Overweight, Obesity, and Depression

A Systematic Review and Meta-analysis of Longitudinal Studies

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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 bidirectional relation between depression and overweight (body mass index 25-29.99) or obesity (body mass index ≥30) 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 (N=58 745) to estimate the effect of possible moderators (sex, age, depression severity). Obesity at baseline increased the risk of onset of depression at follow-up (unadjusted OR, 1.55; 95% confidence interval [CI], 1.22-1.98; $P<.001$). 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; $P<.01$). This association was statistically significant among adults (aged 20-59 years and ≥60 years) but not among younger persons (aged <20 years). Baseline depression (symptoms and disorder) was not predictive of overweight over time. However, depression increased the odds for developing obesity (OR, 1.58; 95% CI, 1.33-1.87; $P<.001$). 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.

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BOTH DEPRESSION AND OBESITY are widely spread problems with major public health implications.[1,2] Because of 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[9] of 17 community-based cross-sectional studies among adults showed a positive overall association between depression and obesity (defined as a body mass index [BMI] [calculated as weight in kilograms divided by height in meters squared] ≥30 or a waist-hip ratio ≥102 cm for men and ≥88 for women). de Wit et al[9] found an overall odds ratio (OR) of 1.18, confirming that depression is associated with an 18% increased risk of being obese. Only sex acted as a moderating factor; in subgroup analyses the association was found in women but not in men, 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[10,11] or through unhealthy lifestyles, develop more obesity over time, whereas it is also possible that obesity, eg, through its negative effects on self-image or somatic consequences, results in the development of depression over time. Longitudinal studies are

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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[8] did discuss some longitudinal studies[12-15] in their overview article, 3 of 4 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,[16-21] and since then a considerable number of longitudinal studies have been published,[22-28] indicating that the volume of evidence on this topic has rapidly increased. Consequently, a meta-analysis that would examine the longitudinal, bidirectional evidence of the association between depression and obesity would be justified as well as needed. 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 unfavorable health outcomes.[29,30]

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 sex, 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 (eg, pregnant women or a population with a specific somatic disease) were excluded. Articles with a follow-up period of less than 1 year, not expressing weight as BMI, or not specifying the way depression was assessed were also excluded. Studies were subdivided in 2 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 articles presenting data on the same cohort differing only in follow-up length, articles presenting data on the longest period were chosen. All relevant citations were screened by 2 of us (F.S.L. and P.F.B.) on the earlier-mentioned criteria.

For inclusion in the meta-analysis, effect sizes had to be expressed as 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 article was contacted and asked to provide the ORs of the association of interest. For each analysis, only 1 effect size per included article was used. Because 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 2 of us independently (F.S.L. and P.F.B.) using a 15-item checklist adapted from Kuijpers et al[31] (eTable, http://www.archgenpsychiatry.com). 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% or more of the maximal possible score, in this case, 9 points or more. The 60% cutoff is a commonly used cutoff point for quality assessments.[31,32] Disagreements among reviewers were resolved in a consensus meeting.

STATISTICAL ANALYSES

Data management, transformation of effect sizes, and calculation of the pooled mean effect sizes were performed using Comprehensive Meta-analysis (CMA) version 2.0.[33] Available data were divided into 2 directions: BMI categories as predictors of depression at follow-up or depression at baseline as a predictor of BMI categories at follow-up. The first comparison included data on initially nondepressed participants followed up and screened on depression at follow-up, although for 2 of the included studies, depression was not assessed at baseline.[12,23] The latter comparison included only data on normal-weight individuals who were followed up for development of depression at follow-up. The analyses were conducted separately for obesity (BMI≥30) and overweight (BMI 25-29.99) categories to see whether there was a difference in effect size between overweight and obesity.

Since considerable heterogeneity was expected, all analyses were performed with a random-effects model. To assess heterogeneity between studies, Q-statistics were calculated. A statistically significant Q indicates a heterogeneous distribution of ORs between studies, meaning that systematic differences, possibly influencing the results, are present.[34] In addition, the I^2 was calculated to describe the percentages of total variation across studies caused by heterogeneity. A 0% value means no heterogeneity, and higher values represent an increase in heterogeneity. Generally, heterogeneity is categorized at 25% (low), 50% (moderate), and 75% (high).[35]

All presented results are based on the 15 included studies. 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 nonsymmetrically distributed across the combined effect size.[36] The presence of publication bias was further tested using the Egger method,[37] 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.[38] If publication bias was observed, the Duval and Tweedie trim and fill procedure[39] 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 modified the depression-BMI association, subgroup analy-

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Table 1. Findings for Overall and Subgroup Analyses of Obesity and Overweight Exposure and the Onset of Depression

	No. of Studies (Sample Size)	OR (95% CI) [*P* Value]	Q-Statistic	*P* Value Heterogeneity	I^2 Value	*P* Value Between Groups
		BMI ≥ 30 Baseline→Depression 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						
F	3 (48 195)	1.67 (1.11-2.51)				.81
M	3 (48 195)	1.31 (1.13-1.15)				
Mean age at baseline, y						
<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, y						
<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)				
		BMI 25-29.99 Baseline→Depression 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						
F	3 (48 195)	0.98 (0.80-1.20)				.43
M	3 (48 195)	1.30 (0.78-2.17)				
Mean age at baseline, y						
<20	2 (3799)	1.05 (0.86-1.29)				.07
20-60	4 (45 859)	1.48 (1.19-1.83)				
>60	1 (3981)	1.77 (1.00-0.32)				
Follow-up duration, y						
<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)				

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CI, confidence interval; OR, odds ratio; US, United States.

ses were performed. Sensitivity analyses were conducted to estimate the effect of sex, mean age at baseline (subdivided into 3 categories: <20 years; 20-59 years; and ≥60 years), length of follow-up (<10 years; ≥10 years), clinical diagnosis or depressive symptoms, quality of article (low, <60%; high, ≥60%), and continent of origin (American or European). For estimation of sex differences, the available adjusted ORs for women were compared with the adjusted ORs for men. We performed analyses only in subgroups containing 2 or more articles, though subgroups with 1 article are mentioned in the results (**Table 1** and **Table 2**).

For articles providing additional adjusted ORs, we compared the adjusted and unadjusted effect sizes. Adjusted effect sizes were only available for the variables sex and age (**Table 3**).

RESULTS

INCLUDED AND EXCLUDED STUDIES

Combining the key words and medical subject headings in the literature search, 2937 articles were found (**Figure 1**). The first screening, designed to select possibly relevant articles according to the previously de-

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Table 2. Findings for Overall and Subgroup Analyses of Depression Exposure and Development of Obesity and Overweight

	No. of Studies (Sample Size)	OR (95% CI) [*P* Value]	Q-Statistic	*P* Value Heterogeneity	I^2 Value	*P* Value Between Groups
		Depression 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						
F	4 (4000)	2.01 (1.11-3.65)				.50
M	4 (4000)	1.43 (0.96-2.13)				
Mean age at baseline, y						
<20	5 (3884)	1.76 (1.42-2.18)				.26
20-60	2 (529)	1.27 (0.88-1.82)				
>60	2 (2221)	1.40 (0.90-2.17)				
Follow-up duration, y						
<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)				
		Depression 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						
F	3 (4267)	1.11 (1.02-1.22)				.51
M	3 (4267)	1.07 (0.98-1.16)				
Mean age at baseline, y						
<20	4 (3391)	1.43 (0.83-2.47)				.22
≥20	3 (1189)	0.96 (0.81-1.41)				
Follow-up duration, y						
<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)				

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CI, confidence interval; NZ, New Zealand; OR, odds ratio; US, United States.

scribed 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.[40] 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[13] discussed the same cohort as one of the included articles,[15] but with a shorter follow-up period. This excluded article, however, showed similar findings as the included article 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 3 studies, we did not receive this information and these studies could not be included.[41-43] Of the remaining 15 studies to be included, 1 author provided crude data[26] and all others

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Table 3. Characteristics of Included Studies

Source	Obesity/ Overweight	Type of Depression Assessment	Continent	Mean Age at Baseline, y	Follow-up, y	Adjustment for	Quality Score	Sample Size[a]
Exposure Obesity/Overweight→Outcome Depression								
Anderson et al,[22] 2007	+/+	Clinical diagnosis	US	15	20	Sex	10	674
Bjerkeset et al,[23] 2008[b]	+/+	Depressive symptoms	Europe	49	11	Sex	7	44 396
Herva et al,[12] 2006[b]	+/+	Depressive symptoms	Europe	14	17	Sex	8	3125
Kasen et al,[24] 2008	+/+	Depressive symptoms	US	27	28	Age	7	544
Koponen et al,[25] 2008	+/+	Depressive symptoms	Europe	47	7		9	472
Roberts et al,[15] 2003	+/ –	Clinical diagnosis	US	63	5		8	1748
Sachs-Ericsson et al,[26] 2007	+/+	Depressive symptoms	US	72	3		7	3981
van Gool et al,[27] 2007	+/+	Depressive symptoms	Europe	49	6		8	447
Total								**55 387**
Exposure Depression→Outcome Obesity/Overweight								
Bardone et al,[16] 1998	–/+	Clinical diagnosis	NZ	18	8	Sex	7	760
Barefoot et al,[17] 1998	+/+	Depressive symptoms	US	19	22	Sex	7	2087
Hasler et al,[18] 2005	+/+	Clinical diagnosis	Europe	19	20		8	367[c]
Koponen et al,[25] 2008	+/+	Depressive symptoms	Europe	47	7		9	472
Pine et al,[19] 1997	+/ –	Clinical diagnosis	US	14	10	Sex	5	644[c]
Pine et al,[20] 2001	+/+	Clinical diagnosis	US	11	15		7	177[c]
Richardson et al,[21] 2003	+/ –	Clinical diagnosis	NZ	19	7	Sex	11	609
Roberts et al,[15] 2003	+/ –	Clinical diagnosis	US	63	5		8	1561
van Gool et al,[27] 2007	+/+	Depressive symptoms	Europe	49	6		8	57
Vogelzangs et al,[28] 2008	+/+	Depressive symptoms	US	73	5	Sex	9	660
Total								**7196**

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); 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 nondepressed 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 nondepressed participants at baseline.

[c] Exact numbers are not available. This is the sample size of all included participants in the study.

provided data expressed as ORs. Because some studies were still ongoing after publication, some authors provided the most recent results,[16,21,26] which were used for analyses.

In the 15 studies included in the meta-analysis,[12,13,16-28] all data on obesity and overweight were expressed in terms of BMI. Overweight was defined as BMI between 25 and 29.99 and obesity, as BMI of 30 or more, according to the World Health Organization definition.[38,44] For examination of the link between overweight/obesity at baseline and development of depression at follow-up, the total number of subjects was 55 387. For the inverse relationship, the number of subjects was 7196 (Table 3). In 7 studies, a structured diagnostic interview was used, leading to a diagnosis of depressive disorder. Four studies did not specify who conducted the interview[15,16,21,22]; in 1, the interview was done by a resident in psychiatry or a psychologist[18]; and in 2 studies,[19,20] 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[14,25,27]; 5, on overweight/obesity exposure and depression at follow-up; and 7, on the inverse association. With the exception of the studies of Bjerkeset et al[23] and Herva et al[12] (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 4 articles to be of high quality (≥9 points), 1 of which[25] analyzed data in both directions and is therefore mentioned twice. The Bjerkeset et al study[23] counts an exceptionally high number of participants and is responsible for the large sample size in the overall group. Because in this study, as well as in the Herva et al study,[12] 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 OR for the association between obesity at baseline and depression at follow-up for the 8 studies in this group was 1.55, with a 95% confidence interval (CI) of 1.22 to 1.98 and a P value of $<.001$ (Table 1) (**Figure 2**). The pooled adjusted OR 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 ORs of the

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selected studies. The percentage of total variation across these studies caused by heterogeneity was small to moderate (I^2=38%). Only 1 apparent outlier was found in the generated funnel plot.[25] 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 et al[23] and Herva et al[12] (OR, 1.56; 95% CI, 1.02-2.40). The Egger test[37] and Duval and Tweedie trim and fill procedure[39] showed no significant risk of publication bias (Egger test intercept=0.39; SE=1.18; P=.38; Duvall and 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 (ie, depressive symptoms 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 symptoms (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 OR 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 OR was considerably lower (OR, 1.08; 95% CI, 1.02-1.14). After removing the studies of Bjerkeset et al and Herva et al, the OR was 1.14 (95% CI, 0.83-1.55).

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

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 OR of the 9 studies examining the effect of depression on obesity over time was 1.58 (95% CI, 1.33-1.87; P<.001) (Table 2) (**Figure 3**). The pooled adjusted OR 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 test intercept=1.71; SE=1.03; P=.07; Duvall and Tweedie adjusted OR=1.13; 95% CI, 0.90-1.41).

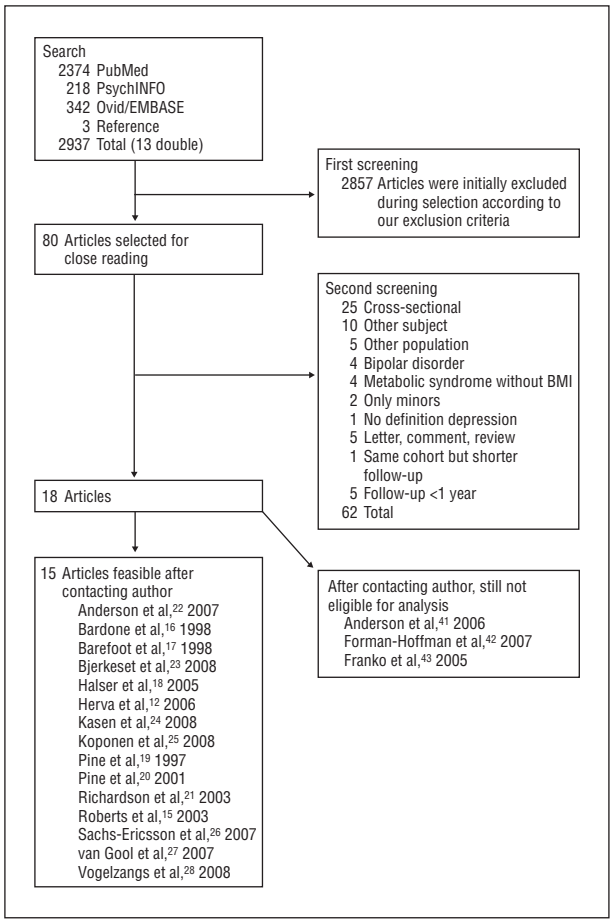

Figure 1. Flowchart illustrating the literature search and exclusion process. BMI indicates body mass index.

The pooled OR for depression exposure on overweight was 1.20 (95% CI, 0.87-1.66; P=.26) (Table 2) (Figure 3). Removing the outlier[18] 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 (ie, 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 test intercept=2.07; SE=1.24; P=.08; Duvall and Tweedie adjusted OR, 0.98; 95% CI, 0.75-1.27; number of imputed studies=3).

COMMENT

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 bidirectional 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 depres-

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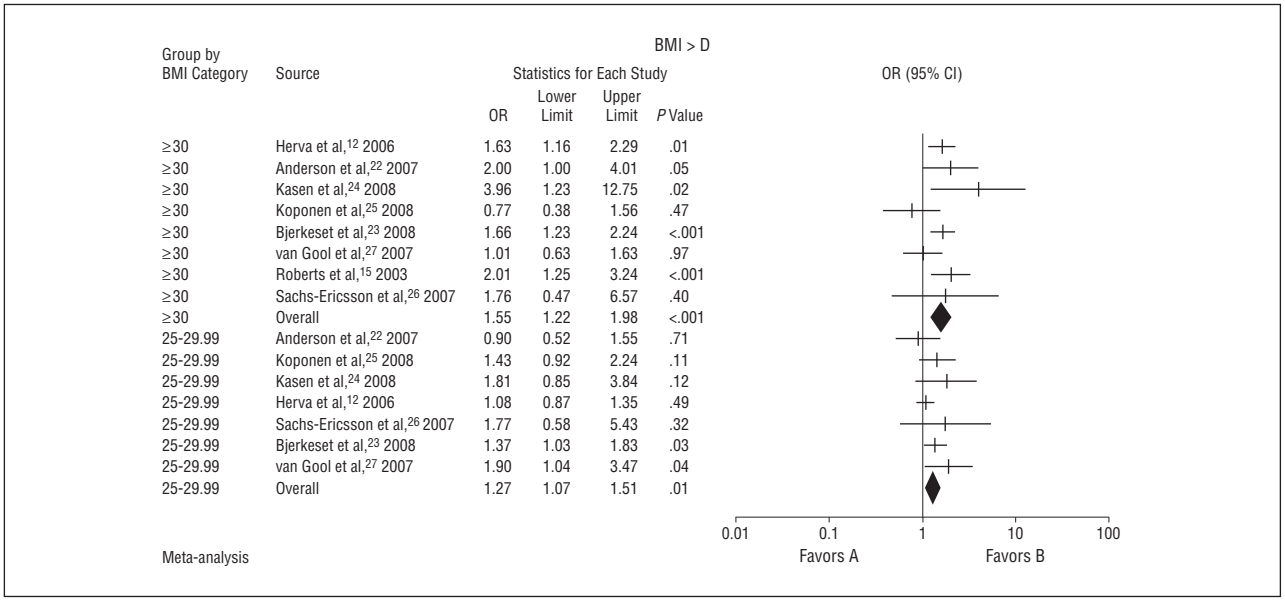

Figure 2. Forest plot of all studies describing baseline obesity (body mass index [BMI] [calculated as weight in kilograms divided by height in meters squared] ≥30) and overweight (BMI 25-29.99) with depression (D) during follow-up. Favors A=negative association between BMI and depression. Favors B=positive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

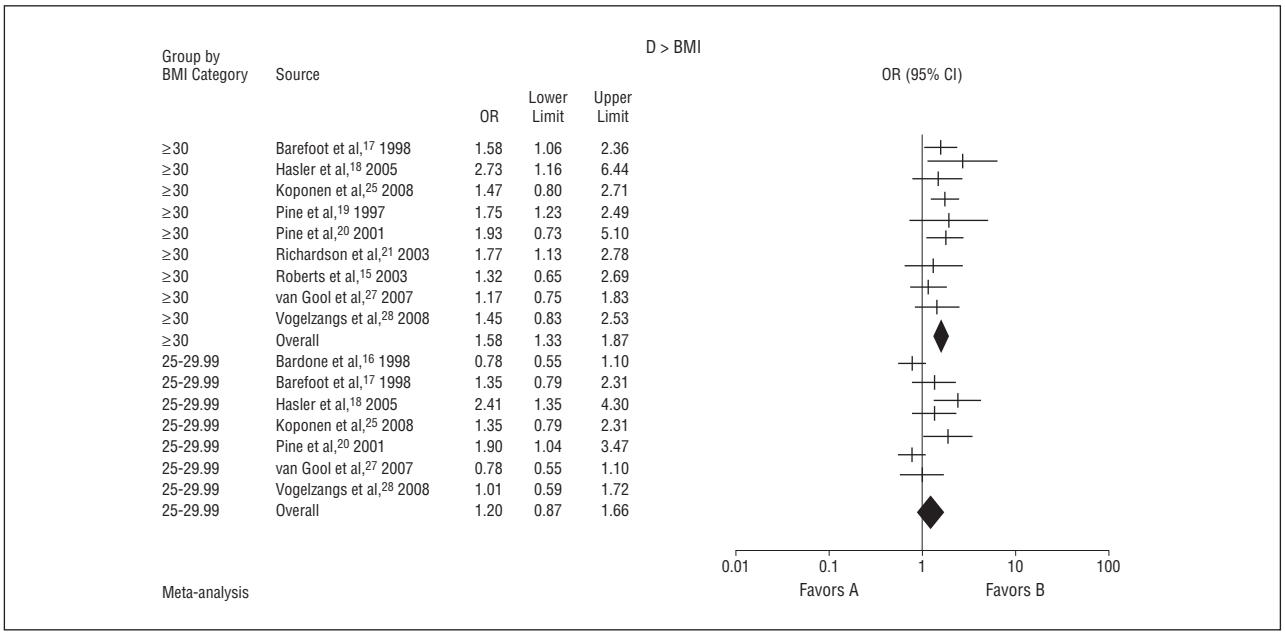

Figure 3. Forest plot of all studies describing baseline depression (D) as a predictor of developing obesity (body mass index [BMI] [calculated as weight in kilograms divided by height in meters squared] ≥30) and overweight (BMI 25-29.99) during follow-up. Favors A=negative association between depression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

sion 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 et al.[9] Possibly time plays a role in the association between depression and obesity. The unfavorable 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 women. 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,[8,10,11,45] 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

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been shown to activate inflammatory pathways[46,47] and inflammation in turn has been associated with depression,[48-50] which in these studies was assessed by means of a depressive symptom report. Because 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, because obesity might involve HPA-axis dysregulation[51,52] and HPA-axis dysregulation is well known to be involved in depression.[53,54] Through HPA-axis dysregulation, obesity might cause development of depression. Finally, obesity involves increased risks of diabetes mellitus and increased insulin resistance,[55] which could induce alterations in the brain[56] and increase the risk of depression.[57] In addition to biological mechanisms, psychological pathways should be mentioned. Being overweight and the perception of overweight increases psychological distress.[58,59] In both the United States and Europe, thinness is considered a beauty ideal, and partly because of social acceptance and sociocultural factors, obesity may increase body dissatisfaction and decrease self-esteem, which are risk factors for depression.[60] Disturbed eating patterns and eating disorders, as well as experiencing physical pain as a direct consequence of obesity, are also known to increase the risk of depression.[61,62]

In our subanalysis, 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, because mean adult BMI is higher in the United States compared with different European countries,[63] among the obese persons in the United States, 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. Björntorp[64] 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 that are found in fat depots and especially in intra-abdominal visceral fat.[65] Another important mechanism is 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 did 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-language 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 tests we performed that did not suggest selective publication bias. A third limitation is that although the total number of included subjects is substantial, the number of included articles is relatively small. Three articles could not be included because they did not include the appropriate available effect size: Anderson et al[41] and Forman-Hoffman et al[42] expressed weight outcomes in terms of weight change, and Franko et al[43] 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 did not likely impact the conclusion of our meta-analysis. Finally, we were not able to broadly adjust for potential covariates because it was only possible to analyze adjustments for age and sex. 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 because of the inability 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, for example, depression characteristics (eg, atypical vs melancholic features), medication use, physical activity, or dietary patterns.

Despite these limitations, the available data sufficiently lead 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.[35]

Our findings of a longitudinal, bidirectional association between depression and obesity are important for clinical practice. Because 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 cotreatment for the ones at risk, which

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could ultimately reduce the burden of both conditions. We sincerely hope this work inspires future research to clarify how 2 major health problems interact, thus improving prevention and treatment strategies.

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