Body Mass Index and Depressive Symptoms: Testing for Adverse and Protective Associations in Two Twin Cohort Studies

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Studies have suggested both adverse and protective associations of obesity with depressive symptoms. We examined the contribution of environmental and heritable factors in this association. Participants were same-sex twin pairs from two population-based twin cohort studies, the Older Finnish Twin Cohort (n = 8,215; mean age = 44.1) and the US Midlife Development in the United States (MIDUS; n = 1,105; mean age = 45.1). Body mass index (BMI) was calculated from self-reported height and weight. Depressive symptoms were assessed using Beck’s Depression Inventory (BDI; Finnish Twin Cohort), and by negative and positive affect scales (MIDUS). In the Finnish Twin Cohort, higher BMI was associated with higher depressive symptoms in monozygotic (MZ) twins (B = 2.01, 95% CI = 1.0, 3.0) and dizygotic (DZ) twins (B = 1.17, 0.5, 1.9) with BMI > 22. This association was observed in within-pair analysis in DZ twins (B = 1.47, CI = 0.4, 2.6) but not in within-pair analysis of MZ twins (B = 0.03, CI = -1.9, 2.0). Consistent with the latter result, a bivariate genetic model indicated that the association between higher BMI and higher depressive symptoms was largely mediated by genetic factors. The results of twin-pair analysis and bivariate genetic model were replicated in the MIDUS sample. These findings suggest an association between obesity and higher depressive symptoms, which is largely explained by shared heritable biological mechanisms.

Keywords: obesity, depression, twin study, epidemiology, mental health

Obese individuals have a higher risk of depression and anxiety (Blaine, 2008; Gariety et al., 2010; Kivimäki et al., 2009; Luppino et al., 2010; Markowitz et al., 2008; Wardle et al., 2011). However, some studies have suggested that higher BMI might be associated with a lower rather than higher risk of depression (Crisp & McGuiness, 1976; Gariety et al., 2010; Lawlor et al., 2007; Palinkas et al., 1996). These conflicting findings may be due to unmeasured confounding factors.

In an attempt to obtain less confounded estimates, recent studies have used instrumental variables regression with genetic variants of body weight (Jokela et al., 2012; Kivimäki et al., 2011; Lawlor et al., 2011; Samaan et al., 2013). The results from these studies have also been mixed, with both adverse (Jokela et al., 2012; Kivimäki et al., 2011) and protective (Lawlor et al., 2011) associations between BMI and depressive symptoms. Furthermore, allelic variation in the FTO gene — which is associated with higher...
overall response rate was 60.8%. The original sample of 307 non-institutionalized, English-speaking adults aged 25 to 74 years in 1995–1996 (Brim et al., 2007). The estimated development in the United States (MIDUS) is based on the MacArthur Foundation Survey of Midlife Development in the United States (MIDUS) is based on a nationally representative random-digit-dial sample of non-institutionalized, English-speaking adults aged 25 to 74 years in 1995–1996 (Brim et al., 2007). The estimated overall response rate was 60.8%. The original sample of 7,108 participants includes a twin subsample (n = 1,908) of 715 MZ twins, 671 same-sex DZ twins, 497 different-sex DZ twins, and 25 twins with unknown zygosity. Zygosity was determined using a self-reported questionnaire on the twin pair’s similarity of eye and hair color and the similarity of appearance during childhood. Only same-sex DZ twin pairs were included in the present study. The survey complied with institutional review board standards of the University of Wisconsin and of the Harvard Medical School, and the study protocol was approved by the human study committees of both schools. All participants provided informed consent for participation.

In MIDUS, negative mood was assessed using a self-reported scale consisting of six items assessing positive affect (e.g., cheerful, full of life) and six items assessing negative affect (e.g., hopeless, so sad nothing could cheer you up) experienced during the last month rated on a 5-point scale (1 = none of the time, 5 = all of the time). These items were derived for the MIDUS questionnaire from six existing standardized scales of depressive symptoms and mental wellbeing (Mroczek & Kolarz, 1998). The 12 items were summed together so that higher scores indicated negative mood (correlation between positive and negative affect scales r = -0.63). Self-reported height and weight were used to calculate BMI. Covariates included sex, age, education (reported on a 12-point scale ranging from 1 = no schooling, 12 = higher education), and smoking (never-smoker, ex-smoker, current smoker).

Statistical Analysis
As within-pair analysis is based on comparing differences within twin pairs, continuous measures of BMI and depressive symptom score from the BDI were used to retain individual variation. However, in order to compare the associations with previous studies, we also ran analyses using dichotomized measures of obesity (BMI ≥ 30 kg/m²) and BDI caseness (BDI score ≥ 10, indicating at least mild depression). In these analyses, we used logistic regression to derive odds ratios with accompanying 95% confidence intervals. The measure of negative mood in the MIDUS study was not dichotomized due to lack of established cut-offs.

Preliminary analyses of data from the Finnish Twin Cohort showed that mean BMI was 23 kg/m² among non-obese individuals and 33 kg/m² among obese individuals. The linear regression coefficients were calculated for a 10-unit increase in BMI to reflect this mean difference in BMI between the non-obese and obese groups. All models were adjusted for sex, age, education, and smoking.

We used within-pair comparison among MZ and DZ twins to examine whether the overall association based on standard regression modeling was replicated in within-twin pair analysis; that is, whether the twin with a higher BMI had higher depressive symptoms than his/her co-twin with a lower BMI (Carlin et al., 2005). In the Finnish Twin Cohort, Tobit regression with floor-censoring was used to take into account the non-negative nature of BMI.
The baseline characteristics of the Finnish Twin Cohort are shown in Table 1. Obesity was associated with the positive skewness in the distribution of BDI depressive symptoms.

In addition, we fitted bivariate twin models using Cholesky decomposition to examine whether the association between BMI and depressive symptoms was mediated by common genes, shared environment, or non-shared environment. To take into account the possibility that health conditions leading to weight loss and underweight might bias the association between BMI and depressive symptoms, we repeated the main analyses in subsamples first excluding twin pairs with either twin having BMI less than 20 kg/m² and then twin pairs with BMI less than 22 kg/m². These cutoffs were arbitrary and were selected only for the purpose of sensitivity analysis.

### Results

#### The Finnish Twin Cohort

The baseline characteristics of the Finnish Twin Cohort study members are shown in Table 1. Obesity was associated with 1.53-fold (95% CI = 1.21, 1.92) increased odds of mild depression in all individuals, the point estimates being 1.78-fold in MZ individuals versus 1.42 in DZ twins (Table 2). These estimates changed little after excluding participants with particularly low BMI from the analysis.

Repeating this analysis with continuous measures of BMI and depressive symptoms showed similar results although the positive association between BMI and depression score was substantially stronger when people with BMI < 20 kg/m² or BMI < 22 kg/m² were removed from the analysis. This strengthening linear association after the exclusion of individuals with low BMI was because individuals with BMI less than 20 had higher levels of depressive symptoms (B = 0.82, 95% CI = 0.33, 1.30) compared to individuals with BMI between 20 and 25.

In DZ twins, the within-pair analysis produced very similar estimates as the standard regression analysis (Table 2), suggesting that the association between higher BMI and higher depressive symptoms was unlikely to be confounded by factors shared by DZ twin pairs. In contrast, in MZ twin pairs there was no within-pair association between BMI and depressive symptoms. After excluding individuals with BMI below 20 kg/m², there was no overlap between the point estimate of the overall association and the confidence interval of the within-pair association, indicating that these estimate were different at p = .05.

Figure 1 shows results from the bivariate quantitative genetic model. There was a positive association between BMI and depressive symptoms, and the majority of this association was attributable to genetic influences, as only this pathway was statistically significant. The genetic correlation indicated 12% overlap in the shared genetic background of BMI and depressive symptoms (r = 0.12, 95% CI = 0.06, 0.17; see Online Supplementary Material Appendix 1 and eTable 1 for details of the genetic correlation and eFigure 1 for the best-fitting genetic model).

#### MIDUS

The prevalence of obesity was three times as high in the MIDUS sample compared to Finnish Twin Cohort (21%...
TABLE 3
Twin-Pair Analysis of BMI in Relation to Negative Mood (Adjusted for Age, Sex, Education, and Smoking): The MIDUS Twin Sample

<table>
<thead>
<tr>
<th>Population</th>
<th>Overall B [95% CI]</th>
<th>p value</th>
<th>Within-pair B [95% CI]</th>
<th>p value</th>
<th>Total N (full pairs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MZ twins</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>2.66 [0.8, 4.5]</td>
<td>0.01</td>
<td>-0.67 [-4.2, 2.9]</td>
<td>0.71</td>
<td>589 (293)</td>
</tr>
<tr>
<td>BMI &gt; 20kg/m²</td>
<td>2.95 [1.0, 4.9]</td>
<td>0.003</td>
<td>-0.55 [-4.3, 3.2]</td>
<td>0.77</td>
<td>560 (274)</td>
</tr>
<tr>
<td>BMI &gt; 22kg/m²</td>
<td>3.50 [1.4, 5.6]</td>
<td>0.001</td>
<td>-1.03 [-4.9, 2.9]</td>
<td>0.60</td>
<td>500 (234)</td>
</tr>
<tr>
<td>DZ twins</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>1.26 [0.4, 2.9]</td>
<td>0.71</td>
<td>1.70 [-0.9, 4.3]</td>
<td>0.20</td>
<td>514 (257)</td>
</tr>
<tr>
<td>BMI &gt; 20kg/m²</td>
<td>1.37 [0.4, 3.1]</td>
<td>0.77</td>
<td>1.66 [-1.1, 4.4]</td>
<td>0.24</td>
<td>489 (233)</td>
</tr>
<tr>
<td>BMI &gt; 22kg/m²</td>
<td>0.74 [-1.2, 2.6]</td>
<td>0.60</td>
<td>1.67 [-1.2, 4.6]</td>
<td>0.26</td>
<td>431 (190)</td>
</tr>
</tbody>
</table>

Note: B for 10-unit increase in BMI with negative mood score as the outcome. Overall regressions are fitted with random-intercept models, within-pair regression are fitted using fixed-effect estimator to compare twin pairs with each other. Only pairs with full data for each member of twin pair are included in the within-pair analysis.

FIGURE 1
Bivariate genetic model (Cholesky decomposition) of the association between body mass index (BMI) and depressive symptoms into pathways mediated by genetic factors, shared environment, and non-shared environment in the Finnish Twin Cohort (panel A; n = 1,329 MZ twin pairs; n = 2,439 DZ pairs) and MIDUS twin sample (panel B; n = 293 MZ twin pairs; n = 257 DZ pairs). Values are standardized regression coefficients (SD = 1), with statistically significant pathways marked with an asterisk (*p < .05). Panel A shows the model for the total sample (n = 1,329 MZ twin pairs; n = 2,439 DZ pairs). See Supplementary Figure 1 in the Online Supplementary Material for the best-fitting models.

Discussion
In two independent cohort studies of MZ and DZ twins, higher BMI was associated with higher depressive symptoms, and this association was mediated mostly by shared genetic factors; the association was not observed when comparing MZ twin pairs with each other.

The main limitation of the present study is the lack of repeated measurements of BMI and depressive symptoms over time. Although the MIDUS study has repeated...
measurements, the number of twin participants was not sufficient for longitudinal analysis (details not shown), and in the Finnish twin cohort, depressive symptoms using the BDI have been assessed only once. Previous results using longitudinal data have suggested a bidirectional association between obesity and depression (Lupino et al., 2010), with each direction mediated by different biological and psychological mechanisms (Kivimäki et al., 2009). Thus, the present results provide evidence on the nature of stable associations between BMI and depressive symptoms but not necessarily about changes over time. Another limitation was the use of self-reported measures only.

Obesity and depressive symptoms may share common pathophysiological pathways, including the HPA axis, immuno-inflammatory reactions and insulin signaling (Capuron et al., 2008; Dixon et al., 2008; Ladwig et al., 2003; Miller et al., 2003; Olzanska-Glinianowicz et al., 2009; Soczynska et al., 2011). For example, obesity and depression may both represent pro-inflammatory states (Ladwig et al., 2003; Miller et al., 2003), which would be consistent with a shared genetic background of body weight and depressive symptoms. Indeed, several genetic variants related to depression are also related to inflammation (Raison & Miller, 2013). The obesity-related FTO gene has been associated with both lower (Kivimäki et al., 2011) and higher (Lawlor et al., 2011; Samaan et al., 2013) symptoms of depression and anxiety, while a 31-SNP genetic risk marker for higher BMI was associated with higher depressive symptoms (Jokela et al., 2012). The associations between obesity-related genes and depressive symptoms in these studies have been largely independent of BMI, suggesting that at least some of the obesity-related genes may be directly related to risk of mental disorders — and not mediated by the phenotypic effects of higher body weight (Samaan et al., 2013). The current findings are in agreement with such a direct genetic association.

Two previous family-based analyses have produced mixed findings on the genetic link between body weight and depressive symptoms (Afari et al., 2010; Choy et al., 2009). In an analysis of 712 MZ and 281 DZ female twin pairs from the Washington twin registry (Afari et al., 2010), 12% of the genetic component of depression was shared with genetic component of obesity, with no contribution from shared or non-shared environmental factors. By contrast, a Dutch family-based study found no shared genetic factors to account for the association between obesity and depressive symptoms in a pedigree analysis of 1,355 women and 1,028 men (Choy et al., 2009). Our results are in agreement with the findings from the Washington twin study.

The non-genetic associations estimated in the two cohorts were not statistically significant in the within-pair comparison of MZ twins or in the bivariate genetic models. The non-significant associations in the within-pair analyses hinted at a possible inverse association between BMI and depressive symptoms. Additional data are needed to test whether such an inverse association would be observed in larger samples. It must be emphasized that the absence of an environmentally mediated association should not be interpreted to indicate that the environmental risk factors increasing the prevalence of obesity would not influence depressive symptoms over time or between populations (Davey, 2011). The results only suggest that environmentally induced variation in BMI is not associated with differences in depressive symptoms among individuals at a particular time.

In sum, twin-pair analysis and quantitative genetic modeling in two twin studies from Finland and the US provided converging evidence for an association between higher BMI and higher depressive symptoms in adults. This association appears to be explained by a shared genetic background rather than environmental factors, but further research is needed to confirm this finding.

Acknowledgments
This research was supported by the Academy of Finland (grant numbers: 124,322, 124,271, 132,944, 141,054, 265,240, and 264,146); the Medical Research Council (MRC, K013351); the US National Institutes of Health (R01HL036310; R01AG034454); and the Finnish Work Environment Fund. The Centre for Cognitive Ageing and Cognitive Epidemiology is supported by the Biotechnology and Biological Sciences Research Council, the Engineering and Physical Sciences Research Council, the Economic and Social Research Council, the MRC, and the University of Edinburgh as part of the cross-council Lifelong Health and Wellbeing initiative. G.D.B. is a Wellcome Trust Fellow and M.K. an Economic and Social Research Council Professor.

Supplementary Material
To view supplementary material for this article, please visit http://dx.doi.org/10.1017/thg.2016.14.

References