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Original Contribution

Examining Overweight and Obesity as Risk Factors for Common Mental Disorders Using Fat Mass and Obesity-Associated (*FTO*) Genotype-Instrumented Analysis

The Whitehall II Study, 1985–2004

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The Mendelian randomization approach exploits genetic variants to improve causal inference when using observational data. The authors examined the relation between long-term obesity and common mental disorders (CMD) by utilizing the known relation between fat mass and obesity-associated (*FTO*) genotype and body mass index (BMI; weight (kg)/height $(m)^2$). Data collection in 2,981 men and 1,164 women (mean age at baseline = 44 years) from the Whitehall II Study (London, United Kingdom) included 4 repeated examinations of BMI and CMD over a 19-year follow-up period (1985–2004), plus an assessment of *FTO* polymorphism rs1421085. In men, there was an association of *FTO* genotype with all measures of adiposity (mean BMI, number of times obese, and, in nonobese persons, number of times overweight). *FTO* was also associated with CMD in men. This was independent of adiposity, thus potentially violating the exclusion restriction assumption. According to both conventional and *FTO*-instrumented regression analysis, measurement of obesity was associated with an increased occurrence of CMD. In the *FTO*-instrumented analysis only, higher BMI and overweight were also associated with CMD. In women, there was no link between *FTO* and adiposity. Mendelian randomization analyses supported the status of long-term obesity as a risk factor for CMD in men—a finding that should be interpreted cautiously because the function of the *FTO* gene is unknown.

anxiety; body mass index; depression; Mendelian randomization analysis; mental health; obesity; risk factors

Abbreviations: BMI, body mass index; CI, confidence interval; CMD, common mental disorders; *FTO*, fat mass and obesity-associated gene; GHQ, General Health Questionnaire.

It is well established that obesity is a risk factor for cardiovascular disease, certain cancers, and premature mortality (1), but it is unclear whether it also increases the risk of common mental health problems, such as depression and anxiety. While there is evidence to suggest that obesity predicts such disorders, this has not been observed in all studies, particularly those that have controlled for potentially confounding factors or excluded subjects with mental disorders at study induction (2–5). Other investigators have reported that obese persons have a reduced rather than an elevated risk of common mental disorders (CMD) (the so-called ''jolly fat'' hypothesis) (6). It is also possible that the direction of causality might actually be the reverse; that is, CMD cause weight gain (3, 7).

A potential technique for advancing research in this field is to utilize genetic data in taking the Mendelian randomization approach (8, 9). This is predicated upon the random assortment of alleles at the time of gamete formation, which leads to population distributions of genetic variants that are generally independent of the environmental exposures that commonly confound risk factor–disorder associations (10). These unconfounded differences in risk factor levels should therefore translate into genuine differences in disorder occurrence if the exposure is truly causally related.

Variants in the fat mass and obesity-associated gene (*FTO*) have been shown to be consistently related to body mass index (BMI; weight (kg)/height $(m)^2$) (11, 12) and have previously been used as an ''unconfounded'' proxy variable for testing the effects of obesity on various physical health outcomes—though not, to our knowledge, on CMD (13–17). The *FTO* genotype, being determined at conception, necessarily precedes the onset of health disorders, including those related to mental health. Thus, any association between *FTO* and CMD should be unaffected by reverse causation bias arising from the potential effects of mental disorder on obesity risk. By contrast, direct measurements of BMI are strongly affected by chronic diseases, plus social circumstances, smoking, and physical activity, all of which may also influence the risk of CMD (18–22).

Accordingly, we adopted the Mendelian randomization approach to examine whether variants in *FTO*, to the extent that they are related to higher long-term overweight and obesity, were associated with an increased risk of CMD in the Whitehall II study population.

MATERIALS AND METHODS

Study population and design

The target population of the Whitehall II Study was all London-based office staff aged 35–55 years working in 20 United Kingdom government departments at baseline in 1985–1988 (23). With a response rate of 73%, the baseline study consisted of 10,308 employees (6,895 men and 3,413 women). The present analysis comprised data from 4 medical examinations: the baseline examination, carried out in 1985–1988, and follow-up examinations conducted in 1991–1993, 1997–1999, and 2003–2004. All of these examinations included a standardized assessment of symptoms of depression and anxiety (subsequently referred to as CMD) and direct measurement of weight and height.

Clinical characteristics

Measurement of demographic characteristics, behavioral risk factors, and chronic health conditions at baseline has been described previously (3) and included marital status, socioeconomic position (as indexed by ''employment grade''), smoking, alcohol consumption, physical activity, diabetes, and coronary heart disease. To take into account the association between the *FTO* genotype and diabetes risk (11), we ascertained diabetes at follow-up examinations, in addition to baseline, based on information on fasting glucose concentration ($\geq$7.0 mmol/L), 2-hour postload glucose concentration ($\geq$11.1 mmol/L), use of antidiabetic medication, or reported physician-diagnosed diabetes (24). In nondiabetic participants, we defined prediabetes as a fasting glucose concentration between 5.6 mmol/L and 6.9 mmol/L or a 2-hour postload glucose concentration between 7.8 mmol/L and 11.0 mmol/L (24).

FTO genotyping

DNA was extracted from blood samples using magnetic bead technology. The *FTO* polymorphism rs1421085 was determined using SNPLex (Applied Biosciences, Inc., Warrington, United Kingdom) by Medical Solutions Plc (Nottingham, United Kingdom) (25). The genotype frequencies did not deviate from Hardy-Weinberg equilibrium ($P = 0.90$).

Body mass index

We measured height and weight at all examinations, from which BMI was calculated. Weight was measured in underwear to the nearest 0.1 kg on Soehnle electronic scales. Height was measured to the nearest 1 mm in bare feet, while the participant stood erect with the head in the Frankfort plane, using a stadiometer. The coefficient for the repeatability of the weight and height measurements over 1 month (assessed as between-subject variability/total (between- plus within-subject) variability), undertaken in 306 participants, was greater than 0.99 for both weight and height at the fourth screening.

Common mental disorders

We assessed the presence of CMD using the self-administered 30-item General Health Questionnaire (GHQ) (26), a screening instrument for depression and anxiety symptoms designed for community settings. Response categories are scored as either 1 or 0 to indicate whether or not a symptom is present. We defined persons with a total score of 5 or more as GHQ ''cases'' and those scoring 0–4 as ''noncases'' (27). GHQ scores have been validated against the Clinical Interview Schedule in this study population. The sensitivity (73%) and specificity (78%) of this measure of ''caseness'' have been found to be acceptable (27).

Statistical analysis

We performed statistical analyses with Stata, version 10 (Stata Corporation, College Station, Texas). The analytic sample included all participants with data on *FTO* genotype and BMI and GHQ caseness at all 4 examinations—a total of 4,145 men and women. Analyses were carried out separately for men and women. We divided participants into 3 groups based on their *FTO* genotype (TT, GT, or GG; i.e., 0, 1, or 2 adiposity-related alleles). To assess long-term adiposity, we constructed 3 different measures: mean BMI level, number of times the participant was found to be overweight (BMI $\geq$25) across the 4 examinations, and number of times the participant was found to be obese (BMI $\geq$30). We used the χ^2 test and analysis of variance to examine differences in baseline characteristics between the *FTO* groups. Linear regression analysis was used to examine the associations of *FTO* genotype with adiposity measures and the number of times a participant was a GHQ case at the 4 screenings.

We performed an instrumental-variables regression analysis using the ''ivreg2'' procedure in Stata to examine whether the *FTO* polymorphism was associated with CMD through its associations with BMI, overweight, and obesity. We used *F* statistics from the first-stage regression to evaluate the strength of the instrument, with values greater than 10 being taken as evidence against weak instruments (28, 29). We

Table 1. Characteristics of Sample Participants ($n = 4,145$) According to Gender, Whitehall II Study, 1985–2004

Characteristic	Men			Women		
	No. of Participants	%	Mean (SD)	No. of Participants	%	Mean (SD)
Baseline examination						
Age, years	2,981		43.8 (5.9)	1,164	44.3 (5.9)	
Marital status (married)	2,975	83.5		1,160	59.2	
Socioeconomic position						
High	1,231	41.3		189	16.2	
Intermediate	1,600	53.7		536	46.1	
Low	150	5.0		439	37.7	
Chronic disease	2,925	9.7		1,136	9.6	
Prevalent coronary heart disease	2,981	0.7		1,164	0.3	
Prevalent diabetes	2,964	0.6		1,160	0.3	
Use of psychotropic drugs	2,980	2.2		1,163	4.2	
High alcohol consumption	2,968	17.6		1,150	3.7	
Physical inactivity	2,956	21.7		1,145	39.5	
Current smoking	2,921	10.9		1,145	15.7	
Last (fourth) clinical examination						
Prediabetes	2,903	15.6		1,137	15.0	
Diabetes	2,903	7.4		1,137	7.9	
All 4 clinical examinations						
Body mass index[a]	2,981		25.4 (3.1)	1,164		25.7 (4.5)
No. of times overweight	2,981		1.7 (1.5)	1,164		1.3 (1.4)
No. of times obese	2,981		0.4 (0.9)	1,164		0.6 (1.2)
No. of times a GHQ case[b]	2,981		0.8 (1.1)	1,164		1.1 (1.2)

Abbreviations: GHQ, General Health Questionnaire; SD, standard deviation.

[a] Weight (kg)/height $(m)^2$.

[b] GHQ score was used as the measure of common mental disorders. Persons with a total score of 5 or more were defined as GHQ "cases," and those scoring 0–4 were defined as "noncases" (27).

compared results from the instrumental-variable estimates of the association between adiposity measures and CMD with results from standard linear regression using the Durbin form of the Durbin-Wu-Hausman statistic (30). To test the robustness of the observed associations, we specified CMD as a dichotomous outcome using various cutoffs that divided the number of times a person was a GHQ case into 2 groups (1–4 times vs. 0 times; 3–4 times vs. 0–2 times; and 4 times vs. 0–3 times). For these analyses, we used standard and instrumental-variables probit regression (the "ivprobit" procedure in Stata), both of which are designed to model dichotomous outcomes. The probit model is defined as $\Pr(y = 1|x) = \Phi(xb)$, where Φ is the standard cumulative normal probability distribution and xb is known as the probit index or probit coefficient.

Diabetes/prediabetes is an outcome of the increased adiposity, as indexed by *FTO*, and is also related to obesity and depression (11, 31, 32). It is possible then that diabetes/prediabetes at least partially explains the association between the adiposity measures and CMD. Therefore, in further sensitivity analyses, we repeated the instrumental-variables analysis with adjustment for diabetes and prediabetes at the last examination.

RESULTS

Table 1 shows the characteristics of the 4,145 study participants. Mean BMI across the 4 medical screenings was 25.4 for men and 25.7 for women. Of the men, 83.0% were never obese, 6.1% were obese on 1 occasion, 5.4% on 2 occasions, 2.8% on 3 occasions, and 2.7% on 4 occasions; corresponding percentages for overweight were 33.6%, 13.7%, 19.5%, 16.5%, and 16.7%. In women, the corresponding proportions were 74.0%, 7.5%, 6.4%, 5.7%, and 6.4% for obesity and 42.2%, 17.6%, 17.8%, 14.1%, and 8.3% for overweight.

Associations with *FTO* gene

As Table 2 shows, the *FTO* genotype was associated with BMI, overweight, and obesity in men but not in women.

Table 2. Associations of Fat Mass and Obesity-Associated (*FTO*) Genotype With Body Mass Index, Overweight, Obesity, and Common Mental Disorders From 4 Repeated Assessments in Men and Women, Whitehall II Study, 1985–2004

Predictor	No. of Participants	BMI[a]		Overweight[b]		Obesity[b]		Common Mental Disorders[c]	
		β	95% CI	β	95% CI	β	95% CI	β	95% CI
Men									
No. of *FTO* adiposity alleles									
0	1,046	0.00	Referent	0.00	Referent	0.00	Referent	0.00	Referent
1	1,442	0.283	0.039, 0.526	0.200	0.064, 0.335	0.018	−0.054, 0.090	0.020	−0.065, 0.105
2	493	0.935	0.608, 1.262	0.331	0.144, 0.519	0.192	0.094, 0.289	0.172	0.058, 0.286
Per-allele increase	2,981	0.433	0.275, 0.592	0.173	0.083, 0.262	0.081	0.034, 0.129	0.074	0.019, 0.129
P for trend		<0.0001		<0.0001		0.001		0.009	
Women									
No. of *FTO* adiposity alleles									
0	448	0.00	Referent	0.00	Referent	0.00	Referent	0.00	Referent
1	543	−0.183	−0.741, 0.376	0.015	−0.196, 0.225	−0.076	−0.441, 0.289	0.073	−0.074, 0.219
2	173	0.310	−0.474, 1.094	0.145	−0.155, 0.445	0.121	−0.391, 0.632	−0.011	−0.217, 0.194
Per-allele increase	1,164	0.077	−0.294, 0.449	0.058	−0.083, 0.120	0.012	−0.089, 0.114	0.012	−0.085, 0.110
P for trend		0.68		0.42		0.81		0.80	

Abbreviations: BMI, body mass index; CI, confidence interval; *FTO*, fat mass and obesity-associated gene; GHQ, General Health Questionnaire.
[a] Mean BMI (weight (kg)/height (m)^2) across 4 repeated clinical examinations conducted over a 19-year follow-up period.
[b] Number of times (range, 0–4) a participant was found to be overweight (BMI 25.0–29.9) or obese (BMI ≥30) in 4 examinations conducted over a 19-year follow-up period. The analysis of overweight did not include obese participants and was therefore based on 2,473 men and 861 women.
[c] Number of times (range, 0–4) a participant was designated a GHQ "case" in 4 examinations conducted over a 19-year follow-up period. GHQ score was used as the measure of common mental disorders.

This suggests that *FTO* provided a valid instrument for adiposity indicators in men only. A formal test for evidence against weak instruments confirmed this finding: In men, the *F* value was 28.80 for mean BMI, 14.29 for overweight, and 11.51 for obesity, but the corresponding results for women were all substantially below 10 (0.17, 0.06, and 0.66, respectively). Despite statistical significance, the mean difference in adiposity between men with both risk alleles and those with no risk alleles was modest. For BMI, it was 0.935 units (95% confidence interval (CI): 0.608, 1.262) (Table 2). This is a small fraction of the observed variation in BMI, because the difference in mean BMI between participants in the top and bottom thirds of the BMI distribution was 6.644 units (95% CI: 6.506, 6.782).

In men, a greater number of *FTO* adiposity alleles was associated with a greater number of times a participant was found to be a GHQ case, but this observation was not apparent in women. In men, the unadjusted beta coefficient for this association was 0.074 (95% CI: 0.019, 0.129; $P = 0.009$) (Table 2). With adjustment for mean BMI across the 4 clinical examinations, this coefficient was attenuated by 4.5%, to 0.071 (95% CI: 0.015, 0.126; $P = 0.01$). Adjustment for overweight or obesity did not further attenuate the coefficient. There was no effect of interaction between *FTO* and adiposity measures on CMD ($P = 0.42$ for mean BMI, $P = 0.07$ for number of times overweight, and $P = 0.13$ for number of times obese).

Table 3 presents the association of the *FTO* genotype with baseline characteristics in men and women. *FTO* genotype was unrelated to these potentially confounding factors.

Association between adiposity measures and CMD in men

Standard regression analysis showed an association between obesity and CMD in both unadjusted and multivariable-adjusted models (Table 4). There was a weak inverse relation between overweight and CMD among nonobese men, but this association became attenuated to the null after adjustment for baseline characteristics (the greatest attenuation was observed when adjusting for age).

In the *FTO* genotype-instrumented analyses, there was a strong association between all adiposity indicators (mean BMI, number of times overweight, and number of times obese) and CMD (Table 4). The regression coefficients for these associations were substantially higher in instrumental-variables analysis than in the standard regression analysis.

The distribution of the CMD measure was skewed (52.1% of men were never a GHQ case, 25.9% were a case once, 12.9% twice, 6.1% 3 times, and 3.0% 4 times). To ensure that our findings were not driven by outliers, we conducted a sensitivity analysis with alternative outcome specifications (Table 5). In standard regression analysis, obesity was associated with a dichotomized CMD outcome irrespective of the cutoff point applied (beta coefficients ranged from 0.056

Table 3. Associations of Fat Mass and Obesity-Associated (*FTO*) Genotype With Factors Potentially Confounding the Relation Between Obesity and Common Mental Disorders in Men and Women, Whitehall II Study, 1985–2004

Baseline Characteristic	No. of *FTO* Adiposity Alleles									*P* Value
	0			1			2			
	No.	%	Mean (SD)	No.	%	Mean (SD)	No.	%	Mean (SD)	
Men										
Maximum no. of participants	1,046			1,442			493			
Age, years			44.0 (6.1)			43.7 (5.9)			44.0 (5.7)	0.75
Marital status (married)		82.8			84.4			82.4		0.45
Socioeconomic position										
High		39.6			41.5			44.4		0.39
Intermediate		54.8			53.7			51.3		
Low		5.6			4.9			4.3		
Chronic disease		8.3			10.8			9.7		0.12
Prevalent coronary heart disease		0.8			0.6			0.8		0.75
Prevalent diabetes		0.5			0.6			0.8		0.72
Use of psychotropic drugs		2.3			2.0			2.2		0.88
High alcohol consumption[a]		16.4			17.4			20.6		0.13
Physical inactivity		23.8			19.8			22.6		0.051
Current smoking		10.4			11.9			9.2		0.20
Women										
Maximum no. of participants	448			543			173			
Age, years			44.0 (6.1)			44.5 (5.8)			44.7 (5.9)	0.13
Marital status (married)		60.5			57.3			61.9		0.44
Socioeconomic position										
High		15.2			16.1			19.7		0.20
Intermediate		44.0			46.5			49.7		
Low		40.9			37.5			30.6		
Chronic disease		10.4			9.2			8.8		0.78
Prevalent coronary heart disease		0.4			0.4			0.0		0.69
Prevalent diabetes		0.5			0.4			0.0		0.69
Use of psychotropic drugs		4.0			4.4			4.1		0.94
High alcohol consumption[b]		3.0			3.5			5.8		0.24
Physical inactivity		41.3			38.0			39.3		0.59
Current smoking		13.3			17.3			17.1		0.20

Abbreviations: *FTO*, fat mass and obesity-associated gene; SD, standard deviation.
[a] >21 alcohol units per week.
[b] >14 alcohol units per week.

($P = 0.03$) to 0.117 ($P = 0.005$), depending on the cutoff). No such association was found for mean BMI or overweight.

In instrumental-variables analysis, there was a robust association between all adiposity indicators and all dichotomized CMD outcomes, with the strongest association being seen for CMD defined as being a GHQ case at all 4 examinations versus being a case at 0–3 examinations ($\beta = 0.857$, $P < 0.0001$); the weakest association, though the effect was still substantial, was found for CMD defined as being a GHQ case in any examination versus none ($\beta = 0.653$, $P = 0.002$) (Table 5).

Role of diabetes and prediabetes

In the last medical examination, 215 men were diabetic and 452 prediabetic (357 had impaired fasting glucose and 95 impaired glucose tolerance). We repeated the main analysis presented in Table 4 with models adjusted for diabetes and prediabetes status. This adjustment slightly attenuated

Table 4. Results From Standard and Fat Mass and Obesity-Associated Gene (*FTO*)-Instrumented Analyses of the Association of Body Mass Index, Overweight, and Obesity With Common Mental Disorders in Men, Whitehall II Study, 1985–2004

Predictor Variable	No. of Men	Analysis of Common Mental Disorders[a]						*P* for Difference Between Coefficients[b]
		Ordinary Least Squares Regression[c]			Instrumental-Variable Regression[c]			
		β[d]	95% CI	*P* Value	β[d]	95% CI	*P* Value	
Unadjusted								
Mean BMI[e]	2,981	0.009	−0.003, 0.021	0.15	0.171	0.030, 0.311	0.02	0.01
No. of times overweight[f]	2,473	−0.027	−0.054, −0.001	0.04	0.516	0.070, 0.963	0.02	0.002
No. of times obese[f]	2,981	0.064	0.022, 0.106	0.003	0.907	0.074, 1.74	0.03	0.01
Multivariable-adjusted[g]								
Mean BMI	2,826	0.010	−0.002, 0.023	0.11	0.166	0.025, 0.308	0.02	0.02
No. of times overweight	2,345	−0.018	−0.045, 0.008	0.18	0.544	0.080, 1.001	0.02	0.002
No. of times obese	2,826	0.052	0.010, 0.094	0.02	0.873	0.041, 1.704	0.04	0.02

Abbreviations: BMI, body mass index; CI, confidence interval; GHQ, General Health Questionnaire.

[a] Number of times (range, 0–4) a participant was designated a GHQ "case" in 4 examinations conducted over a 19-year follow-up period. GHQ score was used as the measure of common mental disorders.

[b] Durbin-Wu-Hausman statistic (30).

[c] Beta coefficients (linear model) from ordinary least squares regression and instrumental-variable regression are on the same scale.

[d] Change per unit increase in the predictor variable.

[e] Mean BMI (weight (kg)/height (m)^2) across 4 repeated clinical examinations conducted over a 19-year follow-up period.

[f] Number of times (range, 0–4) a participant was found to be overweight (BMI 25.0–29.9) or obese (BMI ≥30) in 4 examinations conducted over a 19-year follow-up period. The analysis of overweight did not include obese participants.

[g] Adjusted for age, marital status, socioeconomic position, chronic illness, coronary heart disease, diabetes, use of antidepressants, alcohol intake, physical activity, and smoking. Men with missing data on any of the variables were excluded.

the estimates obtained from the instrumental-variables analysis (by 4.8%–6.7%). The adjusted beta coefficient was 0.166 ($P = 0.03$) for mean BMI ($n = 2{,}903$), 0.553 ($P = 0.04$) for overweight ($n = 2{,}416$), and 0.872 ($P = 0.05$) for obesity ($n = 2{,}903$).

DISCUSSION

In what was, to our knowledge, the first study of its kind, we found evidence to support the hypothesis that long-term obesity may be a causal risk factor for CMD in men. Using genetic data to strengthen causal inference, we found that levels of BMI, overweight, and obesity—to the extent that they were associated with adiposity alleles of *FTO*—were associated with increased risk of CMD. The effect estimates were consistent with but substantially larger than those for obesity and CMD observed in standard regression analysis. Interestingly, we found a direct association between *FTO* and CMD which was largely independent of adiposity levels. Our study benefitted from its large sample size; from directly measured rather than self-reported data on height and weight; and, unusually, from the use of standard clinical examinations repeated on multiple occasions.

Underlying assumptions for gene-instrumented analysis

Our analysis met most (but not all) assumptions for the instrumental-variables approach. First, we confirmed the strong association between increasing number of adiposity alleles (the instrument) and higher adiposity (the exposure) across all 3 adiposity measures undertaken over an approximately 19-year follow-up period. This suggests that *FTO* represents a valid proxy for long-term overweight and obesity in men. In contrast, we did not confirm a link between *FTO* and obesity in women. The fact that much larger studies have shown similar associations of *FTO* and obesity in both women and men makes it unlikely that the lack of association in Whitehall II is real (11, 12). Because of the masked *FTO*-adiposity association in women, instrumental-variables analyses based on the *FTO* genotype were possible for men only.

Second, in theory, the population distribution of genetic variants should lead to a balanced distribution of potentially confounding factors between exposure groups. In agreement with this, we found *FTO* to be unrelated to all potentially confounding factors measured in this study.

Third, in order for *FTO* genotype to be valid as an instrument, it should influence CMD only via its association with the exposure variable of interest, that is, adiposity (30). If, after adjustment for obesity, the *FTO* genotype–CMD gradient holds, this so-called exclusion restriction assumption may be violated, suggesting that the *FTO* gene exerts other (pleiotropic) influences on CMD. The fact that we found little evidence of attenuation of the gradient suggests such pleiotropic effects. Although previous studies have shown that variation in the *FTO* gene alters diabetes-related metabolic traits to the extent expected, given its effect on BMI (17), the precise function of the *FTO* gene is, as yet, unknown. Alternatively, it is also plausible that we observed an association between *FTO* and CMD in men by chance alone.

Table 5. Results From Sensitivity Analysis Using Standard and Fat Mass and Obesity-Associated Gene (*FTO*)-Instrumented Probit Regression to Examine the Associations of Body Mass Index, Overweight, and Obesity With Common Mental Disorders Specified According to 3 Alternative Dichotomous Definitions in Men, Whitehall II Study, 1985–2004

Outcome and Predictor Variable	No. of Men	No. of GHQ Cases	Analysis of Common Mental Disorders (Dichotomous Definition)[a]					
			Ordinary Probit Regression			Instrumental-Variable Regression		
			Probit Coefficient[b]	95% CI	*P* Value	Probit Coefficient[b]	95% CI	*P* Value
GHQ case 1–4 times vs. never								
Mean BMI[c]	2,981	1,429	0.005	−0.010, 0.019	0.54	0.140	0.023, 0.256	0.02
No. of times overweight[d]	2,473	1,152	−0.031	−0.063, 0.000	0.05	0.288	−0.048, 0.623	0.09
No. of times obese[d]	2,981	1,429	0.056	0.007, 0.105	0.03	0.653	0.230, 1.075	0.002
GHQ case 3–4 times vs. 0–2 times								
Mean BMI	2,981	272	0.018	−0.002, 0.038	0.08	0.185	0.061, 0.309	0.004
No. of times overweight	2,473	211	−0.020	−0.065, 0.026	0.40	0.495	0.320, 0.669	<0.0001
No. of times obese	2,981	272	0.080	0.017, 0.143	0.01	0.754	0.318, 1.190	0.001
GHQ case 4 times vs. 0–3 times								
Mean BMI	2,981	91	0.020	−0.008, 0.048	0.16	0.209	0.069, 0.349	0.003
No. of times overweight	2,473	64	−0.057	−0.126, 0.012	0.10	0.512	0.338, 0.685	<0.0001
No. of times obese	2,981	91	0.117	0.035, 0.200	0.005	0.857	0.439, 1.276	<0.0001

Abbreviations: BMI, body mass index; CI, confidence interval; GHQ, General Health Questionnaire.

[a] Number of times (range, 0–4) a participant was designated a GHQ "case" in 4 examinations conducted over a 19-year follow-up period. GHQ score was used as the measure of common mental disorders.

[b] Change per unit increase in the predictor variable.

[c] Mean BMI (weight (kg)/height $(m)^2$) across 4 repeated clinical examinations conducted over a 19-year follow-up period.

[d] Number of times (range, 0–4) a participant was found to be overweight (BMI 25.0–29.9) or obese (BMI ≥30) in 4 examinations conducted over a 19-year follow-up period. The analysis of overweight did not include obese participants.

Comparison with previous studies

As indicated, we are not aware of any other large-scale study that has examined the status of long-term obesity as a risk factor for CMD using a combination of genotype information and serial measurements of phenotype. The association between adiposity and mental disorders has been controversial. Some studies support the "jolly fat" hypothesis (6), whereby obese people are assumed to have reduced risk of mental health problems; other investigators report the converse: "the fat and sad" hypothesis (2). Our study is in agreement with the latter, which supports the most recent meta-analysis finding that, taken together, longitudinal studies show obesity to be a risk factor for depressive disorders (2). Our findings also accord with those of studies showing remission of depressive symptoms following surgically induced weight loss among clinically obese patients (33). The association between obesity and CMD is plausible, because obese persons may experience weight-related stigma and discrimination (34), suffer from obstructive sleep apnea (35), have increased levels of circulating inflammatory cytokines (36), have disturbed neuroendocrine function (37), and lead sedentary lives that limit social contact (19). These factors may predispose a person to increased mental health problems.

We have previously shown in this cohort a dose-response association between long-term obesity and risk of CMD which was robust to adjustment for a range of covariates but was attenuated when only participants free of mental disorder at baseline were included in the analysis (3). Given that the median age of first onset is approximately 30 years for depressive disorder and as early as 11 years for anxiety disorder (38), it is possible that the disorder-free persons in our middle-aged cohort have been particularly resistant to the adverse effects of obesity. Thus, the absence of a predictive association from obesity to CMD in this subgroup might not refute the causal hypothesis in wider populations.

Furthermore, it is possible that the association between obesity and CMD is bidirectional (2). Previous studies have provided support for the hypothesis that long-term CMD may increase the risk of obesity in initially nonobese people (3, 7). This does not preclude a causal association in the opposite direction. Indeed, bidirectional effects between obesity and CMD resulting in a positive feedback "loop" between the 2 conditions remain a possibility and merit further examination. Ideally this should be done in randomized controlled trials of effective treatments of obesity that also measure CMD.

Limitations

There are some important limitations of this study. First, our findings were based on self-reported CMD (27). While the GHQ has been validated, the scale combines potentially heterogeneous symptoms of depression and anxiety. Thus, we cannot be certain how our results would apply to persons meeting the formal criteria (*Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (39), or *International Classification of Diseases*, Tenth Revision (40)) for

specific psychiatric disorders, such as major depressive disorder or anxiety disorders.

Second, in the instrumental-variables models, the effects of BMI (per 1-unit increase) and other adiposity measures on CMD were imprecisely estimated because of the limited variance in genetic instruments (the difference in mean BMI between extreme genotype groups was less than 1 unit). Future studies with multiple adiposity-related polymorphisms from different loci (e.g., *MC4R*) (41) and considerably larger sample sizes are needed to improve precision of the estimation.

Third, this study highlights a potential drawback in the Mendelian randomization approach when it is applied to nonprotein risk factors, such as obesity, and genotypes with unknown function. While protein biomarkers have a single, proximal associated gene, obesity is influenced by multiple genes which may also affect other phenotypes (42). In this study, the direct *FTO*-CMD link, which was not accounted for by measured adiposity, suggests that the exclusion restriction assumption might not have been met. We observed an improbably large instrumental-variable coefficient for the effect of adiposity on CMD which could be partly explained by this violation of the exclusion restriction assumption (43).

Conclusion

CMD account for a substantial proportion of the global burden of disease and have associated economic costs, emphasizing the need to determine risk factors for these disorders (44). Our study utilizing genetic information provides novel evidence that higher adiposity levels might cause CMD, at least in men. This finding should be interpreted cautiously. In addition to reinforcing the need for larger Mendelian randomization investigations to examine the robustness of this association, our study raises concerns about potential direct effects of *FTO* on CMD, which could reduce the value of Mendelian randomization analysis using this genotype as an instrument.

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