0.83)	0.61	0.64 (1.21)	0.43 (0.78)	0.25

Bolded values are statistically significant at $p<0.05$.

participants with complete data – which in turn may have led to inconsistencies in the ability to detect an association, as it has been noted that the effect size tends to be small [20]. While we appeared grossly powered to detect small to medium main effects, power may be effectively over-estimated with the high lower detection limit for the CRP assay used.

A strength of this study is its use of NHANES, a nationwide general population cohort. This study, however, is limited in its ability to capture CRP concentrations more granularly in that approximately half of the CRP measures were below the detectable level, potentially influencing our ability to detect an effect and leading to an overestimation of statistical power. Additionally, the relatively low prevalence of anxiety as measured in the cohort impacted the sample size, and the cross-sectional nature of our study limits its ability to assess temporality.

Despite its nonsignificant findings, this study is a valuable contribution to the body of literature. Future general population studies will require larger samples or should include more individuals with clinically significant anxiety to be sufficiently powered to detect small effects to determine the relation between anxiety and CRP. In addition, future studies may benefit from the use of high-sensitivity CRP, which is better suited to detect milder, sub-clinical inflammation, and is therefore a more sensitive measure than CRP. There is also a need for prospective studies in this area to better discern the temporal relationships between anxiety and inflammation.

Declarations

Author contribution statement

Jane E. Persons, Jess G. Fiedorowicz: Conceived and designed the experiments; Analyzed and interpreted the data; Wrote the paper.

Gary L. Pierce: Conceived and designed the experiments; Wrote the paper.

Table 2
Linear regression of anxiety and depression on C-reactive protein.

	b	SE	t	p-value
Anxiety				
unadjusted	-0.11	0.18	-0.58	0.56
multivariable-adjusted[1]	-0.22	0.17	-1.32	0.19
multivariable-adjusted + obesity[2]	-0.22	0.19	-1.17	0.24
multivariable-adjusted + categorical BMI[3]	-0.15	0.27	-0.54	0.59
multivariable-adjusted + continuous BMI[4]	-0.069	0.55	-0.12	0.90
Depression				
unadjusted	0.20	0.14	1.42	0.16
multivariable-adjusted[1]	0.11	0.13	0.88	0.38
multivariable-adjusted + obesity[2]	-0.0041	0.15	-0.03	0.98
multivariable-adjusted + categorical BMI[3]	-0.0093	0.0055	1.29	0.20
multivariable-adjusted + continuous BMI[4]	0.10	0.42	0.25	0.80

[1] adjusted for age, race, sex, smoking status, education, physical activity level, stroke, myocardial infarction, diabetes, hyperlipidemia, and hypertension.

[2] includes obesity (BMI 30+) and an obesity*anxiety (or depression) interaction term in addition to age, race, sex, smoking status, education, physical activity level, stroke, myocardial infarction, diabetes, hyperlipidemia, and hypertension.

[3] includes categorical BMI (underweight <18.5, normal weight 18.5–24.9, overweight 25.0–29.9, class I obesity 30.0–34.9, class II obesity 35.0–39.9, class III obesity 40.0–49.9, class IV obesity 50.0–59.9, class V obesity >60.0) and categorical BMI*anxiety (or depression) interaction term in addition to age, race, sex, smoking status, education, physical activity level, stroke, myocardial infarction, diabetes, hyperlipidemia, and hypertension.

[4] includes continuous BMI and continuous BMI*anxiety (or depression) interaction term in addition to age, race, sex, smoking status, education, physical activity level, stroke, myocardial infarction, diabetes, hyperlipidemia, and hypertension.

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Competing interest statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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