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Body mass index and depressive symptoms: Testing for adverse and protective associations in two twin cohort studies

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Abstract

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 in the United States survey (MIDUS) (n=1,105; mean age=45.1). Body mass index was calculated from self-reported height and weight. Depressive symptoms were assessed using Beck's Depression Inventory (Finnish Twin Cohort), and by negative and positive affect scales (MIDUS). In the Finnish Twin Cohort, higher body mass index (BMI) was associated with higher depressive symptoms in monozygotic twins (B=2.01, 95%CI=1.0, 3.0) and dizygotic twins (B=1.17, 0.5, 1.9) with BMI>22. This association was observed in within-pair analysis in dizygotic twins (B=1.47, CI=0.4, 2.6) but not in within-pair analysis of monozygotic 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 (Luppino et al., 2010; Wardle, Chida, Gibson, Whitaker, & Steptoe, 2011; Kivimäki et al., 2009; Markowitz, Friedman, & Arent, 2008; Blaine, 2008; Gariepy, Nitka, & Schmitz, 2010). However, some studies have suggested that higher body mass index (BMI) might be associated with a lower rather than higher risk of depression (Crisp & McGuiness, 1976; Lawlor, Hart, Hole, Gunnell, & Smith, 2007; Palinkas, Wingard, & BarrettConnor, 1996; Gariepy, Wang, Lesage, & Schmitz, 2010). 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 (Kivimäki et al., 2011; Lawlor et al., 2011; Jokela et al., 2012; Samaan et al., 2013). The results from these studies have also been mixed, with both adverse (Kivimäki et al., 2011; Jokela et al., 2012) and protective (Lawlor et al., 2011) associations between BMI and depressive symptoms. Furthermore, allelic variation in the *FTO* gene—which is associated with higher obesity risk—has been associated with lower risk of depression (Samaan et al., 2013). Based on these genetic findings, it has been argued that the genetic and non-genetic pathways linking obesity and depression may be different (Lawlor et al., 2011).

In the present study, we applied twin-pair analysis and quantitative genetic modeling to test whether higher BMI is a risk or protective factor for depressive symptoms mediated differently via environmental and genetic pathways. Based on earlier studies, we hypothesized that there is an environmentally mediated risk but genetically mediated protective association between higher BMI and depressive symptoms.

Method

The Older Finnish Twin Cohort study

The Older Finnish Twin Cohort study consists of all Finnish twin pairs of the same sex born before 1958 with both co-twins alive in 1975 (Kaprio & Koskenvuo, 2002). Zygosity was assessed at baseline with questions about the similarity of appearance of a twin pair at an early school age, which has been shown to have high validity against genetic markers in this study (Kaprio & Koskenvuo, 2002). With a response rate of 89%, the cohort comprised of 13,888 twin pairs of known zygosity. The study was approved by the ethics committee of the Helsinki University hospital, and participants provided informed consent.

In a resurvey in 1990 of twins born 1930-1957, the participants were administered the self-reported Beck's Depression Inventory (BDI) which consists of 21 items each rated with a 4-point scale (0=no symptom, 3=severe symptom) (Beck & Steer, 1987). To avoid conceptual overlap between BMI and depressive symptoms, two items referring to change in weight and appetite were excluded in the calculation of the total score in the present study (the inclusion or exclusion of these items did not have substantial influence on the results). The original scale of the 21-item inventory (ranging between 0 and 63) was retained by calculating mean of the 19 items and multiplying this mean by 21, excluding individuals with more than 2 missing items of the 19-item scale. Height and weight were self-reported in 1990, and BMI calculated as weight in kilograms /height in meters^2. Covariates included were sex, age, education (reported on an 8-point scale with a range 1=mandatory schooling to 8=university degree), and smoking (never-smoker, ex-smoker, current smoker).

The Midlife Development in the United States (MIDUS) twin sample

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 monozygotic (MZ) twins, 671 same-sex dizygotic (DZ) twins, 497 different-sex dizygotic twins, and 25 twins with unknown zygosity. Zygosity was determined using 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 6 items assessing positive affect (e.g., "cheerful", "full of life") and 6 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$\geq$30kg/m^2) and BDI caseness (BDI score$\geq$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 23kg/m^2 among non-obese individuals and 33 kg/m^2 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, Gurrin, Sterne, Morley, & Dwyer, 2005). In the Finnish Twin Cohort, tobit regression with floor-censoring was used to take into account 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 20kg/m^2 and then twin pairs with BMI less than 22kg/m^2. These cut-offs 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 vs 1.42 in DZ twins (**Table 2**). These estimates changed little after excluding participants with particularly low BMI from the analysis.

[TABLE 1 AND 2 HERE]

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<20kg/m^2 or BMI<22kg/m^2 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 20kg/m^2, 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=0.05.

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 **Supplementary Table S1** for details of the genetic correlation and **Supplementary Figure S1** for the best-fitting genetic model).

[FIGURE 1 HERE]

MIDUS

The prevalence of obesity was three times as high in the MIDUS sample compared to Finnish Twin Cohort (21% vs. 7%). Compared to normal-weight participants of the total twin sample of MIDUS (BMI between 18.5 kg/m^2 and 25kg/m^2), higher levels of negative mood were observed in overweight (B=0.94, CI=-0.34, 2.22; p=0.15) and obese participants (B=2.38, CI=0.72, 4.03; p=0.005) but not in underweight participants (B=0.00, CI=-3.61, 3.60; p=0.99), with a linear trend of B=1.99 (CI=0.78, 3.20; p=0.001). Thus, the exclusion of participants with low BMI did not have as strong influence on the coefficients as in the Finnish sample.

The total and within-pair regression analyses in the MIDUS sample replicated the results of the Finnish study by showing that the association between BMI and negative mood observed in MZ twins was not observed in within-pair analysis (**Table 3**). The associations were weaker in DZ than in MZ twins, but there were no marked differences between total vs. within-pair regressions among DZ twins.

[TABLE 3 HERE]

The quantitative genetic models also supported the results of the Finnish study as the association between BMI and negative mood supported the genetic pathway but not the environmental pathways (**Figure 1**). The genetic correlation indicated 20% overlap in the shared genetic background between BMI and negative mood (r=0.20, 95%CI=0.08, 0.31; see Online Supplementary Material **Appendix 1** and **Supplementary Table S1** for details of the genetic correlation and **Supplementary Figure S1** for the best-fitting genetic model). The

results were similar when negative and positive affect scales were used as two separate outcomes instead of a single scale (**Supplementary Table S2 and Figure S2**).

Discussion

In two independent cohort studies of monozygotic and dizygotic 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 (Luppino 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 (Soczynska et al., 2011; Olszanecka-Glinianowicz et al., 2009; Capuron et al., 2008; Dixon et al., 2008; Ladwig, Marten-Mittag, Lowel, Doring, & Koenig, 2003; Miller, Freedland, Carney, Stetler, & Banks, 2003). 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 1355 women and 1028 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 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 Smith, 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 United States 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.

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Conflicts of interest: None of the authors have any competing interests.

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Table 1. Characteristics of study participants of the two cohort studies

	Finnish Twin Cohort (n=8224)	MIDUS twin sample (n=1105)
Sex		
Men	42.4 (3488)	43.6 (482)
Women	57.6 (4736)	56.4 (623)
Age (years)†	44.1 (7.8)	45.1 (12.3)
Body mass index (kg/m^2)†	24.5 (3.7)	26.2 (5)
Obese (BMI≥30)	7.3 (603)	20.9 (231)
Depressive symptoms (BDI score)†	5.30 (5.89)	-
Negative mood†	-	49 (9.8)
Smoking		
Never-smoker	50.0 (4108)	52.5 (580)
Ex-smoker	22.3 (1835)	26.5 (293)
Current smoker	27.7 (2281)	21.0 (232)
Education		
Primary	35.9 (2955)	9.7 (107)
Secondary	53.2 (4376)	61.6 (679)
Tertiary	10.9 (893)	28.7 (316)

Note: Values are percentages (and numbers) of participants unless otherwise indicated. † Values are means (and standard deviations)

Table 2. Twin-pair analysis of BMI and depressive symptoms, adjusted for age, sex, education and smoking. The Finnish Twin Cohort.

	Depression (Dichotomous measure)		**Depression Score (Continuous measure)**				
Population	OR* (95% CI)	*P*	Overall B† (95% CI)	*P*	Within-pair B† (95% CI)	*P*	Total N (full pairs)
MZ twins							
All	1.78 (1.1, 2.9)	0.03	0.90 (0.1, 1.7)	0.03	-0.17 (-1.6, 1.3)	0.50	2846 (1324)
BMI > 20kg/m^2	1.83 (1.1, 2.9)	0.02	1.69 (0.8, 2.5)	<0.001	-0.33 (-1.9, 1.2)	0.39	2580 (1133)
BMI > 22kg/m^2	1.78 (1.1, 2.9)	0.02	2.01 (1.0, 3.0)	<0.001	0.03 (-1.9, 2.0)	0.86	2022 (817)
DZ twins							
All	1.42 (1.1, 1.8)	0.08	0.73 (0.2, 1.3)	0.01	0.86 (0.0, 1.7)	0.08	5369 (2435)
BMI > 20kg/m^2	1.44 (1.1, 1.9)	0.06	0.99 (0.4, 1.6)	0.001	1.27 (0.3, 2.2)	0.02	4986 (2128)
BMI > 22kg/m^2	1.42 (1.1, 1.9)	0.07	1.17 (0.5, 1.9)	0.001	1.47 (0.4, 2.6)	0.02	4041 (1501)

* Odds ratio for obese (BMI $\geq$ 30kg/m^2) versus non-obese (BMI < 30kg/m^2) with dichotomous depression as the outcome.

† B for 10-unit increase in BMI with continuous depression score as the outcome. Overall regressions are fitted with random-intercept tobit 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.

Table 3. Twin-pair analysis of BMI in relation to negative mood (adjusted for age, sex, education and smoking). The MIDUS twin sample

	Negative Mood Score				
Population	Overall B† (95% CI)	*P-value*	Within-pair B† (95% CI)	*P-value*	Total N (full pairs)
MZ twins					
All	2.66 (0.8, 4.5)	0.01	-0.67 (-4.2, 2.9)	0.71	589 (293)
BMI > 20kg/m^2	2.95 (1.0, 4.9)	0.003	-0.55 (-4.3, 3.2)	0.77	560 (274)
BMI > 22kg/m^2	3.50 (1.4, 5.6)	0.001	-1.03 (-4.9, 2.9)	0.60	500 (234)
DZ twins					
All	1.26 (-0.4, 2.9)	0.71	1.70 (-0.9, 4.3)	0.20	514 (257)
BMI > 20kg/m^2	1.37 (-0.4, 3.1)	0.77	1.66 (-1.1, 4.4)	0.24	489 (233)
BMI >22 kg/m^2	0.74 (-1.2, 2.6)	0.60	1.67 (-1.2, 4.6)	0.26	431 (190)

† 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.

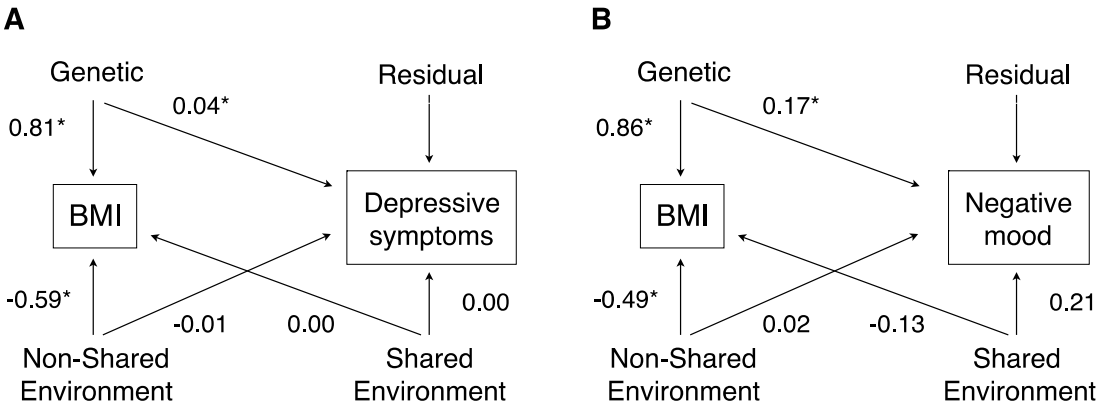

Figure 1. Bivariate genetic model (Cholesky decomposition) of the association between body mass index (BMI) and depressive symptoms into pathways mediated by genetic factors, shared environment, and non-shared environment in the Finnish Twin Cohort (panel A; n=1,329 MZ twin pairs; n=2,439 DZ pairs) and 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 (* $p<0.05$). Panel A shows the model for the total sample (n=1,329 MZ twin pairs; n=2,439 DZ pairs), See **eFigure 1** of Online Supplementary Material for the best-fitting models.

Twin Research and Human Genetics

Body mass index and depressive symptoms: Testing for adverse and protective associations in two twin cohort studies

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Supplementary material

Appendix 1

Supplementary Table S1

Supplementary Table S2

Supplementary Figure S1

Supplementary Figure S2

Appendix 1.

Table S1 shows the intraclass correlations and cross-trait correlations for BMI and depressive symptoms (or negative mood) in both cohorts.

In the Finnish Twin Cohort, univariate analyses indicated that the best-fitting models for BMI included additive genetic component (a^2=0.65) and non-shared environmental component (e^2=0.35) but no shared environment (χ^2=0.0, df=1). The same was true for depressive symptoms (a^2=0.36, e^2=0.64; χ^2=0.0, df=1 for the exclusion of shared environment). Adding non-additive (or dominant) genetic effects (r=1.0 in MZ twins, r=0.25 in DZ twins) to the AE model suggested better fit for the ADE model for depressive symptoms (a^2=0.16, d^2=0.23, e^2=0.61; χ^2=6.6, df=1, p=0.01) but not for BMI (χ^2=2.0, df=1, p=0.16).

In the bivariate model fitted with the Finnish Twin Cohort data (excluding individuals with BMI below 20 to take into account the effects of underweight), all shared environmental factors could be omitted without decline in model fit (χ^2=0). Omitting non-shared environmental covariance between BMI and depressive symptoms also had no influence (χ^2=0). Other paths could not be excluded without significantly decreasing model fit. The final model and its standardized path coefficients are shown in **Figure S1**. Genetic correlation between BMI and depressive symptoms was calculated using the formula

$$r_A = \frac{X_{11} * X_{21}}{\sqrt{X_{11}^2} * \sqrt{X_{21}^2 + X_{22}^2}}$$

where the values are non-standardized path coefficients for the common genetic component of BMI (X_{11}), common genetic component of depressive symptoms (X_{21}), and unique genetic component of depressive symptoms (X_{22}). This indicated a genetic correlation of r=0.12 (95%CI=0.06, 0.17) between BMI and depressive symptoms (r=0.24, CI=-0.02, 0.50 for the additive genetic components only).

Similar results were observed in the MIDUS sample, in which variation in both body mass index (a^2= 0.76, e^2=0.24) and negative mood (a^2=0.42, e^2=0.58) were accounted by genetic and non-shared environment with no contribution from shared environment (χ^2=0.0, df=1). Including non-additive genetic effects did not improve model fit for BMI (χ^2=0.2, df=1, p=0.65) or negative mood (χ^2=0.0, df=1). In the bivariate model, omitting all shared environmental factors did not significantly weaken model fit (χ^2=0.3, df=3), and the non-shared environmental covariance could also be omitted without significant change in model fit (χ^2=0.1, df=1). Other paths could not be excluded withouth significant decrease in model fit. The final model and its standardized path coefficients are shown in **Figure S1**. The genetic correlation between BMI and negative mood was 0.20 (95%CI=0.08, 0.31).

Supplementary Table S1. Intraclass and cross-trait correlations.

	Finnish Twin Cohort		MIDUS	
	MZ (n=2846)	DZ (n=5369)	MZ (n=589)	DZ (n=514)
Intraclass correlation				
Body mass index	0.65 (0.62, 0.68)	0.29 (0.26, 0.33)	0.73 (0.68, 0.79)	0.39 (0.30, 0.50)
Depressive symptoms	0.40 (0.36, 0.44)	0.13 (0.09, 0.17)	-	-
Negative mood	-	-	0.44 (0.36, 0.54)	0.22 (0.11, 0.34)
Cross-trait correlation				
BMI & Depressive symptoms†	0.09 (0.05, 0.13)	0.00 (-0.03, 0.03)	-	-
BMI & Negative mood	-	-	0.16 (0.08, 0.24)	0.01 (-0.08, 0.10)

† Calculated for twin pairs with BMI>20 to exclude the effects of underweight.

Supplementary Table S2. Twin-pair analysis of BMI with positive and negative in the MIDUS sample, adjusted for age, sex, education and smoking.

	Positive Affect				
Population	Overall B† (95% CI)	*P-value*	Within-pair B† (95% CI)	*P-value*	Total N (full pairs)
MZ twins					
All	-0.12 (-0.3, 0)	0.08	0.08 (-0.2, 0.3)	0.56	594 (293)
BMI >20	-0.14 (-0.3, 0)	0.05	0.08 (-0.2, 0.3)	0.57	564 (274)
BMI >22	-0.17 (-0.3, 0)	0.03	0.15 (-0.1, 0.4)	0.30	503 (234)
DZ twins					
All	-0.11 (-0.2, 0)	0.07	-0.15 (-0.3, 0)	0.13	514 (257)
BMI >20	-0.12 (-0.3, 0)	0.06	-0.14 (-0.3, 0.1)	0.18	489 (233)
BMI >22	-0.09 (-0.2, 0.1)	0.23	-0.15 (-0.4, 0.1)	0.19	431 (190)

	Negative Affect				
Population	Overall B† (95% CI)	*P-value*	Within-pair B† (95% CI)	*P-value*	Total N (full pairs)
MZ twins					
All	0.21 (0.1, 0.3)	<0.001	0 (-0.2, 0.2)	0.98	589 (293)
BMI >20	0.23 (0.1, 0.3)	<0.001	0.01 (-0.2, 0.3)	0.94	560 (274)
BMI >22	0.27 (0.1, 0.4)	<0.001	0.02 (-0.2, 0.3)	0.87	500 (234)
DZ twins					
All	0.04 (-0.1, 0.1)	0.42	0.05 (-0.1, 0.2)	0.52	514 (257)
BMI >20	0.04 (-0.1, 0.1)	0.45	0.06 (-0.1, 0.2)	0.50	489 (233)
BMI >22	0.00 (-0.1, 0.1)	0.97	0.06 (-0.1, 0.2)	0.53	431 (190)

† B for 10-unit increase in BMI with positive and negative affect scores as the outcomes. Overall regressions are fitted with random-intercept models, within-pair regression are fitted using fixed-effect estimator to compare sibling-pairs with each other. Only pairs with full data for each member of sibling pair are included in the within-pair analysis.

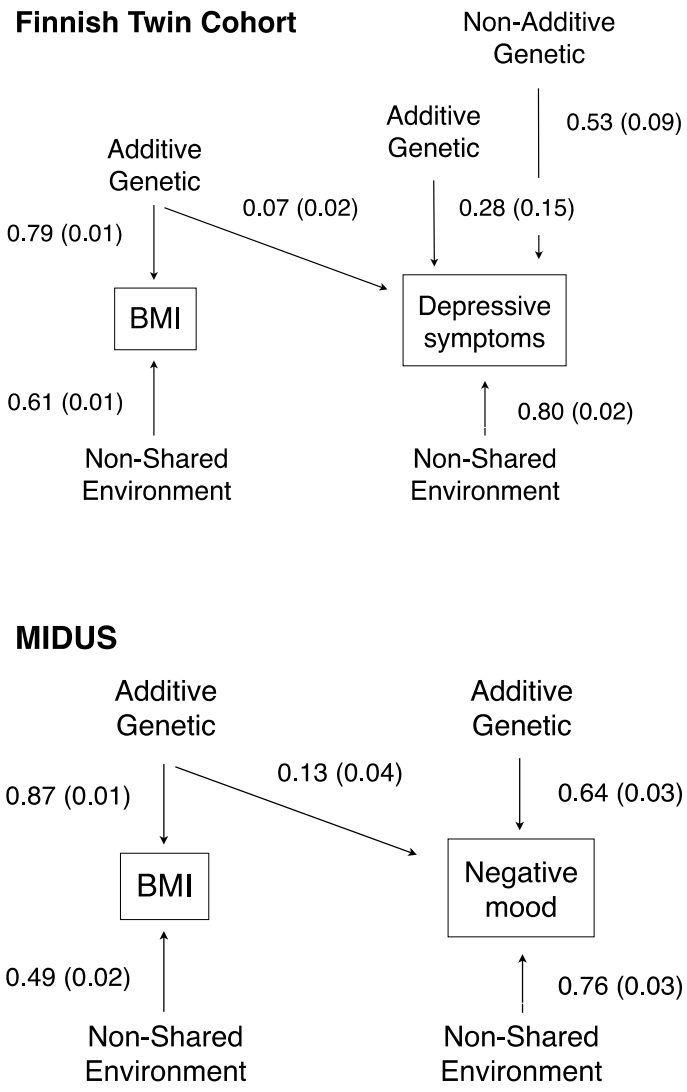

Figure S1. Best-fitting Cholesky decomposition models of the association between BMI and mental health in the Finnish Twin Cohort (n=1,136 MZ pairs; n=2,132 DZ pairs, including only twin pairs with BMI≥20) and MIDUS twin sample (n=274 MZ pairs; n=233 DZ pairs). Values are standardized path coefficients (and their standard errors), all associations are statistically significant at the $p<0.05$ level except for the additive genetic component in Finnish twins ($p=0.06$).

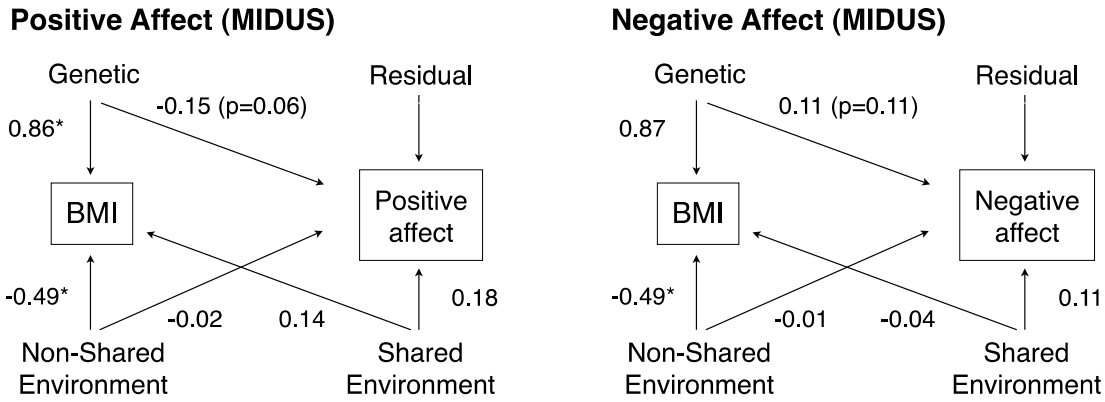

Figure S2. Cholesky decomposition of the association of body mass index (BMI) with positive affect and negative affect into pathways mediated by genetic factors, shared environment, and non-shared environment in the MIDUS twin sample. Values are standardized regression coefficients (SD=1), statistically significant pathways are marked with an asterisk (* $p<0.05$). n=293 MZ twin pairs, n=257 DZ pairs.