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Can familial factors account for the association of body mass index with poor mental health in men or women?☆

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Abstract

Objective—This study examined if associations between body mass index (BMI) and mental and physical health were independent of genetic and familial factors.

Method—Data from 2831 twins (66% female) were used in an epidemiological co-twin control design with measures of BMI and mental and physical health outcomes. Generalized estimating equation regressions assessed relationships between BMI and health outcomes controlling for interdependency among twins and demographics. Within-pair regression analyses examined the association of BMI with health outcomes controlling for genetic and familial influences.

Results—Adjusted analyses with individual twins found associations in women between BMI and perceived stress ($P=.01$) and depression ($P=.002$), and the link between BMI and depression ($P=.03$) was significant in men. All physical health outcomes were significantly related to BMI. Once genetic and familial factors were taken into account, mental health outcomes were no longer significantly associated with BMI. BMI in women remained related to ratings of physical health ($P=.01$) and body pain ($P=.004$), independent of genetic and familial influences.

Conclusion—These findings suggest that genetic and familial factors may account for the relationship between increased weight and poor mental health.

Keywords

Obesity; Mental health; Genetics; Familial; Body mass index

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1. Introduction

Obesity is the biggest public health problem in the United States today. More than two thirds of Americans are overweight or obese according to recent calculations [1]. The obesity epidemic is also a global issue as an estimated 500 million people worldwide are overweight [2]. In the United States, the economic burden of obesity is substantial at \$215 billion annually from both direct and indirect costs [2]. Obesity is associated with numerous negative health outcomes including diabetes, cardiovascular disease and functional impairment [3]. There is also evidence that overweight and obesity are related to mental health factors [4] like depression [5,6], anxiety [7,8], stress [9,10] as well as elements of physical health like fatigue [11,12] and pain [13,14]. For individuals with overweight or obesity, the presence of these mental and physical complaints further compounds negative health outcomes and decreases quality of life.

It is still uncertain if an individual's increase in body mass index (BMI) leads to decreased mental health or the other way around [15], and bidirectional pathways also have been proposed [16]. Although there is a substantial literature supporting associations between obesity and poor mental and physical health, the varied methodology has made it difficult to examine underlying mechanisms of these relationships [4]. Overweight and obesity have been conceptualized in clinical terms by grouping individuals into weight classes (i.e., underweight, normal, overweight, obese) according to BMI ranges [8,11,17–20], and BMI also has been used as a continuous variable to examine its relationship with various psychological and physical constructs [5,8,20,21]. Some observational studies have reported increased occurrence of mental health symptoms in overweight or obese clinical samples [22,23], and others have examined relationships in population-based studies [5,8,10,18,19,24]. Further, prospective studies have tried to uncover the directionality of the BMI–health relationship, with inconclusive results [12,15,24,25]. Studies examining individual differences suggest that the relationship between obesity and mental health could be sex-dependent, with more robust associations in women for depression and mental health functioning [19,21,26] and in men for stress [27]. Further, the association between obesity and mental health outcomes like depression may be specific to individuals in the United States as studies of other populations worldwide have not supported this relationship [28]. Overall, the literature supports an association between obesity and mental health symptoms, but the directionality and mechanisms of this relationship are still unknown.

Previous research suggests that genetics might contribute to the shared risk for both obesity and depression [29]. Yet few studies have considered that the relationship between increasing weight and mental health could be influenced by genetic vulnerability (e.g., shared genes contributing to mechanisms of both obesity and mental health) and familial experiences (e.g., childhood family environment that contains risk factors for high BMI and poor mental health). Twin studies offer the opportunity to discern whether genetic and familial influences might underlie associations of BMI and mental health. Thus, the goals of this study were to (a) examine the associations of BMI with indices of mental health in male and female twins from the community-based University of Washington Twin Registry, (b) examine the influence of genetic and familial factors on any BMI-mental health associations and (c) examine the relationship between BMI and physical health factors to contextualize analyses of mental health outcomes.

To do this, we used a co-twin control study design which is widely used in the epidemiology literature [30,31]. In contrast to classical twins studies that are used to estimate the proportion of genetic contribution to a trait or condition, co-twin control studies are used increasingly often to investigate exposure–disease relationships [32], including hypotheses related to nutrition and obesity [33,34]. In a co-twin control design, exposure differences

within twin pairs are examined in relationship to the differences in outcomes within the pairs. Typically, initial analyses examine all twins as a group and use statistical methods to correct for similarity within pairs. These analyses mimic studies of unrelated individuals. Within-pair analyses compare both members of a twin pair to each other. In this study, we ask whether twins who share the same family environment and genes but differ in BMI also consistently differ in measures of mental and physical health previously associated with BMI in samples of unrelated individuals. Such analyses examine whether genetic or familial factors may contribute to both increasing weight and worse mental or physical health.

2. Methods

2.1. Participants and procedures

The University of Washington Twin Registry is a community-based sample of twins derived from the driver's license applications of Washington State. Full details of the construction and characteristics of the University of Washington Twin Registry are described elsewhere [35]. In brief, Washington State driver's license numbers are derived from a person's name and date of birth; thus, the Department of Licensing asks every new applicant if she/he is a twin to avoid issuing duplicate license and identification numbers to twins. Because state agencies in Washington are permitted by law to share data, the Department of Licensing provides a list of all new drivers' license applicants who are twins to the University of Washington. The University of Washington invites each member of the pair to join the Registry and to complete an initial enrollment survey.

A follow-up Health Survey was mailed to all members of the Registry in 2006 and again to new members and nonrespondents in 2008, achieving a 58% response rate. Twins who responded to the Health Survey were significantly more likely to be female (66% versus 52%, $P<.001$), older (35 versus 30 years, $P<.001$) and monozygotic (MZ; 52% versus 48%, $P=.03$) than the nonrespondents. The Health Survey obtained self-reported information on demographics, height and weight to calculate BMI, as well as mental and physical health indicators. All members of the Registry who completed the Health Survey in 2006 and 2008 were initially eligible for the present study ($N=3035$). Of these, 2831 met specific criteria for inclusion: (a) no history of gastric bypass or other weight-reduction surgery, (b) ages 18–70 years at the time of completion of the Health Survey, (c) known zygosity assignable from a similarity questionnaire and (d) co-twins raised together until at least 15 years of age. All Registry procedures and data collection involved in this study were approved by the University of Washington Institutional Review Board. Informed consent was obtained from all twins.

2.2. Measures

2.2.1. Demographics and zygosity—Demographic information consisted of age, sex, race/ethnicity (categorized as white/nonwhite), marital status, education (categorized as less than high school, high school graduate or educational attainment beyond high school) and income. To assess zygosity, we used questions about childhood similarity that reliably classify zygosity with an accuracy of 95%–98% compared with zygosity determined by biological indicators [36].

2.2.2. BMI—A continuous BMI score was derived from self-reported height and weight (kg/m^2). As BMI was our primary predictor of interest, the accuracy of these self-reported values was essential. To assess the validity of the BMI indicator, a random sample of 77 participants from the Registry who were presenting to the clinic for an in-person evaluation underwent a clinical assessment where measured height and weight were obtained (a subset of the participants in the current study was included in this sample). The self-reported

(range=149– 213 cm, mean=171.9 cm) and measured (range=149–210 cm, mean=171.1 cm) height, as well as the self-reported (range=45– 134 kg, mean=77.6 kg) and measured (range=45–137 kg, mean= 77.5 kg) weight, achieved excellent agreement (intraclass correlation coefficient=0.99 for both height and weight).

2.2.3. Mental health—To assess general mental health functioning, we used the mental health component scale of the Short Form-8 (SF-8 MCS) [37], a widely used measure of health status. Values for the SF-8 MCS are standardized with a mean of 50 for the general population, with higher values reflecting better mental health. The 10-item Cohen Perceived Stress Scale (PSS) [38], which assesses subjective reactions to demands from stressful experiences, was used to measure stress. This instrument yields scores ranging from 0 to 38 and has demonstrated good reliability elsewhere [39], as well as in the present sample (Cronbach's $\alpha=0.89$). To evaluate anxiety symptoms, we used the six-item anxiety subscale of the Brief Symptom Inventory (BSI) [40], commonly administered in medical and psychiatric populations. Scores range from 0 to 24, and the anxiety subscale is valid and has demonstrated acceptable reliability estimates in previous investigations [41] and in the present sample (Cronbach's $\alpha=0.85$). Symptoms of depression were assessed with the Patient Health Questionnaire-2 (PHQ-2) [42], a two-item measure of key depressive symptoms, with scores ranging from 0 to 6. The PHQ-2 has demonstrated good validity and reliability estimates in previous investigations [43] and in the present study (Cronbach's $\alpha=0.80$).

2.2.4. Physical health—To assess overall physical health functioning, we used the physical health component scale of the SF-8 (SF-8 PCS) [37], with higher values reflecting better physical health. Fatigue and pain were each measured by one item asking respondents to indicate the degree to which they have experienced fatigue and the degree to which they have experienced pain over the past 4 weeks, on a 0 (“no fatigue” or “no pain”) to 10 (“severe fatigue” or “severe pain”) Likert scale.

2.3. Statistical analyses

Descriptive statistics were calculated as means and standard deviations for continuous variables and percentages for categorical variables. All analyses were stratified by sex. To investigate the overall associations of BMI and the seven mental and physical health outcomes, we fit generalized estimating equations linear regression models to account for the lack of independence of members of twin pairs. Significance was determined by Wald tests. All analyses were conducted after controlling for a priori specified covariates, which included age, race/ethnicity, marital status and education.

The initial cross-sectional analysis of individual twins, described above, does not directly compare BMI within twin pairs. Because, if raised together, MZ twins share 100% of their genetic and familial factors and dizygotic twins share about 50% of their genes and 100% of their family environment, within-pair analyses control for possible genetic and familial confounds because twins within each pair are compared to one another [32]. Therefore, we next estimated the within-pair effects that are adjusted for genetic and familial influences. These analyses also control for age and sex. We calculated the within-pair differences in BMI, the mental and physical health indicators, and all covariates. These within-pair difference scores were created by designating the co-twin with the higher BMI in the twin pair as Twin 1 and subtracting the scores on all variables for Twin 2 from Twin 1 to maintain a consistent directionality within pairs and ease interpretation of the impact of higher BMIs. The within-pair difference values were then used in the subsequent regression models. If within-pair associations are attenuated and rendered nonsignificant compared to the overall effect obtained in our initial regression analyses, we can conclude that genetic

and familial factors contribute to these associations. Alternately, a within-pair association that remains robust compared to the overall effect provides evidence that the association between BMI and health is independent of genetic and familial factors. Significance level was set at $P < .05$. All analyses were conducted with SPSS, Version 20.0 (IBM Inc.).

3. Results

3.1. Descriptive characteristics

The final analytic data set included 2831 individual twins, 1870 (66%) of which were women. Table 1 describes the characteristics of the sample as a whole and stratified by sex. The mean age of the twins was 35 years; 54% were MZ, 91% were white, 50% were married or living with a partner, 41% obtained at least a bachelor's degree, and 29% had a household income of \$80,000 or higher. The average BMI was 25.4 kg/m², and about 42% of twins were overweight or obese. Men and women did not significantly differ in zygosity, race/ethnicity, marital status, education, income or BMI.

3.2. Adjusted associations between BMI and health indicators

3.2.1. Mental health—Results from adjusted analyses that controlled for the effects of age, race/ethnicity, marital status and education are presented in Table 2. In women, higher BMI was significantly associated with higher perceived stress ($P = .01$) and depression scores ($P = .002$), which appeared to be independent of age, race, marital status and education. The positive association between BMI and depression was statistically significant for men ($P = .03$).

3.2.2. Physical health—Statistically significant overall associations were found between BMI and all physical health indicators for women after controlling for the effects of age, race/ethnicity, marital status and education (Table 2). With the exception of the relationship between BMI and fatigue which approached significance, the same pattern of results was evident for men. Thus, increased BMI was consistently associated with lower self-reported physical health and, usually, with increased experiences of fatigue and pain for both men and women.

3.3. Within-pair associations between BMI and health indicators

For all within-pair analyses (Table 3), we included only twin pairs where both members of the pair completed the Health Survey. Response rates for the mental and physical health indicators differed. Thus, among the initial sample of 2831 individual twins, between 1046 and 1188 individual female twins and between 434 and 512 individual male twins were included.

3.3.1. Mental health—None of the associations between BMI and mental health indicators in women remained significant in within-pair analyses, although the size of the effect for perceived stress was similar to the effect in overall analyses. As expected, there were no significant within-pair associations between BMI and mental health indicators in men.

3.3.2. Physical health—Unlike the nonsignificant within-pair associations for BMI with mental health indicators, strong associations were still found between BMI and various physical health indicators among women. Specifically, increased within-pair differences in BMI were found to be significantly associated with decreased within-pair differences in ratings of physical health functioning ($P = .01$) and increased pain ($P = .004$). Among men, none of the within-pair associations of BMI with physical health indicators were significant.

4. Discussion

By using an analytic method that treats twins as unrelated individuals, we replicated prior findings associating BMI with adverse self-reported health outcomes [20,21]. The findings were partially consistent with previous studies that demonstrate sex-dependent associations between weight and mental health indices [19,21,27]. In addition, higher BMI was strongly related to worse physical health functioning and increased physical symptoms in both men and women.

The twin design provided a unique opportunity to expand the above findings and examine the impact of genetic and familial factors on the association of BMI with mental and physical health by using within-pair comparisons that control for shared genetic and familial factors. The within-pair analyses suggest that the relationship between BMI and mental health in women and depression in men may reflect underlying genetic or family environment influences rather than obesity itself. In other words, shared genetic or familial factors may partially account for the relationship between obesity and poor mental health. Studies that examine obesity–mental health relationships without controlling for these factors should be cautious in interpreting the relationship as direct rather than due to potentially confounding genetic or familial factors. These findings from a twin sample suggest that the impact of increasing weight, especially on women's mental health, may be more strongly determined by family experiences and genetic predispositions than by BMI alone.

In contrast, associations between BMI and physical health in women were present even after accounting for genetic and familial factors. Thus, worse self-reported health and increased pain at higher BMI may be related to excess body adiposity itself (e.g., high blood pressure, mechanical stress on joints), rather than genetic or familial factors. The pattern was slightly different for men in that the relationship between BMI and physical health factors did not persist in within-pair comparisons, a finding that should be replicated in larger samples.

Genetic contributions to obesity are well recognized [44,45], as is the genetic influence on depression [46]. Familial and social factors also have recognized influences on BMI [47], particularly for women [48]. Familial factors also have been identified in binge-eating disorder [49]. Shared genetic and familial risk factors for both obesity and depression could underlie the current findings, and other studies have investigated this hypothesis. Although prior research had not found evidence of a shared genetic liability for depression and body composition [50], more recent research corroborates the influence of genetic and environmental factors on the BMI–depression relationship in women [29]; the influence of shared genetic factors on BMI and depression in men has not been examined. At least one specific genetic variant has been identified that could represent a risk factor for both obesity and depression. The fat mass and obesity-associated gene (*FTO*) has been supported as a risk factor for high BMI in depressed subjects and not in nondepressed controls [51], but recent evidence suggests *FTO* may have independent effects on BMI and depression [52].

This study found a significant relationship between stress and BMI in women only. Although the association was slightly stronger in men than women, the association was not statistically significant in men, likely due to the smaller sample size for men. Thus, the lack of statistical significance could be due to the smaller male group rather than a substantive difference between men and women. A female-specific relationship between stress and weight has been found in smaller studies [53,54] and supports the theory that women, especially those who do restrain eating or diet, are more likely to change eating behaviors under stress and depression than men [55]. However, a recent meta-analysis of longitudinal studies found that stress was a risk factor for weight gain only in men [27]. More research is

needed to determine the possible sex-specific associations and causal mechanisms of stress and BMI.

Our findings are consistent with studies reporting higher current depression measured with the PHQ in higher BMI groups [18,56] and other studies demonstrating increased likelihood of obesity in those with current depression [7]. We did not find support for a relationship between BMI and anxiety, and the evidence for this association in the literature is mixed, especially when examining anxiety symptoms within the past year or less [24]. The association is stronger when measuring anxiety as any lifetime diagnosis of an anxiety disorder [7,18,24], rather than current or recent anxiety symptoms. Together, our findings contribute further evidence to the existing literature on the BMI and mental health relationship.

The findings also have implications for the clinical care of overweight and obese patients. In some studies, people with depression have less success in weight-loss treatment, although methodological differences in measuring depression or in clinical samples may have contributed to inconsistency in these findings across studies [57]. Investigation of the efficacy of treatment approaches that intervene more strongly on environmental factors that influence both BMI and depression, such as sedentary behavior and poor social support, may be warranted, at least in those with comorbid depression and obesity. Through reciprocal interactions (reduced depression may aid in weight loss, and weight loss may reduce the physical symptoms of depression), addressing mediating factors may have a strong positive impact on the mental and physical health of patients with comorbid obesity and depression. Another implication of these data is that when depression and obesity coexist, alternative social or familial factors that may contribute to depression besides obesity, such as early-childhood trauma, stressful life events, lack of social support, substance abuse and family history of depression, should be explored and addressed.

The study has several limitations. First, the study sample was primarily derived from residents of the Pacific Northwest and was made up of mainly young, well-educated, Caucasian individuals. Therefore, the limited sample diversity is not representative of the United States population at large. Second, responders to the Health Survey did differ in gender, age and zygosity from the Registry as a whole; thus, it is possible that an unidentified response bias could have influenced the findings. Third, our findings are based on cross-sectional data, and therefore, we cannot determine a potential causal pathway between obesity and facets of health. Finally, unlike classical twin methods, the co-twin control study design cannot delineate the relative importance of genetic and familial factors or identify any specific genetic or familial factors that may be contributing to the link between weight and health. Therefore, future research with larger samples can examine the proportion of shared genetic variance between BMI and mental health indicators.

In conclusion, we found a significant association between BMI and perceived stress in women and BMI and depression symptoms in both men and women. These associations were no longer significant after accounting for genetic and familial influences in within-pair analyses. In contrast, the significant links between BMI and physical health indicators in women remained significant in within-pair analyses. Our findings suggest that genes or factors in the family environment may account for the relationship between increased weight and poor mental health, especially in women. Continued research to investigate what underlying genetic or familial factors may be driving the relation between BMI and stress in women as well as BMI and depressive symptoms in both men and women may bear fruit in terms of improving the overall care for overweight and obese patients as well as the success of weight-loss treatment.

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Table 1
Characteristics of twins in the University of Washington Twin Registry Health Survey

Characteristics	All twins (<i>N</i> =2831)	Males (<i>n</i> =961)	Females (<i>n</i> =1870)
Age, mean years (S.D.)	35.0 (13.9)	35.05 (14.3)	35.0 (13.8)
Monozygotic, %	53.9	51.9	54.9
White, %	90.7	93.1	89.4
Married or living with a partner, %	49.9	45.3	52.0
Education, %			
Less than high school graduate	2.2	2.2	2.2
High school graduate	10.8	13.0	9.4
Some college, no degree	34.6	34.1	35.0
Technical/vocation	11.2	9.4	12.1
Bachelor's degree or higher	41.2	41.3	41.2
Annual household income, %			
<\$20,000	22.5	21.7	22.9
\$20,000–\$39,999	18.5	16.5	19.6
\$40,000–\$59,000	17.5	16.3	18.2
\$60,000–\$79,999	13.0	12.7	13.0
>\$80,000	28.5	32.8	26.3
BMI, mean kg/m ²	25.4 (5.5)	25.6 (4.8)	25.3 (5.8)
Weight category, %			
BMI<18.5 (underweight)	2.7	1.7	3.3
BMI=18.5–24.99 (normal weight)	54.9	49.6	57.7
BMI=25–29.99 (overweight)	25.8	34.7	21.1
BMI>30.0 (obese)	16.6	14.0	17.9

Note. *N* is the number of individuals in the study; *n* is the number of individuals by group.

Table 2
Adjusted associations between continuous BMI and mental and physical health indices

Indicator	Males				Females					
	N	M	B	95% CI	P	N	M	B	95% CI	P
Mental health										
SF-8 MCS	898	50.80	-0.04	(-0.18; 0.09)	.53	1721	48.41	-0.08	(-0.17; 0.01)	.07
PSS	898	12.07	0.09	(-0.01; 0.20)	.09	1707	14.23	0.08	(0.02; 0.14)	.01
BSI	901	2.09	-0.001	(-0.05; 0.04)	.97	1716	3.03	0.004	(-0.03; 0.04)	.79
PHQ-2	901	0.86	0.02	(0.00; 0.04)	.03	1725	1.00	0.02	(0.01; 0.03)	.002
Physical health										
SF-8 PCS	898	53.41	-0.27	(-0.40; -0.13)	<.001	1721	52.31	-0.30	(-0.38; -0.22)	<.001
Fatigue	878	2.77	0.04	(0.00; 0.08)	.05	1650	3.40	0.03	(0.01; 0.05)	.006
Pain	901	2.56	0.10	(0.06; 0.13)	<.001	1706	2.87	0.07	(0.05; 0.09)	<.001

Note. *N* is the number of individuals, *M* is the mean, *B* is the unstandardized slope from the generalized estimating equations linear regression model, and CI is the confidence interval; all analyses controlled for age, race/ethnicity, marital status and education.

Table 3
Within-pair associations of continuous BMI and health indices among same-sex twin pairs

Indicator	Males				Females			
	N	B	95% CI	P	N	B	95% CI	P
Mental health								
SF-8 MCS	256	0.06	(-0.32; 0.43)	.77	594	0.07	(-0.20; 0.34)	.61
PSS	250	0.12	(-0.20; 0.42)	.46	556	0.08	(-0.12; 0.27)	.45
BSI	251	0.03	(-0.10; 0.16)	.60	563	0.06	(-0.04; 0.15)	.27
PHQ-2	253	-0.03	(-0.09; 0.03)	.32	569	-0.004	(-0.04; 0.03)	.83
Physical health								
SF-8 PCS	256	0.20	(-0.16; 0.55)	.28	594	-0.28	(-0.50; -0.06)	.01
Fatigue	243	-0.07	(-0.19; 0.06)	.30	523	0.06	(-0.02; 0.13)	.13
Pain	249	0.03	(-0.08; 0.14)	.61	556	0.10	(0.03; 0.18)	.004

Note. N is the number of twin pairs; B is the unstandardized slope from the regression model.