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ORIGINAL ARTICLE

Association of metabolically healthy obesity with depressive symptoms: pooled analysis of eight studies

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The hypothesis of metabolically healthy obesity posits that adverse health effects of obesity are largely avoided when obesity is accompanied by a favorable metabolic profile. We tested this hypothesis with depressive symptoms as the outcome using cross-sectional data on obesity, metabolic health and depressive symptoms. Data were extracted from eight studies and pooled for individual-participant meta-analysis with 30 337 men and women aged 15–105 years (mean age = 46.1). Clinic measures included height, weight and metabolic risk factors (high blood pressure, high triglycerides, low high-density lipoprotein cholesterol, high C-reactive protein and high glycated hemoglobin). Depressive symptoms were assessed using clinical interview or standardized rating scales. The pooled sample comprised 7673 (25%) obese participants (body mass index $\geqslant$30 kg m^{-2}). Compared to all non-obese individuals, the OR for depressive symptoms was higher in metabolically unhealthy obese individuals with two or more metabolic risk factors (1.45; 95% confidence interval (CI) = 1.30, 1.61) and for metabolically healthy obese with $\leqslant$1 metabolic risk factor (1.19; 95% CI = 1.03, 1.37), adjusted for sex, age and race/ethnicity. Metabolically unhealthy obesity was associated with higher depression risk (OR = 1.23; 95% CI = 1.05, 1.45) compared with metabolically healthy obesity. These associations were consistent across studies with no evidence for heterogeneity in estimates (all I^2-values $<$ 4%). In conclusion, obese persons with a favorable metabolic profile have a slightly increased risk of depressive symptoms compared with non-obese, but the risk is greater when obesity is combined with an adverse metabolic profile. These findings suggest that metabolically healthy obesity is not a completely benign condition in relation to depression risk.

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INTRODUCTION

Obesity is an established risk factor for cardiovascular disease and some cancers, but may also affect mental health.[1–5] Summary estimates from meta-analyses of observational studies support an increased risk of depression among the obese,[1,4,6] although this association may not be universal.[7–9] It has been suggested that the adverse health consequences of obesity may depend on whether other metabolic risk factors are present.[10–15] Not all obese individuals suffer from common metabolic complications of obesity, such as high blood pressure, high triglycerides, low high-density lipoprotein cholesterol (HDL-C) and elevated inflammatory markers, and such obesity is regarded as metabolically healthy.[16] The hypothesis of 'metabolically healthy obesity' postulates that obesity is not a health risk in those free from metabolic abnormalities,[13] but evidence for the hypothesis is inconsistent across health outcomes.[12,16,17]

Only few studies have examined the metabolically healthy obesity hypothesis in relation to mental health. The hypothesis was recently tested in the English Longitudinal Study of Aging,[18] in which obesity appeared to be associated with depression risk more strongly in metabolically unhealthy obese than in metabolically healthy obese participants. However, the difference between the obesity groups was modest, and it is unknown whether these results are apparent in other populations. We pooled individual-participant data from eight studies with over 30 000 men and women aged 15–105 years. In doing so, we are able to examine whether obesity is differentially associated with depressive symptoms in metabolically healthy and unhealthy individuals, and also whether specific metabolic risk factors, if any, contribute to this difference.

MATERIALS AND METHODS

Participants

We searched the data collections of the Inter-University Consortium for Political and Social Research (http://www.icpsr.umich.edu/icpsrweb/ICPSR/) and the Economic and Social Data Service (http://www.esds.ac.uk/) to identify eligible large-scale cohort studies. Studies were eligible for inclusion if they contained data on obesity, five metabolic risk factors (blood pressure, HDL, triglycerides, blood glucose and C-reactive protein inflammation) and depressive symptoms, and had a sufficiently large sample size (n>1000). We located seven such cohorts: the Costa Rican Longevity and Healthy Aging Study (CRELES; n = 1731) from 2005;[19] the Midlife in the United States (MIDUS; n = 1214) biomarker sub-study from 2004 to 2009;[20] the British National Child Development Study (NCDS;

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$n = 7237$) biomedical sub-study from 2002 to 2004;[21] the National Health and Nutrition Examination Survey III (NHANES III; $n = 7790$) from 1988 to 1994; the three more recent continuous National Health and Nutrition Examination Surveys (NHANES) from 2005 to 2006 ($n = 1998$), 2007 to 2008 ($n = 2238$) and 2009 to 2010 ($n = 2406$).[22,23] In addition, we included data from the British Whitehall II study ($n = 5723$),[24] which we have previously used to examine the association between obesity and mental health.[25–27] All the studies included are well characterized (details of the cohorts are available in Supplementary Material) and were approved by the relevant local ethics committees.

Measures

In all studies, height and weight were measured in a medical examination. Body mass index (BMI) was calculated as weight in kg per (height in m).[2] Obesity was defined as BMI $\geqslant 30$ kg m^{-2} and overweight as BMI $\geqslant 25$ kg m^{-2} but below 30 kg m^{-2}. Metabolic risk markers included high blood pressure (>130 mm Hg systolic or >85 mm Hg diastolic), high triglycerides (>1.7 mmol l^{-1}), low HDL cholesterol (< 1.03 mmol l^{-1} in men, < 1.29 mmol l^{-1} in women), impaired glucose metabolism (glycated hemoglobin HA1c >6%) and high C-reactive protein (>3.0 mg dl^{-1}), as used previously in the definition of metabolically healthy obesity.[28] Except for the NCDS sample, in which detailed medication information was not available, high blood pressure was assigned also to individuals using hypertensive medication, and high blood glucose was assigned to individuals using diabetic medication. Metabolically unhealthy obesity was defined as having a BMI $\geqslant 30$ kg m^{-2} and two or more metabolic risk factors (high blood pressure, high triglycerides, low HDL cholesterol, impaired glucose metabolism, high C-reactive protein). Metabolically healthy obesity refers to obese individuals with no or one metabolic risk factor.

Depressive symptoms were assessed with the Center for Epidemiologic Studies Depression scale (CES-D)[29] in MIDUS and Whitehall II; Geriatric Depression Scale (GDS)[30] in CRELES; depression score of the Clinical Interview Schedule (CIS-R)[31] mental health interview in NCDS; Diagnostic Interview Schedule (DIS)[32] in NHANES III; and Depression Screening Questionnaire based on the Patient Health Questionnaire (PHQ)[33] in the three continuous NHANES studies. All depression measures were categorized into dichotomous outcome variables using predefined thresholds.

Statistical analysis

We examined the association of obesity (0 = BMI < 30, 1 = BMI $\geqslant$ 30) and metabolic health status (0 = no or one metabolic risk factor, 1 = two or more metabolic risk factors) with a binary depressive symptoms outcome using logistic regression, adjusted for age, sex and race/ethnicity (0 = White/Caucasian, 1 = Black/African, 2 = Other) in the basic model. Individuals with BMI $\leqslant$ 18.5 were excluded from the analysis. The associations of obesity and depressive symptoms in metabolically healthy and unhealthy individuals were calculated based on the main and interaction effects of the logistic regression model. The cohort-specific estimates were then pooled in a random-effect meta-analysis, and heterogeneity between studies was examined by I^2 statistic. To examine whether metabolic health moderated the associations of overweight with depressive symptoms, the analysis was repeated with overweight (BMI above 25 kg m^{-2} but below 30 kg m^{-2}) as the body weight risk group, using normal weight as the reference category, and excluding obese and underweight individuals from the analysis. Appropriate sampling weights were used in CRELES and all NHANES studies.

In additional analysis, the models were further adjusted for age, sex, race/ethnicity, smoking (0 = non-smoker, 1 = ex-smoker, 2 = current smoker), physical activity (self-reported frequency of leisure-time moderate and/or vigorous activity), alcohol consumption (self-reported frequency of drinking alcohol) and educational level (or occupational level in Whitehall II). Metabolically unhealthy individuals may also carry more weight, especially abdominal visceral fat,[34] than their metabolically healthy counterparts in the same obesity category, which might be related to differences in depressive symptoms. This possibility was examined by adjusting the analysis for waist circumference. To avoid overlap between obesity status and waist circumference in the same model, we created a new variable indicating the participant's deviation from the average waist circumference of his/her obesity status group (non-obese or obese), and

Table 1. Characteristics of the included cohorts

	CRELES	*MIDUS*	*NCDS*	*NHANES III*	*NHANES 2005*	*NHANES 2007*	*NHANES 2009*	*Whitehall II*
Participants (*n*)	1731	1214	7237	7790	1998	2238	2406	5723
Age (years, s.d.)	73.2 (8.3)	54.6 (11.7)	46.0	26.8 (7.1)	45.1 (19.8)	49.4 (18.4)	48.0 (18.4)	61.0 (5.9)
Age range (min–max)	60–105	34–84	46	15–39	18–85	18–80	18–80	50–74
Sex (% females)	54.7 (946)	56.3 (683)	49.7 (3594)	53.7 (4187)	50.8 (1014)	49.7 (1112)	51.4 (1236)	28.1 (1606)
Ethnic background								
White/Caucasian	—	93.6 (934)	—	28.2 (2193)	48.5 (969)	47.9 (1072)	47.8 (1150)	92.4 (5284)
Black/African	—	2.7 (27)	—	32.9 (2566)	22.9 (458)	18.7 (419)	16.4 (394)	4.8 (272)
Other	—	3.7 (37)	—	38.9 (3031)	28.6 (571)	33.4 (747)	35.8 (862)	2.9 (163)
Depressive symptoms	9.7 (168)	16.1 (195)	16.5 (1195)	4.9 (383)	5.9 (118)	8.4 (188)	8.6 (206)	15.0 (861)
Body mass index (kg m^{-2}, s.d.)	26.9 (4.8)	29.7 (6.5)	27.3 (4.8)	26.2 (5.8)	29.1 (7.2)	28.8 (6.2)	29.2 (6.8)	26.8 (4.3)
Normal weight	37.1 (643)	23.6 (287)	34.6 (2502)	51.0 (3976)	31.2 (623)	28.7 (643)	28.0 (673)	36.1 (2066)
Overweight	40.9 (708)	35.7 (433)	41.9 (3030)	28.4 (2213)	32.7 (654)	35.7 (798)	34.5 (831)	45.2 (2584)
Obese	22.0 (380)	40.7 (494)	23.6 (1705)	20.6 (1601)	36.1 (721)	35.6 (797)	37.5 (902)	18.7 (1073)
Hypertension	81.2 (1406)	67.1 (814)	41.6 (3007)	20.0 (1560)	41.7 (834)	45.5 (1018)	44.0 (1058)	54.7 (3128)
Glycated hemoglobin (HbA1c)	27.2 (470)	37.9 (460)	4.1 (300)	5.7 (443)	15.7 (314)	23.3 (521)	22.5 (542)	8.4 (481)
Low HDL cholesterol	58.5 (1013)	29.7 (361)	11.0 (793)	34.6 (2699)	21.8 (435)	28.6 (641)	30.7 (739)	10.7 (614)
High triglycerides	44.2 (765)	27.5 (334)	49.6 (3589)	20.1 (1563)	30.1 (601)	29.8 (667)	26.5 (638)	25.8 (1478)
C-reactive protein	14.7 (56)	44.9 (222)	37.8 (644)	8.0 (1793)	22.9 (165)	18.2 (145)	16.2 (146)	41.4 (444)
Metabolic risk factors								
None	5.8 (100)	14.4 (175)	29.0 (2096)	45.5 (3,541)	31.5 (630)	28.9 (647)	29.7 (714)	29.4 (1683)
One	22.2 (385)	27.8 (338)	32.3 (2337)	33.7 (2629)	33.0 (659)	30.1 (674)	30.8 (742)	36.5 (2091)
Two	29.6 (513)	25.0 (304)	26.7 (1931)	15.6 (1217)	22.0 (439)	23.1 (516)	21.8 (525)	21.8 (1246)
Three	28.9 (501)	20.3 (246)	9.3 (671)	4.5 (351)	9.3 (185)	11.7 (262)	12.0 (288)	8.9 (510)
Four	12.5 (216)	9.1 (111)	2.5 (178)	0.6 (49)	3.6 (71)	5.4 (120)	4.9 (119)	2.9 (165)
Five	0.9 (16)	3.3 (40)	0.3 (24)	0.0 (3)	0.7 (14)	0.8 (19)	0.7 (18)	0.5 (28)
Metabolically healthy obese (%)[a]	14.8	22.1	32.4	52.9	43.8	43.1	44.8	37.3

Abbreviations: CRELES, Costa Rican Longevity and Healthy Aging Study; HDL, high-density lipoprotein; MIDUS, Midlife in the United States; NCDS, British National Child Development Study; NHANES, National Health and Nutrition Examination Survey. Note: Values are unweighted percentages (and numbers) of participants unless otherwise indicated. Data are shown for participants included in the main analyses. [a]Percentage of obese (body mass index $\geqslant$30) participants.

included the interaction effect between this variable and obesity status in the analysis to take into account differences in waist circumference among the non-obese and obese participants.

In order to keep the number of participants constant across different models, all missing values of covariates were imputed using linear regression imputation with age, sex and race/ethnicity as the predictor variables. Less than 5% of the observations were imputed in each study. We used logistic regression to investigate the associations of covariates with metabolically healthy obesity (outcome variable 0 = metabolically healthy obese, 1 = metabolically unhealthy obese). For this analysis, alcohol consumption, physical activity and education were standardized into z-scores (mean = 0, s.d. = 1) in each study to make the estimates comparable across studies for a meta-analysis; waist circumference and smoking status were used as unstandardized variables.

RESULTS

Study-specific characteristics of the participants are shown in Table 1. Depending on the study, 16–46% of obese participants were defined as metabolically healthy, that is, with no more than 1 metabolic risk factor. In the pooled analysis with normal weight as the reference category, obesity was associated with higher risk of depressive symptoms (odd ratio (OR) = 1.35; CI = 1.22, 1.50), whereas overweight was not (OR = 1.01; CI = 0.92, 1.11). The risk of depressive symptoms increased in a dose–response pattern with increasing number of metabolic risk factors with ORs of 1.00 (no metabolic risks, reference group), 1.32 (one risk factor), 1.45 (two risk factors), 1.99 (three risk factors) and 2.06 (four or five risk factors). A linear trend analysis indicated that the risk of depressive symptoms was OR = 1.22 (CI = 1.15, 1.29) higher for every additional metabolic risk factor in the pooled sample.

Figure 1 shows that compared to metabolically healthy non-obesity, higher risk of depressive symptoms was observed both for metabolically unhealthy non-obesity (OR = 1.31; CI = 1.16, 1.48) and metabolically healthy obesity (OR = 1.29; CI = 1.12, 1.50). This association with depressive symptoms was significantly stronger for metabolically unhealthy obesity (OR = 1.71; CI = 1.40, 2.09), as indicated by the non-overlapping confidence intervals and point estimates of the two groups. There was no evidence for heterogeneity in the effect sizes for these associations across studies (all $I^2 = 0\%$, $P > 0.57$). The association between overweight (BMI between 25 and 30 kg m^{-2}) and depressive symptoms appeared to be stronger for metabolically unhealthy overweight (OR = 1.29; CI = 0.84, 1.99) than for metabolically healthy overweight (OR = 0.98; CI = 0.87, 1.11), but these associations were not statistically significant, as indicated by the overlapping point estimates and CIs of the two groups.

Figure 1 also shows that compared to all non-obese participants (metabolically healthy or unhealthy), depression risk was higher for metabolically unhealthy obesity (OR = 1.45; CI = 1.30, 1.61) than for metabolically healthy obesity (OR = 1.19; CI = 1.03, 1.37). The risk of depressive symptoms associated with obesity increased almost linearly with the number of metabolic risk factors, but there were no substantial differences between specific metabolic risk factors in contributing to this association (Figure 1). Obese individuals with no metabolic risk factors did not have elevated depression risk (OR = 1.08), although adjusting for baseline covariates increased this summary estimate to OR = 1.20 (CI = 0.91, 1.57; Figure 1).

Compared to metabolically healthy obesity, metabolically unhealthy obesity was associated with OR = 1.23 (CI = 1.05, 1.45) higher depression risk in the base model adjusted for sex, age and race/ethnicity. Among the obese individuals, only higher risk of being metabolically unhealthy compared to being metabolically healthy was associated with current smoking (OR = 1.50; CI = 1.28, 1.76), lower physical activity (OR = 0.83 per 1 s.d. difference; CI = 0.76, 0.90), higher waist circumference (OR = 1.27 per

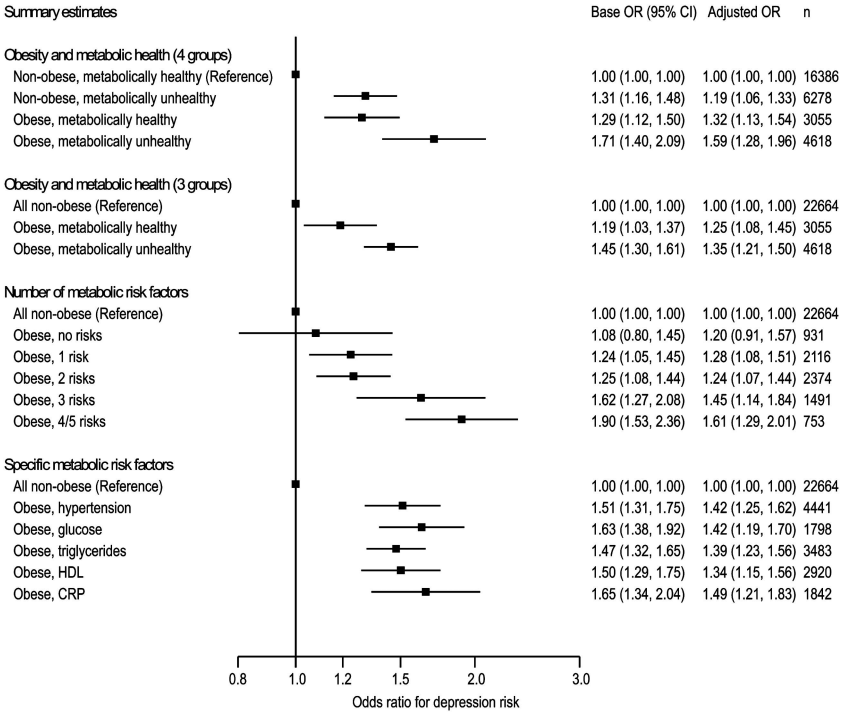

Figure 1. Pooled estimates across eight studies for the risk of depressive symptoms associated in obese individuals compared to non-obese individuals (total $n = 30\,337$). Metabolically healthy status is defined as having ⩽1 metabolic risk factors. The base models are adjusted for age, sex and race/ethnicity. The fully adjusted models are further adjusted for smoking, physical activity, alcohol consumption, education and waist circumference deviation from the person's obesity group mean waist circumference value. See Supplementary material for study-specific results.

5 cm; CI = 1.21, 1.33) and lower education (OR = 0.81 per 1 s.d. difference; CI = 0.74, 0.88), but not alcohol consumption. Adjusting for smoking, physical activity, alcohol consumption, waist circumference deviation and education attenuated the risk difference in depressive symptoms between metabolically healthy and unhealthy obesity (OR = 1.10; CI = 0.93, 1.30 in the fully adjusted model). The increasing depression risk associated with increasing number of metabolic risk factors co-occurring with obesity was also attenuated, but remained substantially similar to the base model, as reported in the 'Adjusted OR' column of Figure 1.

Details of the study-specific results are reported in Supplementary Figure 1.

COMMENT

Results from eight cohort studies with over 30 000 participants suggest that metabolically healthy and unhealthy obesity is associated with an increased risk of depressive symptoms, but the metabolically unhealthy obese have 23% higher odds of depressive symptoms compared to the metabolically healthy obese (defined as no more than 1 metabolic risk factor). The elevated depression risk associated with obesity increased almost linearly with increasing number of metabolic risk factors co-occuring with obesity. These findings support the hypothesis of metabolically healthy obesity in depression,[18] but only partly as the risk of depressive symptoms among metabolically healthy obese was higher than in persons with normal weight.

The main strength of the current study is its multi-cohort design with a large pooled sample size. While results from literature-based meta-analyses can be biased by selective publication of positive results, the present analysis was based on publicly available databases and not published results. It is reasonable to assume that these data sets are generally representative of observational cohort studies in the United States and United Kingdom, so the present results are unlikely to be subject to a major publication bias. With the large pooled sample size, we were able to quantify robust associations that could not have been estimated precisely in single studies. Depressive symptoms were assessed with clinical interviews in two of the eight cohorts studies and with three different self-rating scales in six of the other cohort studies. This variability did not seem to introduce substantial heterogeneity in the associations, as the risk for depressive symptoms associated with obesity was consistent across cohorts.

The present analysis was based on cross-sectional data, so temporal direction of the association could not be investigated. Longitudinal data indicate that the association between obesity and depression is bidirectional, so that obesity increases later depression risk and depression increases later obesity risk.[1] Similar bidirectional associations have been reported for associations between metabolic syndrome and depression,[35] and diabetes and depression,[36] suggesting that obesity, metabolic abnormalities and depressive symptoms may be connected via multiple pathways. A recent report from a 2-year follow-up of study members in the English Longitudinal Study of Aging,[18] using a 2-year longitudinal setting, showed that metabolically unhealthy obese people had a higher risk of future depression than the metabolically unhealthy obese.

The mechanisms determining metabolically healthy and unhealthy obesity states are not well known.[11,12,16,17] One crucial factor may be where the person's fat is stored, with excess visceral fat being more detrimental for metabolic health than excess subcutaneous fat.[16] In addition, our current analysis showed that people classified as metabolically healthy obese and metabolically unhealthy obese have different health characteristics, such as lower smoking prevalence, higher physical activity and higher educational level, suggesting that both physiological and behavioral factors may be involved. There are also several common biological states that link obesity and metabolic factors to depression, including inflammation,[37–39] impaired glycaemic control[40,41] and dysregulation of the hypothalamic–pituitary–adrenocortical axis.[42,43] A different set of factors may distinguish the depression risk of metabolically healthy obese individuals from non-obese individuals, including negative self-image, social stigma and discrimination, functional limitations in daily life and physical inactivity.[3,44,45]

In conclusion, the present results from a pooled analysis of men and women aged 15–105 years indicate that metabolically healthy obesity is associated with higher risk of depressive symptoms than being non-obese, and that this elevated risk increases with increasing number of metabolic risk factors co-occuring with obesity. These findings suggest that metabolically healthy obesity is not a completely benign condition in relation to mental health risk.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Supplementary Information accompanies the paper on the Molecular Psychiatry website (http://www.nature.com/mp)