Chapter 3

Overweight, obesity and depression: a systematic review and meta-analysis of longitudinal studies

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Abstract

Context: Association between obesity and depression has repeatedly been established. For treatment and prevention purposes it is important to acquire more insight into their longitudinal interaction.

Objective: To conduct a systematic review and meta-analysis on the longitudinal relationship between depression, overweight and obesity, and to identify possible influencing factors.

Data Sources: Studies were found using PubMed, PsycInfo and Embase databases, and selected on several criteria.

Study Selection: Studies examining the longitudinal bi-directional relation between depression and overweight (BMI 25-29.99 kg/m²) or obesity (BMI ≥30 kg/m²) were selected.

Data Extraction: Unadjusted and adjusted odds ratios [ORs] were extracted or provided by the authors.

Data Synthesis: Overall unadjusted ORs were calculated, and subgroup analyses were performed for the 15 included studies (total N=58745), to estimate the effect of possible moderators (gender, age, depression severity). Obesity at baseline increased the risk of onset of depression at follow-up (unadjusted OR: 1.55; 95% CI: 1.22-1.98; $p \leq .001$). This association was more pronounced among Americans than among Europeans ($p = .05$), and for depressive disorder than for depressive symptoms ($p = .05$). Overweight increased the risk of onset of depression at follow-up (unadjusted OR: 1.27; 95% CI: 1.07-1.51; $p \leq .01$). This association was statistically significant among adults (20-60 and ≥ 60 years) but not among younger persons (< 20 years). Baseline depression (symptoms and disorder) was not predictive of overweight over time. However, depression increased the odds for developing obesity with 1.58 (95% CI: 1.33-1.87; $p \leq .01$). Subgroup analyses did not reveal specific moderators of the association.

Conclusions: This meta-analysis confirms a reciprocal link between depression and obesity. Obesity was found to increase the risk of depression, most pronounced among Americans and for clinically diagnosed depression. In addition, depression was found to be predictive of developing obesity.

Context

Both depression and obesity are widely spread problems with major public health implications.[1;2] Due to the high prevalence of both depression and obesity, and the fact that they both carry an increased risk for cardiovascular disease,[3;4] a potential association between depression and obesity has been presumed and repeatedly been examined. Such an association has been confirmed at the cross-sectional level.[5-7] A recent systematic review[8] examined primarily cross-sectional studies showing a weak association between obesity and depression, though significance tests were not performed. In addition, a recent meta-analysis[6] of 17 community-based cross-sectional studies among adults showed a positive overall association between depression and obesity (defined as BMI ≥ 30 kg/m² or a waist-hip ratio ≥ 102 cm for men and ≥ 88 for women). De Wit *et al.* found an overall OR of 1.18, confirming that depression is associated with an 18% increased risk of being obese. Only gender acted as a moderating factor, as in subgroup analyses the association was found in females but not in males, whereas age and continent of residence did not affect the association.

Although cross-sectional evidence is informative, it does not provide detailed insight into the exact mechanisms linking depression and obesity. It could be that depressed persons – through dysregulated stress systems[9;10] or through unhealthy lifestyles – develop more obesity over time, whereas it is also possible that obesity – e.g. through its negative effects on self-image or somatic consequences – results in the development of depression over time. Longitudinal studies are essential in providing more information on the direction of the association. With this information, prevention and intervention strategies could be improved. Although Atlantis and Baker did discuss some longitudinal studies[11-14] in their overview paper, three out of four studies were based on the same cohort and only described the effect of obesity on the development of depression. Several studies (among slightly younger samples) available at the time were not included,[15-20] and since then a considerable number of longitudinal studies have been published,[21-27] indicating that the volume of evidence on this topic has rapidly increased. Consequently, a meta-analysis that would examine the longitudinal, bi-directional evidence of the association between depression and obesity would be justified as well as needed. In order to explore a potential dose-response association, it is important to differentiate between overweight and obesity since the latter is the more severe condition and most strongly associated with biological dysregulation and unfavourable health outcomes.[28;29]

The current meta-analysis summarizes available prospective cohort studies and examines whether depression is predictive of the development of overweight and obesity and, in turn, whether overweight and obesity are predictive of the development of depression. In addition, possible moderators will be identified by examining the consistency of the longitudinal associations in subgroups stratified by gender, age, follow-up duration, depression assessment, quality assessment and continent of origin.

Methods

Study selection

A systematic computerized literature search of PubMed, Embase and PsycInfo databases was performed for studies published in English up to March 2008, combining the following key words and medical subject headings: depression, depressive disorder, depressive symptoms, major depression, metabolic syndrome, overweight, obesity, adiposity, body mass index, intra-abdominal fat, waist-hip ratio and waist circumference. No limitations in the search strategy were inserted. References from all relevant literature were hand-searched and used to identify additional relevant studies. Studies presenting solely cross-sectional analyses were excluded as were case reports, comments, letters and reviews. Articles discussing subjects other than the direct relationship between unipolar depression and obesity in an adult population and articles examining a highly specific population (e.g. pregnant women or a population with a specific somatic disease) were excluded. Articles with a follow-up period of less than one year, not expressing weight as body-mass-index or not specifying the way depression was assessed were also excluded. Studies were subdivided in two categories: studies assessing a clinical depression diagnosis and studies assessing depressive symptoms. This subdivision was made according to the outcome of the authors (if the authors presented the participants as having a depressive disorder, we put the article in the 'diagnosis category'). In the case of different manuscripts presenting data on the same cohort, differing only in follow-up length, manuscripts presenting data on the longest time period were chosen. All relevant citations were screened by two authors (FL and PB) on the above mentioned criteria.

For inclusion in the meta-analysis effect sizes had to be expressed as odds ratios (ORs). If this was not the case, the published effect sizes were transformed into ORs. If transformation was not possible, the corresponding author of that particular manuscript was contacted and asked to provide the ORs of the association of interest. For each analysis only one effect size per included article was used. As adjustments for confounders differed considerably through the selected studies, we decided to analyze primarily unadjusted data for homogeneity of results. Available or provided adjusted data were used for additional analyses.

Quality assessment

The methodological quality of all included studies was assessed by two authors independently (FL and PB) using a 15-item checklist adapted from Kuijpers *et al.*[30] (Appendix). Each item was indexed with a (+) score (= 1 point) or a (-) score (= 0 points). Objective measurements of height and weight assessments were included as quality criteria. An article was defined as 'high quality' when it scored ≥60% of the maximal possible score, in this case 9 points or more. The 60% cut-off is a commonly used cut-off point for quality assessments.[30;31] Disagreements among reviewers were resolved in a consensus meeting.

Criteria	(15 items, maximum score = 15)	Score (+ / - / ?)
Study population		
A	Inclusion criteria/sampling procedure of cohort described?	
B	Population characteristics described?	
C	In- and exclusion criteria described?	
Follow-up		
D	At least 5 years?	
Response		
E	Response at baseline: studies population ≥ 75% of originally selected population?	
F	Information (mainly on depression and BMI status) about responders versus non-responders?	
G	Loss to follow-up < 20%?	
H	Information about completers versus non-completers?	
Measurements		
I	Are depression assessments for clinical diagnosis according *DSM-IV* criteria?	
J	Same depression measurement both at baseline and follow-up?	
K	BMI calculated using measured anthropometry at baseline?	
L	BMI calculated using measured anthropometry at follow-up?	
Analysis / outcome		
M	Correction for potential confounders?	
Data presentation		
N	Are given numbers usable/transformable for meta-analysis?	
O	Are given numbers usable/transformable for meta-analysis after contacting the author(s)?	

'+' score = 1. '-' score = 0. '?' score = 0.

Appendix: This appendix describes all criteria for quality assessment.

Statistical Analyses

Data management, transformation of effect sizes and calculation of the pooled mean effect sizes were performed using the Comprehensive Meta-analysis (CMA) version 2.0 program. Available data were divided into the two directions: BMI categories as predictors of depression at follow-up or depression at baseline as predictor of BMI categories at follow-up. The first comparison included data on initially non-depressed participants, followed and screened on depression at follow-up, although for two of the included studies depression was not assessed at baseline.[11;22] The latter comparison included only data on normal weight individuals, who were followed for development of depression at follow-up. The analyses were conducted separately for obesity (BMI >30 kg/m²) and overweight (BMI 25-29.99 kg/m²) categories in order to see whether there is a difference in effect size between overweight and obesity.

Since considerable heterogeneity was expected, all analyses were performed with the random effect model. To assess heterogeneity between studies, Q-statistics were calculated.

A statistically significant Q indicates a heterogeneous distribution of odds ratios between studies, meaning that systematic differences, possibly influencing the results, are present.[32] In addition the I^2 was calculated to describe the percentages of total variation across studies caused by heterogeneity. A zero percent (0%) value means no heterogeneity, and higher values represent an increase in heterogeneity. Generally heterogeneity is categorised at 25% (low), 50% (moderate) and 75% (high).[33]

All presented results are based on the 15 included studies. In order to examine the possibility of publication bias, we first inspected the funnel plot, which plots a measure of study size (the standard error or precision) as a function of effect size. Visual inspection of a funnel plot provides an indication of publication bias when larger and smaller studies are non-symmetrically distributed across the combined effect size.[34] The presence of publication bias was further tested using Egger's method[35] which quantifies the bias captured by the funnel plot by regressing the standard normal deviation on precision defined as the inverse of the standard error.[36] If publication bias is observed, the Duval & Tweedy Trim and Fill Procedure[37] was used to calculate an estimate of the effect size after considering publication bias (adjusted effect size). Possible outliers were visually identified and tested for their effect on the significance of the effect size.

To determine whether factors such as age or follow-up duration modify the depression-BMI association, subgroup analyses were performed. Sensitivity analyses were conducted to estimate the effect of gender, mean age at baseline (subdivided into three categories : <20 years; 20-59 years and ≥60 years), length of follow-up (<10; ≥10 years), clinical diagnosis or depressive symptomatology, quality of article (low <60%; high ≥60%) and continent of origin (American or European). For estimation of gender differences, the available adjusted odds ratios for females were compared with the adjusted odds ratios for males. We performed analyses only in subgroups containing two or more articles, though subgroups with one article are mentioned in the results (Tables 2 and 3).

For articles providing additional adjusted ORs, we compared the adjusted and unadjusted effect sizes. Adjusted effect sizes were only available for the variables gender and age (Table 1).

Results

Included and excluded studies

Combining the key words and medical subject headings in the literature search, 2937 articles were found (see Figure 1). The first screening, designed to select possibly relevant articles according to the previously described criteria, left us with 80 articles for further evaluation. Most excluded articles had a cross-sectional design or discussed another subject, for example the association between lower urinary tract symptoms and depressive symptoms.[38] Bipolar disorder was another relatively frequent reason for exclusion. The remaining 80 articles

were examined in more detail, and 62 were excluded for the reasons shown in Figure 1. One of the excluded articles[12] discussed the same cohort as one of the included articles,[14] but with a shorter follow-up period. This excluded article, however, showed similar findings as the included paper from that cohort. Consequently, 18 studies remained for inclusion in the meta-analysis. For most studies, the data could not be immediately used in the meta-analysis. In these cases, authors were contacted and asked to provide the ORs of the association of our interest. For three studies, we did not receive this information and these studies could not be included.[39-41] Of the remaining 15 studies to be included, one author provided crude data[25] and all others provided data expressed as ORs. As some studies were still ongoing after publication, some authors provided the most recent results,[15;20;25] which were used for analyses.

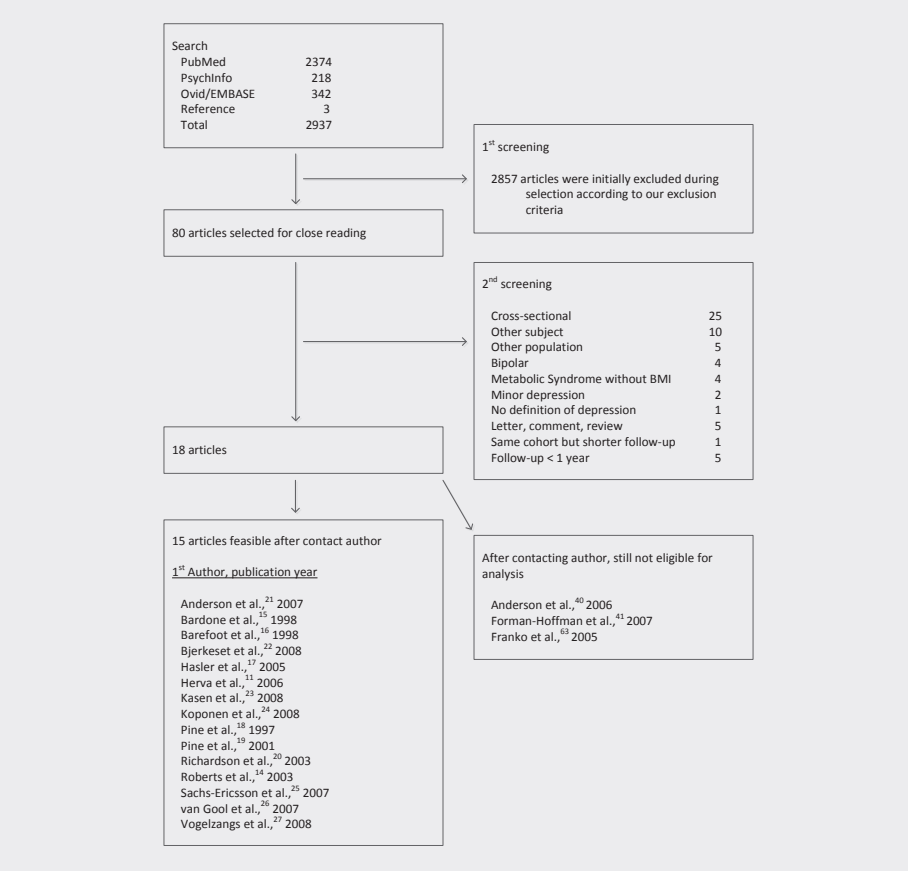

Figure 1. Flowchart illustrating the literature search and exclusion process. BMI indicates body mass index.

	Nr. of studies (Sample size)	OR (95% CI) [*P* value]	Q-Statistic	*P* value Heterogeneity	I^2 value	*P* value between groups
BMI ≥ 30 baseline → D follow-up						
Overall studies						
Unadjusted	8 (55 387)	1.55 (1.22-1.98) [< .001]	11.32	.13	38.15	> .99
Adjusted	4 (48 739)	1.57 (1.23-2.01) [< .001]	11.64	.11	39.84	
Subgroup analyses						
Sex						
Females	3 (48 195)	1.67 (1.11-2.51)				.81
Males	3 (48 195)	1.31 (1.13-1.51)				
Mean age at baseline, years						
< 20	2 (3799)	1.70 (1.25-2.30)				.52
20 - 59	4 (45 859)	1.34 (0.83-2.19)				
≥ 60	2 (5729)	1.98 (1.26-3.10)				
Follow-up duration, years						
< 10	4 (6648)	1.26 (0.78-2.03)				.24
≥ 10	4 (48 739)	1.72 (1.40-2.13)				
Diagnosis vs Symptoms						
Clinical	3 (2966)	2.15 (1.48-3.12)				.05
Symptoms	5 (52 421)	1.36 (1.03-1.80)				
Quality						
High	2 (1146)	1.24 (0.49-3.17)				.59
Low	6 (54 241)	1.62 (1.28-2.05)				
Continent						
Europe	4 (48 440)	1.33 (0.98-1.81)				.05
US	4 (6947)	2.12 (1.48-3.03)				

	Nr. of studies (Sample size)	OR (95% CI) [*P* value]	Q-Statistic	*P* value Heterogeneity	I^2 value	*P* value between groups
BMI 25 – 25.99 baseline → D follow-up						
Overall studies						
Unadjusted	7 (53 639)	1.27 (1.07-1.51) [< .01]	6.94	.33	13.56	.10
Adjusted	4 (48 739)	1.08 (1.02-1.14) [< .01]	5.08	.75	0	
Subgroup analyses						
Sex						
Females	3 (48 195)	0.98 (0.80-1.20)				.43
Males	3 (48 195)	1.30 (0.78-2.17)				
Mean age at baseline, years						
< 20	2 (3799)	1.05 (0.86-1.29)				.07
20 - 59	4 (45 859)	1.48 (1.19-1.83)				
≥ 60	1 (3981)	1.77 (1.00-1.32)				
Follow-up duration, years						
< 10	3 (4900)	0.89 (0.71-1.12)				.14
≥ 10	4 (48 739)	1.19 (0.97-1.45)				
Diagnosis vs Symptoms						
Clinical	2 (1218)	1.12 (0.74-1.84)				.88
Symptoms	5 (52 421)	1.28 (1.07-1.54)				
Quality						
High	2 (1146)	1.17 (0.80-1.70)				.64
Low	5 (52 493)	1.32 (1.06-1.63)				
Continent						
Europe	4 (48 440)	1.29 (1.05-1.58)				.95
US	3 (5199)	1.27 (0.77-2.09)				

Table 1. Findings for overall and subgroup analyses of obesity and overweight exposure and the onset of depression.
Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in squared meters); CI, confidence interval; OR, odds ratio; US, United States.

In the 15 studies included in the meta-analysis[11;12;15-27] all data on obesity and overweight were expressed in terms of body mass index (BMI). Overweight was defined as BMI between 25 and 29.99 kg/m² and obesity as BMI ≥30 kg/m², according to the WHO definition.[42] For examination of the link between overweight/obesity at baseline and development of depression at follow-up, the total number of subjects was 55387. For the inverse relationship, the number of subjects was 7196 (Table 1). In seven studies, a structured diagnostic interview was used, leading to a diagnosis of depressive disorder. Four studies did not specify who conducted the interview,[14;15;20;21] in one the interview was done by a resident in psychiatry or a psychologist,[17] and in two studies[18;19] the psychiatric interview was conducted by a trained interviewer. Eight studies assessed depression by a depressive symptom questionnaire. Three of the selected articles presented longitudinal data on both directions,[14;24;26] five on overweight/obesity exposure and depression at follow-up, and seven on the inverse association. With the exception of the studies of Bjerkeset[22] and Herva[11] (where baseline depression assessments were not performed) all studies on baseline BMI predicting subsequent depression excluded depressed individuals at baseline. Among studies on baseline depression and BMI at follow-up, all studies examined normal weight individuals at baseline. According to our quality criteria, we found four articles to be of 'high quality' (≥9 points), one of which[24] analysed data in both directions and is therefore mentioned twice. Bjerkeset's study[22] counts an exceptional high number of participants, and is responsible for the large N in the overall group. Because, in this study, as well as in Herva's study,[11] baseline depression assessments were not performed, we repeated the overall analyses after removal of these studies, both together and separately.

Obesity and overweight as predictors of depression at follow-up

Table 1 presents the findings of overall and subgroup analyses for obesity exposure on depression. The pooled odds ratio for the association between obesity at baseline and depression at follow-up for the eight studies in this group was 1.55, with a 95% confidence interval [CI] of 1.22-1.98, and a *p*-value of ≤ .001 (Table 1, Figure 2). The pooled adjusted odds ratio was very similar (OR=1.57, 95% CI 1.23-2.01). Heterogeneity between studies was not significant (Q=11.32, *p*=.13) suggesting that there were no severe systematic differences between the odds ratios of the selected studies. The percentage of total variation across these studies caused by heterogeneity was small to moderate (I^2 = 38%). Only one apparent outlier was found in the generated funnel plot.[24] Removing this study and repeating the analysis led to a slight decrease in heterogeneity (Q=7.45, *p*=.28, I^2= 20%) and a slight increase in effect size outcome (OR=1.66, 95% CI: 1.35-2.05), confirming the observed lack of heterogeneity. Overall ORs were still significant after removal of the studies of Bjerkeset and Herva (OR=1.56; 95%CI: 1.02-2.40). The Egger's test and Duval & Tweedy Trim and Fill Procedure showed no significant risk of publication bias (Egger's test's intercept =0.39, SE=1.18, *p*=.38; Duvall & Tweedie: adjusted OR=1.51; 95% CI: 1.17-1.95; number of imputed studies=1).

Subgroup analyses showed significant differences for continent of residence and depression severity (i.e. depressive symptomatology or a clinical diagnosis depression). The ORs between American and European studies differed significantly (p=.05), indicating that the overall association found was stronger among Americans. Significant difference was also found between the ORs for depression outcome as a clinical diagnosis and as depressive symptomatology (p= .05). This indicates that the effect of the overall association is stronger when depression was assessed by means of a diagnostic clinical interview rather than a self-report symptom list.

Analyses on overweight exposure (Table 1, Figure 2) resulted in a pooled odds ratio of 1.27 (95%CI: 1.07-1.51, p<.01). Heterogeneity was low (Q = 6.94; p=.33; I^2 = 14%) and no outliers were identified. Although still significant, the adjusted pooled odds ratio was considerably lower (OR=1.08, 95% CI 1.02-1.14). After removing the studies of Bjerkeset and Herva the OR was 1.14 (95% CI: 0.83-1.55).

Subgroup analyses showed that baseline overweight is associated with depression in subjects aged 20 years or older, but not in younger individuals. The difference between these age groups showed a trend (p=.07). Based on the Egger's test and Duval & Tweedy Trim and Fill Procedure, there was no indication of publication bias (Egger's test intercept=0.47, SE=1.15, p=.35; Duvall & Tweedie: adjusted OR=1.16; 95% CI: 0.98-1.37; number of imputed studies=2).

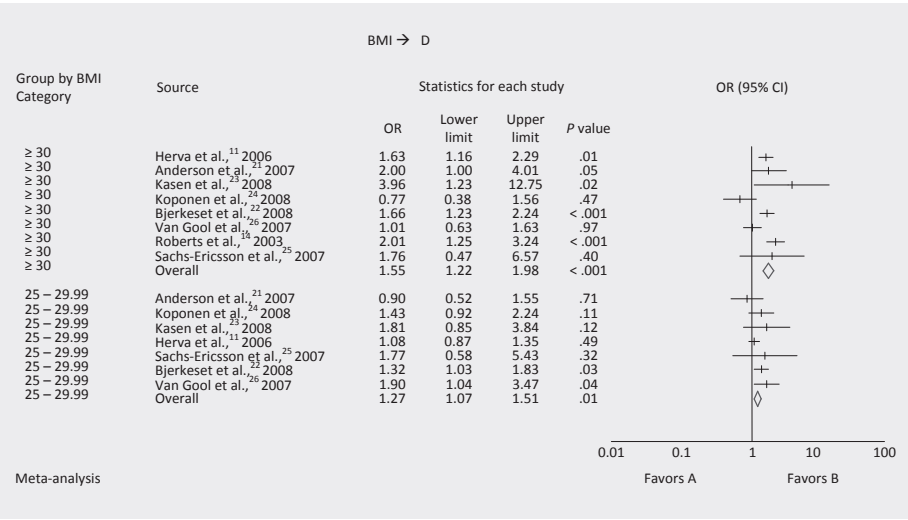

Figure 2. Forest plot of all studies describing baseline obesity (body mass index [BMI] [calculated as weight in kilograms divided by height in squared meters] ≥ 30) and overweight (BMI 25 – 29.99) with depression (D) during follow-up. Favors A = negative association between BMI and depression. Favors B = positive association between BMI and depression. OR indicates odds ratio; CI, confidence interval.

	Nr. of studies (Sample size)	OR (95% CI) [*P* value]	Q-Statistic	*P* value Heterogeneity	I^2 value	*P* value between groups
D baseline → BMI ≥ 30 follow-up						
Overall studies						
Unadjusted	9 (6436)	1.58 (1.33-1.87) [< .001]	4.43	.82	0	.37
Adjusted	4 (4000)	1.40 (1.15-1.71) [< .001]	11.18	.19	28.45	
Subgroup analyses						
Sex						
Females	4 (4000)	2.01 (1.11-3.65)				.50
Males	4 (4000)	1.43 (0.96-2.13)				
Mean age at baseline, years						
< 20	5 (3884)	1.76 (1.42-2.18)				.26
20 - 59	2 (529)	1.27 (0.88-1.82)				
≥ 60	2 (2221)	1.40 (0.90-2.17)				
Follow-up duration, years						
< 10	5 (3359)	1.43 (1.13-1.81)				.24
≥ 10	4 (3275)	1.76 (1.35-2.25)				
Diagnosis vs Symptoms						
Clinical	4 (2991)	1.71 (1.33-2.19)				.41
Symptoms	5 (3643)	1.48 (1.17-1.87)				
Quality						
High	3 (1741)	1.59 (1.18-2.16)				.95
Low	6 (4893)	1.57 (1.28-1.93)				
Continent						
Europe	3 (896)	1.49 (0.97-2.28)				.86
US	5 (5129)	1.61 (1.29-2.01)				
NZ	1 (609)	1.77 (1.13-2.78)				

	Nr. of studies (Sample size)	OR (95% CI) [*P* value]	Q-Statistic	*P* value Heterogeneity	I^2 value	*P* value between groups
D baseline → BMI 25 – 29.99 follow-up						
Overall studies						
Unadjusted	7 (4382)	1.20 (0.87-1.66) [.26]	19.06	< .01	68.52	.26
Adjusted	3 (3507)	0.98 (0.83-1.16) [.81]	1.71	.43	0	
Subgroup analyses						
Sex						
Females	3 (4267)	1.11 (1.02-1.22)				.51
Males	3 (4267)	1.07 (0.98-1.16)				
Mean age at baseline, years						
< 20	4 (3391)	1.43 (0.83-2.47)				.22
≥ 20	3 (1189)	0.96 (0.81-1.41)				
Follow-up duration, years						
< 10	4 (1749)	0.89 (0.71-1.11)				≤ .01
≥ 10	3 (2631)	1.81 (1.29-2.54)				
Diagnosis vs Symptoms						
Clinical	2 (937)	1.17 (0.49-2.80)				.91
Symptoms	5 (3643)	1.24 (0.84-1.82)				
Quality						
High	2 (1132)	1.17 (0.80-1.70)				.83
Low	5 (4108)	1.24 (0.80-1.92)				
Continent						
Europe	3 (896)	1.32 (0.68-2.57)				.07
US	3 (2924)	1.34 (0.95-1.91)				
NZ	1 (760)	0.78 (0.55-1.10)				

Table 2. Findings for overall and subgroup analyses of depression exposure and development of obesity and overweight.
Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in squared meters); CI, confidence interval; NZ, New Zealand; OR, odds ratio; US, United States.

Depression as a predictor of obesity and overweight at follow-up

Table 2 presents the findings for overall and subgroup analyses of depression exposure and obesity. The pooled odds ratio of the nine studies examining the effect of depression on obesity over time was 1.58 (95%CI: 1.33-1.87, $p \leq .001$) (Table 2, Figure 3). The pooled adjusted odds ratio was slightly lower (OR=1.40, 95% CI: 1.15-1.71). The heterogeneity was zero (Q = 4.43, p=.82, I^2 = 0%), and no outliers were identified.

Subgroup analyses did not show any significant differences between subgroups. The publication bias tests indicated a trend and the estimated number of imputed studies was 5 (Egger's test intercept=1.71, SE=1.03, p=.07; Duvall & Tweedie adjusted OR=1.13; 95% CI: 0.90-1.41).

The pooled odds ratio for depression exposure on overweight was 1.20 (95% CI: 0.87-1.66, p=.26) (Table 2, Figure 3). Removing the outlier[17] did not change the results. Performing subgroup analyses, a significant association was found with regard to the follow-up duration, indicating that an association is present when subjects are exposed to depression for a longer period of time (i.e. follow-up ≥ 10 years). Other subgroup analyses did not show significant differences, but demonstrated a trend for the continent of origin (p= .07). Again, we found a trend for the possibility of publication bias (Egger's test intercept= 2.07, SE=1.24, p=.08; Duvall & Tweedie: adjusted OR=0.98; 95% CI: 0.75-1.27; number of imputed studies=3).

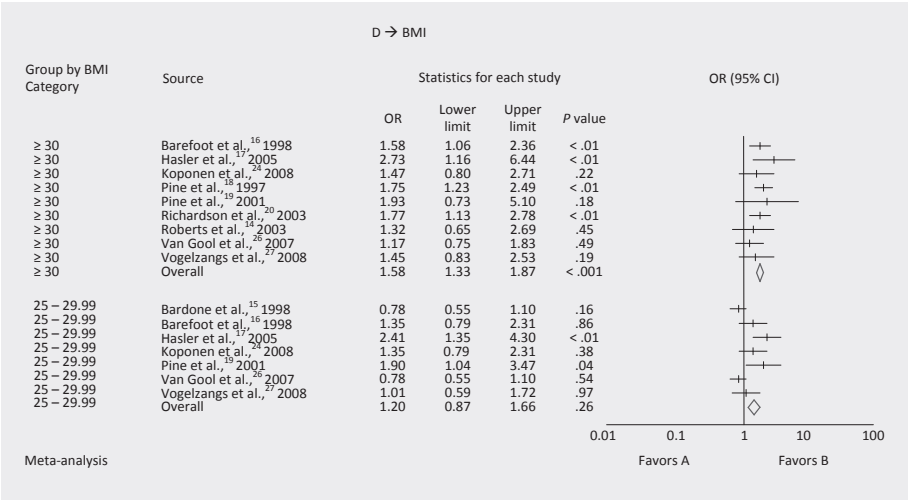

Figure 3. Forest plot of all studies describing baseline depression (D) as a predictor of developing obesity (body mass index [BMI] [calculated as weight in kilograms divided by height in squared meters] ≥ 30) and overweight (BMI 25 – 29.99) during follow-up. Favors A = negative association between depression and BMI. Favors B = positive association between depression and BMI. OR indicates odds ratio; CI, confidence interval.

Source	Obesity / Overweight	Type of Depression Assessment	Continent	Mean Age at Baseline, years	Follow-up, years	Adjustment for	Quality Score	Sample Size[a]
Exposure Obesity/Overweight → Outcome Depression								
Anderson et al.,[21] 2007	+/+	Clinical diagnosis	US	15	20	Sex	10	674
Bjerkeset et al.,[22] 2008[b]	+/+	Depressive symptoms	Europe	49	11	Sex	7	44 396
Herva at al.,[11] 2006[b]	+/+	Depressive symptoms	Europe	14	17	Sex	8	3125
Kasen et al.,[23] 2008	+/+	Depressive symptoms	US	27	28	Age	7	544
Koponen et al.,[24] 2008	+/+	Depressive symptoms	Europe	47	7		9	472
Roberts et al.,[14] 2003	+/-	Clinical diagnosis	US	63	5		8	1748
Sachs-Ericsson et al.,[25] 2007	+/+	Depressive symptoms	US	72	3		7	3981
van Gool et al.,[26] 2007	+/+	Depressive symptoms	Europe	49	6		8	447
Total								**55 387**
Exposure Depression → Outcome Obesity/Overweight								
Bardone et al.,[15] 1998	-/+	Clinical diagnosis	NZ	18	8	Sex	7	760
Barefoot et al.,[16] 1998	+/+	Depressive symptoms	US	19	22	Sex	7	2087
Hasler et al.,[17] 2005	+/+	Clinical diagnosis	Europe	19	20		8	367[c]
Koponen et al.,[24] 2008	+/+	Depressive symptoms	Europe	47	7		9	472
Pine et al.,[18] 1997	+/-	Clinical diagnosis	US	14	10	Sex	5	644[c]
Pine et al.,[19] 2001	+/+	Clinical diagnosis	US	11	15		7	177[c]
Richardson et al.,[20] 2003	+/-	Clinical diagnosis	NZ	19	7	Sex	11	609
Roberts et al.,[14] 2003	+/-	Clinical diagnosis	US	63	5		8	1561
van Gool et al.,[26] 2007	+/+	Depressive symptoms	Europe	49	6		8	57
Vogelzangs et al.,[27] 2008	+/+	Depressive symptoms	US	73	5	Sex	9	660
Total								**7196**

Table 3. Characteristics of included studies.

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in squared meters); NZ, New Zealand; US, United States; +, the article discusses an association with overweight or obesity; –, the article does not discuss an association with overweight or obesity. [a] For exposure Obesity/Overweight → Outcome Depression, this is the number of participants included in the analysis with an obese or overweight BMI at baseline and depression status at follow-up, meaning analyses were performed based on a non-depressed population at baseline. For Exposure Depression→Outcome Obesity/Overweight, this is the number of participants included in the analysis with depression status at baseline and an obese or overweight BMI at follow-up, meaning analyses were performed based on a normal-weight population at baseline. [b] Because depression status was only measured at follow-up, the baseline population could also include depressed individuals at baseline. Therefore, the sample size given in the article was used and not the sample size indicating the number of non-depressed participants at baseline. [c] Exact numbers are not available. This is the sample size of all included participants in the study.

Discussion

To our knowledge, this is the first meta-analysis examining longitudinally whether overweight and obesity increase the risk of developing depression and whether depression increases the risk of developing overweight and obesity. We found bi-directional associations between depression and obesity: obese persons had a 55%-increased risk of developing depression over time, whereas depressed persons had a 58% increased risk of becoming obese. The association between depression and obesity was stronger than the association between depression and overweight, which reflects a dose-response gradient.

Our longitudinal results provided additional, innovative insights into the already established cross-sectional association between depression and obesity. Interestingly, the results of our longitudinal meta-analysis found a larger pooled effect size (ORs between 1.20 and 1.58) than the pooled OR of 1.18 reported in the cross-sectional meta-analysis of de Wit.[6] Possibly time plays a role in the association between depression and obesity. The unfavourable effect of depression on development of obesity, and the effect of obesity on development of depression may be reinforced by time. The earlier described cross-sectional association was only present in females. However, our longitudinal meta-analysis confirms a reciprocal association between obesity and depression in both men and women.

Although evidence of a biological link between overweight, obesity and depression remains complex and not definitive,[8-10;42] it seems relevant to highlight the most current lines of reasoning within the possibility of a biological pathway. First we will discuss the direction of obesity exposure on depression outcome. Obesity can be seen as an inflammatory state, as weight gain has shown to activate inflammatory pathways,[43;44] and inflammation in turn has been associated with depression,[45-47] which in these studies was assessed by means of a depressive symptom report. As inflammation plays a role in both obesity and depression, inflammation could be the mediator of the association. Also, the hypothalamic-pituitary-adrenal axis (HPA-axis) might play a role, as obesity might involve HPA-axis dysregulation,[48;49] and HPA-axis dysregulation is well known to be involved in a depression. [50;51] Through HPA-axis dysregulation obesity might cause development of depression. Finally, obesity involves increased risks of diabetes and increased insulin resistance[52] which could induce alterations in the brain[53] and increase the risk of depression.[54] In addition to biological mechanisms, psychological pathways should be mentioned. Being overweight and the perception of overweight increases psychological distress.[55;56] In both the United States and Europe thinness is considered a beauty ideal, and partly due to social acceptance and sociocultural factors, obesity may increase body dissatisfaction and decrease self-esteem which are risk factors for depression.[57] Disturbed eating patterns and eating disorders, as well as experiencing physical pain as direct consequences of obesity, are also known to increase the risk of depression.[58;59]

In our sub analysis the effect of obesity on the development of depression was found to be stronger in American studies. Although it is not likely that biological mechanisms underlying

the obesity and depression onset risk are different across cultures, the sociocultural mechanisms could be different and more stringent in one culture than the other. In addition, as mean adult BMI is higher in the United States compared to different European countries,[60] among the obese persons in the US, the average BMI may be higher than among the obese persons in Europe, and consequently, the observed difference across continents could partly indicate a dose-response association. The association of baseline obesity was also more pronounced among subjects whose depression at follow-up was assessed by means of a clinical interview, rather than using a self-reporting questionnaire. This could be due to a higher preciseness of the depression outcome when confirmed by a psychiatric diagnosis, whereas depressive symptoms may be more often biased by confounding covariates. It also clearly indicates that obesity may really cause a clinically relevant and severe psychiatric outcome.

The fact that depression causes an increase of weight over time may also be caused by neuroendocrine disturbances. Bjorntorp[61] argued that depression induces (abdominal) obesity through long-term activation of the HPA-axis. Cortisol, in the presence of insulin, inhibits lipid mobilizing enzymes, a process mediated by glucocorticoid receptors which are found in fat depots and especially in intra-abdominal visceral fat.[62] Another important mechanism is through the adoption of an unhealthy lifestyle, such as insufficient physical exercise and unhealthy dietary preferences, possibly leading to obesity. Finally, the use of antidepressants is known to possibly induce weight gain,[10] though many of the included studies were community based studies in which depressed subjects often do not undergo pharmacological treatment. In addition, the results of studies using a clinical diagnosis for depression, in which subjects were more likely to be treated with antidepressants, were not different from results of studies that used symptoms of depression.

This study had several limitations. First, the search was restricted to a computerized search for English literature. Nonetheless, we are not aware of missing non-English written literature, as our literature search or hand-search for references did not yield any empirical longitudinal studies in other languages. Second, unpublished literature was not included, possibly resulting in a slight increased risk of publication bias for the included studies on baseline depression. However, we feel we included the majority of available longitudinal articles, which was also confirmed by the Egger's tests we performed, which did not suggest selective publication bias. A third limitation is that although the total number of included subjects is substantial, the number of included manuscripts is relatively small. Three articles could not be included because they did not include the appropriate available effect size: Forman-Hofmann and Anderson[39;40] expressed weight outcomes in terms of weight change, and Franko[63] presented obesity outcomes as a function of increase or decrease of depressive symptoms and depression outcomes as a function of weight loss and weight gain. However, the results of these excluded studies were comparable since they all supported evidence of a longitudinal link between depression and obesity, and consequently exclusion not likely

impacted the conclusion of our meta-analysis. Finally, we were not able to broadly adjust for potential covariates, as it was only possible to analyse adjustments for age and gender. None of the included studies reported on factors such as family history, hormonal status or the use of medication. Therefore true effects and magnitude of possible predictors and covariates remain unknown, due to the lacking possibility to examine an extensive range of conjectured factors.

Longitudinal epidemiological research is especially warranted to further establish the moderators and underlying mechanisms that link obesity to the onset of depression and depression to the onset of obesity. Additionally, these studies should examine more clearly the potential roles of e.g. depression characteristics (e.g. atypical versus melancholic features), medication use, physical activity or dietary patterns.

Despite these limitations, the available data sufficiently leads to the conclusion that depression and obesity interact reciprocally. The results were statistically highly significant and heterogeneity turned out to be low according to statistical guidelines.[33]

Our findings of a longitudinal bidirectional association between depression and obesity are important for clinical practice. As weight gain appears to be a late consequence of depression, care providers should be aware that within depressive patients weight should be monitored. In overweight or obese patients mood should be monitored. This awareness could lead to prevention, early detection and co-treatment for the ones at risk, which could ultimately reduce the burden of both conditions. We sincerely hope this work inspires future research to clarify how two major health problems interact, thus being able to improve prevention and treatment strategies.

References

1. Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. *PLoS Med* 2006;3:e442.
2. Murray CJ, Lopez AD. Alternative projections of mortality and disability by cause 1990-2020: Global Burden of Disease Study. *Lancet* 1997;349:1498-1504.
3. Penninx BW, Beekman AT, Honig A et al. Depression and cardiac mortality: results from a community-based longitudinal study. *Arch Gen Psychiatry* 2001;58:221-227.
4. WHO. Obesity and overweight. 2009.
5. Scott KM, Bruffaerts R, Simon GE et al. Obesity and mental disorders in the general population: results from the world mental health surveys. *Int J Obes (Lond)* 2008;32:192-200.
6. de Wit L, Luppino F, van Straten A, Penninx B, Zitman F, Cuijpers P. Depression and obesity: a meta-analysis of community-based studies. *Psychiatry Res* 2010;178:230-235.
7. Faith MS, Matz PE, Jorge MA. Obesity-depression associations in the population. *J Psychosom Res* 2002;53:935-942.
8. Atlantis E, Baker M. Obesity effects on depression: systematic review of epidemiological studies. *Int J Obes (Lond)* 2008;32:881-891.
9. Bornstein SR, Schuppenies A, Wong ML, Licinio J. Approaching the shared biology of obesity and depression: the stress axis as the locus of gene-environment interactions. *Mol Psychiatry* 2006;11:892-902.
10. Stunkard AJ, Faith MS, Allison KC. Depression and obesity. *Biol Psychiatry* 2003;54:330-337.
11. Herva A, Laitinen J, Miettunen J et al. Obesity and depression: results from the longitudinal Northern Finland 1966 Birth Cohort Study. *Int J Obes (Lond)* 2006;30:520-527.
12. Roberts RE, Kaplan GA, Shema SJ, Strawbridge WJ. Are the obese at greater risk for depression? *Am J Epidemiol* 2000;152:163-170.
13. Roberts RE, Strawbridge WJ, Deleger S, Kaplan GA. Are the fat more jolly? *Ann Behav Med* 2002;24:169-180.
14. Roberts RE, Deleger S, Strawbridge WJ, Kaplan GA. Prospective association between obesity and depression: evidence from the Alameda County Study. *Int J Obes Relat Metab Disord* 2003;27:514-521.
15. Bardone AM, Moffitt TE, Caspi A, Dickson N, Stanton WR, Silva PA. Adult physical health outcomes of adolescent girls with conduct disorder, depression, and anxiety. *J Am Acad Child Adolesc Psychiatry* 1998;37:594-601.
16. Barefoot JC, Heitmann BL, Helms MJ, Williams RB, Surwit RS, Siegler IC. Symptoms of depression and changes in body weight from adolescence to mid-life. *Int J Obes Relat Metab Disord* 1998;22:688-694.
17. Hasler G, Pine DS, Kleinbaum DG et al. Depressive symptoms during childhood and adult obesity: the Zurich Cohort Study. *Mol Psychiatry* 2005;10:842-850.
18. Pine DS, Cohen P, Brook J, Coplan JD. Psychiatric symptoms in adolescence as predictors of obesity in early adulthood: a longitudinal study. *Am J Public Health* 1997;87:1303-1310.
19. Pine DS, Goldstein RB, Wolk S, Weissman MM. The association between childhood depression and adulthood body mass index. *Pediatrics* 2001;107:1049-1056.

20. Richardson LP, Davis R, Poulton R et al. A longitudinal evaluation of adolescent depression and adult obesity. *Arch Pediatr Adolesc Med* 2003;157:739-745.

21. Anderson SE, Cohen P, Naumova EN, Jacques PF, Must A. Adolescent obesity and risk for subsequent major depressive disorder and anxiety disorder: prospective evidence. *Psychosom Med* 2007;69:740-747.

22. Bjerkeset O, Romundstad P, Evans J, Gunnell D. Association of Adult Body Mass Index and Height with Anxiety, Depression, and Suicide in the General Population: The HUNT Study. *Am J Epidemiol* 2007.

23. Kasen S, Cohen P, Chen H, Must A. Obesity and psychopathology in women: a three decade prospective study. *Int J Obes (Lond)* 2008;32:558-566.

24. Koponen H, Jokelainen J, Keinanen-Kiukaanniemi S, Kumpusalo E, Vanhala M. Metabolic syndrome predisposes to depressive symptoms: a population-based 7-year follow-up study. *J Clin Psychiatry* 2008;69:178-182.

25. Sachs-Ericsson N, Burns AB, Gordon KH et al. Body mass index and depressive symptoms in older adults: the moderating roles of race, sex, and socioeconomic status. *Am J Geriatr Psychiatry* 2007;15:815-825.

26. van Gool CH, Kempen GI, Bosma H, van Boxtel MP, Jolles J, van Eijk JT. Associations between lifestyle and depressed mood: longitudinal results from the Maastricht Aging Study. *Am J Public Health* 2007;97:887-894.

27. Vogelzangs N, Kritchevsky SB, Beekman AT et al. Depressive symptoms and change in abdominal obesity in older persons. *Arch Gen Psychiatry* 2008;65:1386-1393.

28. Joshi AV, Day D, Lubowski TJ, Ambegaonkar A. Relationship between obesity and cardiovascular risk factors: findings from a multi-state screening project in the United States. *Curr Med Res Opin* 2005;21:1755-1761.

29. Kenchaiah S, Evans JC, Levy D et al. Obesity and the risk of heart failure. *N Engl J Med* 2002;347:305-313.

30. Kuijpers T, van der Windt DA, van der Heijden GJ, Bouter LM. Systematic review of prognostic cohort studies on shoulder disorders. *Pain* 2004;109:420-431.

31. Van der Kooy K., van Hout H, Marwijk H, Marten H, Stehouwer C, Beekman A. Depression and the risk for cardiovascular diseases: systematic review and meta analysis. *Int J Geriatr Psychiatry* 2007;22:613-626.

32. Borenstein M., Hedges L.V., Higgins J., Rothstein H. Comprehensive Meta-analysis [computer program], Version 2. *Engelwood, NJ: Biostat* 2005.

33. Lipsey M.W.Wilson D.B. Practical Meta-Analysis. *SAGE Publications Inc* 2001.

34. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557-560.

35. Rothstein H, Sutton A.J., Borenstein M. Publication Bias in Meta-analysis : Prevention, Assessment And Adjustments. *John Wiley & Sons Inc* 2005.

36. Egger M, Davey SG, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629-634.

37. Borenstein M., Hedges L.V., Higgins J., Rothstein H. Introduction to Meta-Analysis. *John Wiley & Sons Inc* 2009.

38. Duval S, Tweedie R. Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics* 2000;56:455-463.

39. Anderson SE, Cohen P, Naumova EN, Must A. Association of depression and anxiety disorders with weight change in a prospective community-based study of children followed up into adulthood. *Arch Pediatr Adolesc Med* 2006;160:285-291.

40. Forman-Hoffman VL, Yankey JW, Hillis SL, Wallace RB, Wolinsky FD. Weight and depressive symptoms in older adults: direction of influence? *J Gerontol B Psychol Sci Soc Sci* 2007;62:S43-S51.

41. Laumann EO, Kang JH, Glasser DB, Rosen RC, Carson CC. Lower urinary tract symptoms are associated with depressive symptoms in white, black and Hispanic men in the United States. *J Urol* 2008;180:233-240.

42. WHO, 2009. Global Database on Body Mass Index, Adapted from WHO 1995, WHO 2000 and WHO 2004.

43. Bean MK, Stewart K, Olbrisch ME. Obesity in America: implications for clinical and health psychologists. *J Clin Psychol Med Settings* 2008;15:214-224.

44. Emery CF, Fondow MD, Schneider CM et al. Gastric bypass surgery is associated with reduced inflammation and less depression: a preliminary investigation. *Obes Surg* 2007;17:759-763.

45. Bremmer MA, Beekman AT, Deeg DJ et al. Inflammatory markers in late-life depression: results from a population-based study. *J Affect Disord* 2008;106:249-255.

46. Shoelson SE, Herrero L, Naaz A. Obesity, inflammation, and insulin resistance. *Gastroenterology* 2007;132:2169-2180.

47. Vaccarino V, Johnson BD, Sheps DS et al. Depression, inflammation, and incident cardiovascular disease in women with suspected coronary ischemia: the National Heart, Lung, and Blood Institute-sponsored WISE study. *J Am Coll Cardiol* 2007;50:2044-2050.

48. Milaneschi Y, Corsi AM, Penninx BW, Bandinelli S, Guralnik JM, Ferrucci L. Interleukin-1 Receptor Antagonist and Incident Depressive Symptoms Over 6 Years in Older Persons: The InCHIANTI Study. *Biol Psychiatry* 2008.

49. Pasquali R, Vicennati V. Activity of the hypothalamic-pituitary-adrenal axis in different obesity phenotypes. *Int J Obes Relat Metab Disord* 2000;24 Suppl 2:S47-S49.

50. Belanoff JK, Kalehzan M, Sund B, Fleming Ficek SK, Schatzberg AF. Cortisol activity and cognitive changes in psychotic major depression. *Am J Psychiatry* 2001;158:1612-1616.

51. Walker BR. Activation of the hypothalamic-pituitary-adrenal axis in obesity: cause or consequence? *Growth Horm IGF Res* 2001;11 Suppl A:S91-S95.

52. Holsboer F. The corticosteroid receptor hypothesis of depression. *Neuropsychopharmacology* 2000;23:477-501.

53. Lee WJ, Lee YC, Ser KH, Chen JC, Chen SC. Improvement of insulin resistance after obesity surgery: a comparison of gastric banding and bypass procedures. *Obes Surg* 2008;18:1119-1125.

54. Huber TJ, Issa K, Schik G, Wolf OT. The cortisol awakening response is blunted in psychotherapy inpatients suffering from depression. *Psychoneuroendocrinology* 2006;31:900-904.

55. Ajilore O, Haroon E, Kumaran S et al. Measurement of brain metabolites in patients with type 2 diabetes and major depression using proton magnetic resonance spectroscopy. *Neuropsychopharmacology* 2007;32:1224-1231.

56. Atlantis E, Ball K. Association between weight perception and psychological distress. *Int J Obes (Lond)* 2008;32:715-721.

57. Derenne JL, Beresin EV. Body image, media, and eating disorders. *Acad Psychiatry* 2006;30:257-261.

58. Beesdo K, Jacobi F, Hoyer J, Low NC, Hofler M, Wittchen HU. Pain associated with specific anxiety and depressive disorders in a nationally representative population sample. *Soc Psychiatry Psychiatr Epidemiol* 2009.

59. Hoek HW, van Harten PN, Hermans KM, Katzman MA, Matroos GE, Susser ES. The incidence of anorexia nervosa on Curacao. *Am J Psychiatry* 2005;162:748-752.

60. Gadalla T, Piran N. Psychiatric comorbidity in women with disordered eating behavior: a national study. *Women Health* 2008;48:467-484.

61. Bjorntorp P. Do stress reactions cause abdominal obesity and comorbidities? *Obes Rev* 2001;2:73-86.

62. Bjorntorp P. The regulation of adipose tissue distribution in humans. *Int J Obes Relat Metab Disord* 1996;20:291-302.

63. Franko DL, Striegel-Moore RH, Thompson D, Schreiber GB, Daniels SR. Does adolescent depression predict obesity in black and white young adult women? *Psychol Med* 2005;35:1505-1513.