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Risk of future depression in people who are obese but metabolically healthy: The English Longitudinal Study of Ageing

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Abstract

There is some evidence to suggest that obesity is a risk factor for the development of depression, although this is not a universal finding. This discordance might be ascribed to the existence of a 'healthy obese phenotype'– that is, obesity in the absence of the associated burden of cardio-metabolic risk factors. We examined whether the association of obesity with depressive symptoms is dependent on the individual's metabolic health. Participants were 3851 men and women (aged 63.0 ± 8.9 yrs, 45.1% men) from the English Longitudinal Study of Ageing, a prospective study of community dwelling older adults. Obesity was defined as body mass index ≥ 30 kg/m^2. Based on blood pressure, HDL-cholesterol, triglycerides, glycated haemoglobin, and C-reactive protein, participants were classified as 'metabolically healthy' (0 or 1 metabolic abnormality) or 'unhealthy' (≥ 2 metabolic abnormalities). Depressive symptoms were assessed at baseline and at 2 years follow up using the 8-item Centre of Epidemiological Studies Depression (CES-D) scale. Obesity prevalence was 27.5%, but 34.3% of this group was categorized as metabolically healthy at baseline. Relative to non-obese healthy participants, after adjustment for baseline CES-D score and other covariates, the metabolically unhealthy obese participants had elevated risk of depressive symptoms at follow-up (odds ratio [OR] = 1.50, 95% CI, 1.05–2.15), although the metabolically healthy obese did not (OR = 1.38, 95% CI, 0.88–2.17). The association between obesity and risk of depressive symptoms appears to be partly dependent on metabolic health, although further work is required to confirm these findings.

Introduction

Obesity and depression are important sources of disease burden, but the extent to which these two conditions are related to each other remains unclear. Although a recent meta-analysis of prospective cohort studies suggest that people with greater body mass index (BMI) have an increased risk of depressive symptoms,[1] several individual studies report no association between obesity and these symptoms[2] and another group of studies show greater

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Author contributions

MH had full access to the data, and takes responsibility for the integrity and accuracy of the results. All authors contributed to the concept and design of study, drafting and critical revision of the manuscript.

Conflict of interest

None of the authors have any competing interests to declare.

BMI to be associated with reduced risk of future mental health problems[3] and suicide[4]. Recent Mendelian randomization studies, using adiposity-related genetic variants as an unconfounded instrument variable for obesity have also produced inconsistent findings. For example, using the fat mass and obesity-associated (FTO) genotype as a proxy for higher BMI, obesity was associated with increased risk of depressive symptoms in men participating in the Whitehall II study,[5] but lower likelihood of psychological distress and antidepressant use in a study of Danish adults.[6] One possible explanation for these inconsistencies is that the association between obesity and depressive symptoms is context specific, such that the nature of the association differs in different populations. However, this is likely to explain only a small part of the discrepancies as conflicting findings have been reported between studies from the same country.

Obesity is typically accompanied by unfavourable metabolic profiles, such as high glucose, adverse lipid levels, systemic inflammation and elevated blood pressure, but it is increasingly recognised that this may not always be the case. [7–9] An attempt to capture this heterogeneity is the concept of "metabolically healthy obesity", used to describe individuals with a BMI≥ 30 kg/m^2 but an otherwise healthy metabolic profile.[7,8] There is convincing evidence to show adverse effects of obesity on health,[10,11] but some recent research suggests that metabolically healthy obesity is not associated with increased cardiovascular disease risk[12–17] although the findings are not entirely consistent.[18,19] Since metabolically healthy obesity might simply reflect the early stages of excess adiposity, it is difficult to separate the effects of time being obese from the impact of ageing on metabolism. In this regard it is useful to utilise cohort studies of older participants.

In the present study, that was based on a general population sample of older adults, we extend this line of research to examine, for the first time, whether the association of obesity with depressive symptoms is dependent on the individual's metabolic health. Since some studies have demonstrated an association of depression with metabolic syndrome[20,21] and its individual components such as impaired glycaemic control[22–24] and inflammatory markers,[25] we hypothesized that metabolically healthy obesity would not be associated with risk of depression.

Materials and Methods

Study sample and procedures

The English Longitudinal Study of Ageing (ELSA) is an ongoing cohort study that contains a nationally representative sample of the English population living in households.[26] The ELSA cohort consists of men and women born on or before 29 February 1952. The sample was drawn from households that have participated in Health Survey for England (HSE) in 1998, 1999, and 2001 ("wave 0"). HSE recruits participants using multistage stratified probability sampling with postcode sectors selected at the first stage and household addresses selected at the second stage. For the purposes of the present analyses, data collected at wave 2 (2004–05) were used as the baseline as this was the first occasion clinical information was gathered. Follow up for depressive symptoms was made two years later (2006–07). Participants gave full informed written consent to participate in the study

and ethical approval was obtained from the London Multi-centre Research Ethics Committee.

Measurements

At baseline, data collection consisted of biological, psychosocial, demographic and health related information. Demographic and health-related questions included cigarette smoking (current, previous or non-smoker), the frequency of participation in vigorous, moderate, and light physical activities (more than once per week, once per week, one to three times per month, hardly ever), frequency of alcohol intake (daily, 5–6/wk, 3–4/wk, 1–2/wk, 1–2/month, once every couple of months, 1–2/year, never) and doctor diagnosed cardiovascular disease, hypertension, diabetes. Participants were categorized as having diabetes if they reported a doctor's diagnosis and/or use of diabetic medication. Depressive symptoms were assessed at baseline and follow up using the 8-item Centre of Epidemiological Studies Depression (CES-D) scale. As in previous studies, we used a score of ≥4 to define cases of elevated depressive symptoms.[27] The CES-D is highly validated for use in older adults and displays excellent psychometric properties.[28,29]

Nurses collected anthropometric data (weight, height), blood pressure (BP), and blood samples. Participants' body weight was measured using Tanita electronic scales without shoes and in light clothing, and height was measured using a Stadiometer with the Frankfort plane in the horizontal position. BMI was calculated using the standard formulae [weight (kilograms)/height (meters) squared]. Waist circumference was recorded twice mid-way between the iliac crest and lower rib using measuring tape. An average of the first two measurements was used provided these differed by no more than 3cm; otherwise a third reading was taken and the two closest results utilised. Systolic and diastolic BP was measured with an Omron HEM-907 blood pressure monitor three times in the sitting position after 5-minute rest between each reading. The initial reading was discarded and an average of the second and third BP recordings was used for the present analyses. Blood samples were analyzed for C-reactive protein (CRP), high density lipoprotein (HDL) cholesterol, triglycerides, and glycated haemoglobin (HbA1c). Blood analysis was carried out at the Royal Victoria Infirmary (Newcastle-upon-Tyne, UK). Detailed information on the technicalities of the blood analysis, the internal quality control, and the external quality assessment for the laboratory have been described elsewhere.[30]

Statistical analyses

Normal weight (BMI 18–29.9 kg/m^2) and obesity (BMI ≥ 30 kg/m^2) was defined using the conventional criteria. Metabolic risk was based on existing criteria[8] according to availability of data, and defined as ≥ 2 metabolic risk factors, from: hypertension risk (clinic BP >130/85 mmHg, or hypertension diagnosis, or use of anti-hypertensive medication), impaired glycaemic control (HbA1c > 6.0% or doctor's diagnosed diabetes), systemic inflammation (CRP≥ 3mg/l), adverse HDL cholesterol (<1.03 mmol/l in men and <1.30 mmol/l women), and adverse triglycerides (≥ 1.7 mmol/l). Participants were then categorized into four groups: 'metabolically healthy non-obese'; 'metabolic unhealthy non-obese'; 'metabolically healthy obese'; and 'metabolically unhealthy obese'. We used χ^2 and ANOVA with Scheffe post-hoc tests to examine differences in baseline characteristics with

respect to these categories. We calculated odds ratios (OR) and 95% confidence intervals (CI) for the risk of elevated depressive symptoms at follow up in relation to obesity/metabolic health categories using multiple logistic regression. In multivariate models we adjusted for several covariates in a step-wise fashion: Model 1 contained basic variables including age, sex, baseline CES-D score; Model 2 contained additional behavioural and clinical covariates, including smoking, alcohol, physical activity, cardiovascular disease, and central obesity (waist). This modeling strategy was planned *a priori* based on existing data linking these covariates with obesity and mental health.[31] All analyses were conducted using SPSS version 20.

Results

A total of 8,688 participants (82% of wave 1 participants) attended the wave 2 (baseline) clinical assessment. The present study reports only on those that consented and were eligible and able to give blood (n=5903); this excluded men and women with clotting and bleeding disorders, or taking anti-coagulant medication (this drug can sometimes cause problems in clotting after venepuncture). After excluding 875 participants that did not attend the wave 3 follow up, and a further 1177 because of missing data, the final analytic sample comprised 3851 individuals (aged 63.0 ± 8.9 yrs, 45.1% men). In comparison with the baseline sample, the sub-group used in the present analyses were slightly younger (63.0 vs. 63.8 yrs, $p<0.001$), had a lower prevalence of longstanding illness/disability (50.4% vs. 58.1%, $p<0.001$), and better health behaviours including lower rates of smoking (13.2% vs. 17.9%, $p<0.001$) and greater physical activity (32.6% vs. 23.4%, $p<0.001$, vigorously active ≥1/wk). While these differences are statistically significant, the absolute difference was small.

Obesity prevalence was 27.5%, but 34.3% of this group was categorized as metabolically healthy at baseline (Table 1). Compared with metabolically unhealthy obese and non-obese, metabolically healthy obese participants were on average younger, contained a lower proportion of smokers, and had intermediate levels of risk factors. Central adiposity was comparable across healthy and unhealthy obese groups and considerably greater compared with non-obese groups. However, the metabolically healthy obese had lower BMI than their unhealthy counterparts.

Risk of depressive symptoms according to obesity and metabolic health

At baseline 11.7% of the sample was classified with elevated depressive symptoms (CES-D ≥4). In cross-sectional analyses, compared to the metabolically healthy non-obese, the metabolically unhealthy obese participants had elevated odds of depression at baseline (age and sex adjusted OR = 1.49, 95% CI, 1.15–1.92), although the metabolically healthy obese did not (age and sex adjusted OR = 1.04, 95% CI, 0.73–1.50). In prospective analysis adjusted for baseline CES-D score and other covariates, both the metabolically unhealthy non-obese and obese participants experienced an increased risk of elevated depressive symptoms at follow-up (Table 2). No such risk was observed in metabolically healthy obese participants (fully adjusted OR=1.38, 95% CI, 0.88–2.17). We further categorized non-obese participants into lean (BMI <25 kg/m^2) and overweight (BMI 25–29.99 kg/m^2). In analyses adjusted for age, sex, and baseline CES-D score, the metabolically healthy overweight

participants also did not experience an increased risk of future depression (OR = 0.94, 95% CI, 0.65–1.35) and there was a marginally increased risk for metabolically unhealthy overweight (OR = 1.39, 95% CI, 0.96–2.01). There was a stronger association in the metabolically unhealthy lean participants (OR = 1.76, 95% CI, 1.10–2.82). Nevertheless, these associations were lost in the fully adjusted models.

Sensitivity analyses

We repeated the main analysis in a sub-cohort excluding 451 participants with existing depressive symptoms (CES-D≥4) at baseline. There were 238 new incident cases of depression at follow up, and in comparison with healthy non-obese participants only the metabolically unhealthy obese participants had elevated odds of incident depression (OR = 1.56, 95% CI, 1.09–2.22), but not their metabolically healthy obese counterparts (OR = 1.45, 95% CI, 0.92–2.30) nor unhealthy non-obese participants (OR = 1.38, 95% CI, 0.98–1.94). Further adjustment for BMI only marginally changed the effect estimate for metabolically unhealthy obesity (OR = 1.75, 95% CI, 1.00–3.05), suggesting that morbid obesity did not explain the results.

Metabolically healthy obese participants in this study were younger, thus they might have been obese for a shorter period of time. In order to distinguish whether the observed associations were being driven by obesity time period effects we examined BMI data from “wave 0”, which were collected from Health Survey for England where the sample was initially recruited from. These data were collected approximately 4–5 years before the baseline (“wave 2”) of the present study. In further analysis we found that 69.5% of the metabolically healthy obese participants were in fact classified as obese already at wave 0. We repeated the main analyses excluding any metabolically healthy obese participants that were not already obese at wave 0 although the results were virtually unchanged; compared to the metabolically healthy non-obese, the metabolically healthy obese participants did not have elevated risk of future depression (age, sex, baseline CES-D adjusted OR = 1.20, 95% CI, 0.73–1.98) despite being obese for at least 4–5 years prior to baseline.

In a sub-sample of participants with available data on fasting blood glucose (n=2902), we re-ran the analysis substituting HbA1c data with fasting glucose ≥ 5.5 mmol/l to re-define metabolic risk. In this sub-sample, 26.6% was obese, and 37.8% of obese participants were classified as metabolically healthy. Compared to the metabolically healthy non-obese, only the metabolically unhealthy obese participants had elevated risk of depression at follow-up after adjustment for age, sex and baseline CES-D score (OR = 1.92, 95% CI, 1.38–2.67), although neither the metabolically unhealthy non-obese (OR = 1.17, 95% CI, 0.83–1.65) nor metabolically healthy obese were at risk of depression (OR = 0.96, 95% CI, 0.60–1.56).

Association of individual metabolic factors with subsequent depressive symptoms

In further analysis we examined the associations between individual metabolic risk factors and depression. There was a dose-response association between the number of metabolic risk factors and risk of depression, although the risk only became significant in participants with more than one risk factor (see online supplementary material; Table S1). Adverse triglycerides, impaired glycaemic control, and low grade inflammation were associated with

depression at follow-up in models adjusted for age, sex and baseline CES-D score, although only the latter two risk factors remained significant in mutually adjusted models (Table 3).

Discussion

The aim of this study was to examine the association between metabolically healthy obesity and risk of depression over two years follow up. Although a recent meta-analysis of prospective cohort studies suggest obesity is associated with an increased risk of depressive symptoms,[1] there are inconsistencies in the literature.[2–4,6] Indeed, a previous analysis of ELSA data has demonstrated an association between waist circumference and depressive symptoms in women, but a nearly significant inverse association between BMI and depression.[32] However, those analyses did not account for metabolic risk factors and did not examine the healthy obesity phenotype. The main findings from the present study show that metabolically unhealthy obese participants were at elevated risk of developing depression although the metabolically healthy obese were not. These results were independent of central adiposity. Also the findings do not simply reflect an effect of obesity chronicity because over two-thirds of the metabolically healthy obese participants had been obese for at least 4–5 years prior to baseline. We are not aware of any previous work that has examined the association between metabolically healthy obesity and risk of depression, and these results might partly explain the equivocal findings in this area.

A metabolically healthy phenotype was observed in 34.3% of the obese sample from the present study, which is comparable with data from some studies, although prevalence figures have ranged widely (from 10–30%) depending on the definition used.[7,8] For example, in a sample of 5440 participants of the National Health and Nutrition Examination Surveys (NHANES), 31.7% of obese adults were defined as metabolically healthy.[8] Metabolically healthy overweight and obese individuals from NHANES were of younger age, non-Hispanic black race/ethnicity, had higher physical activity levels, and smaller waist circumference. The metabolically healthy obese participants from the present study were also younger, displayed higher physical activity levels, but comparable waist circumference compared with at-risk obese counterparts.

In previous studies metabolic syndrome has been associated with depressive symptoms,[20,21, 33–35] although the findings are not entirely consistent.[36–38] However, individual components of the metabolic syndrome including impaired glycaemic control[22–24] and inflammatory markers[25] appear to be particularly important in driving the association, which was also observed in this study. The mechanisms underlying the association between metabolic abnormalities and depression remain unclear. One of the driving factors might be disturbances in key stress axes including the hypothalamic pituitary adrenal axis and sympathetic nervous system. Disturbances in these axes have been associated with depressive symptoms[39] and are linked to insulin resistance and the cascade of events in the metabolic syndrome.[40–42] Depression could also result from the biochemical changes directly caused by disturbances in metabolic abnormalities. For example, preliminary evidence found brain abnormalities, such as reduced white matter volume and enlarged cerebrospinal fluid space, in obese adolescents with type 2 diabetes, which might result from a combination of subtle vascular changes and glucose abnormalities.[43]

The metabolically unhealthy non-obese participants were also at elevated risk of developing depressive symptoms. One of the striking features of this group was the high CRP concentration, indicative of systemic inflammation, which was in fact comparable to the levels seen in the unhealthy obese group. Although the brain is generally regarded as being protected from the damaging effects of an inflammatory immune response, signals of systemic inflammation and elevated levels of peripheral inflammatory markers can affect the levels of pro-inflammatory cytokines in the brain[44] and a recent meta-analysis confirmed higher concentrations of pro-inflammatory cytokines in depressed individuals.[45] Clinically, it is important to identify metabolically unhealthy non-obese individuals, as early intervention with exercise and diet may help prevent these participants from developing obesity and diabetes,[46] and delay the onset of overt disease.

There is presently no consensus for the definition of metabolically healthy obesity. In the present study metabolic risk was based on an adaptation of previous criteria[8] according to availability of data, and the results were not largely different using measures of fasting glucose or HbA1C as an indicator of impaired glycaemic control. The decision to use a categorization of more than one metabolic risk factor in defining metabolically unhealthy was based on previously published work,[8] and was justified in the present study as we observed a threshold effect in that risk of depression was evident only in participants with more than one metabolic risk factor (see online supplementary material; Table S1). We did not assess metabolic risk factors at follow-up, thus it is possible that some of the healthy participants at baseline did go on to develop metabolic abnormalities. Nevertheless, given the short follow up period of 2 years it is unlikely that this could have influenced our results. Many of the metabolically healthy obese participants had been obese for at least 4–5 years prior to baseline suggesting that short-term exposure to obesity is an unlikely explanation for the null association with depressive symptoms. Although ELSA is designed to be nationally representative, the present sample was younger and healthier that the overall cohort due to limitations placed on blood sampling protocols.

In summary, we demonstrated that metabolically healthy obesity is not associated with risk of depression. The association between obesity and depression appears to be dependent on metabolic profile, which may partially explain why previous findings in the area have been inconsistent.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Characteristics of the study population at baseline (N=3,851).

	Metabolically healthy non-obese (n=1822)	Metabolically unhealthy non-obese (n=972)	Metabolically healthy obese (n=362)	Metabolically unhealthy obese (695)
Age (yrs)	62.3±8.8	64.9±9.2	61.3±8.5[b]	62.8±8.6
Men (%)	44.1	52.4	42.5[b]	38.8
Depressive symptoms (%CES-D>3)	10.6	11.0	11.2[e]	15.5
Current smokers (%)	9.9	14.6	5.8[a]	10.2
Alcohol (% at least one drink/wk)	70.7	61.2	66.3	50.2
Vigorous physical activity (% at least once/wk)	39.4	28.8	31.2[e]	23.3
HDL cholesterol (mmol/l)	1.67±0.37	1.40±0.36	1.54±0.30[a]	1.37±0.32
Triglycerides (mmol/l)	1.34±0.71	2.24±1.06	1.51±0.73[a]	2.34±1.74
Body mass index (kg/m^2)	25.2±2.6	26.4±2.3	32.7±2.9[a]	34.2±4.0
Waist (cm)	88.2±11.9	92.8±14.0	104.0±13.7[c]	106.4±18.2
HbA1c (%)	5.38±0.38	5.75±0.86	5.46±0.41[b]	5.90±0.95
Fasting glucose (mmol/l)*	4.87±0.54	5.14±1.04	5.01±0.72[e]	5.26±1.30
Systolic BP (mmHg)	130.0±17.1	139.0±18.7	134.7±15.8[a]	140.4±18.3
Diastolic BP (mmHg)	73.4±9.8	76.1±11.9	76.5±8.6[d]	79.0±11.6
C-reactive protein (mg/l)	1.93±3.41	5.11±7.73	2.90±4.48[a]	6.26±7.59

Values are means ± SD unless otherwise stated. **Obesity** defined as BMI ≥ 30 kg/m^2; **Metabolic risk** defined as ≥ 2 metabolic risk factors, including, hypertension risk (clinic BP >130/85 mmHg, or hypertension diagnosis, or use of anti-hypertensive medication), diabetes risk (HbA1c > 6% or doctor's diagnosed diabetes), low grade inflammation (CRP≥ 3mg/l), adverse HDL cholesterol profile (<1.03 mmol/l in men and <1.30 mmol/l women), adverse triglycerides (≥ 1.7 mmol/l).

*data available in a sub-sample of participants.

*a*significantly different (p<0.05) compared with all other groups;

*b*significantly different compared with metabolically unhealthy obese and non-obese;

*c*significantly different compared with both non-obese groups;

*d*significantly different compared with metabolically healthy non-obese;

*e*significantly different compared with metabolically unhealthy obese.

Table 2

Odds ratio (95% confidence interval) for the association of metabolic health and obesity with risk of depression over 2 years follow up. (N=3,851).

	Cases/N	Model 1 OR (95% CI)	Model 2 OR (95% CI)
Metabolically healthy non-obese	160/1822	1.00 (ref)	1.00
Metabolically unhealthy non-obese	123/972	1.53 (1.16–2.03)	1.44 (1.08–1.92)
Metabolically healthy obese	41/362	1.31 (0.88–1.96)	1.38 (0.88–2.17)
Metabolically unhealthy obese	105/695	1.53 (1.14–2.06)	1.50 (1.05–2.15)

Model 1; adjustment for age, sex, baseline CESD score.

Model 2; adjustment for age, sex, baseline CESD score, smoking, physical activity, alcohol, cardiovascular disease, central obesity.

Table 3

The association between individual metabolic risk factors and incident depression.

	Model 1 OR (95% CI)	Model 2 OR (95% CI)
Hypertension	1.20 (0.96–1.50)	1.13 (0.90–1.43)
Impaired glycaemic control	1.58 (1.18–2.11)	1.49 (1.10–2.00)
Adverse HDL-Cholesterol	1.10 (0.80–1.52)	0.92 (0.66–1.29)
Adverse triglycerides	1.27 (1.01–1.59)	1.18 (0.93–1.50)
Inflammation	1.37 (1.09–1.72)	1.30 (1.02–1.66)

Model 1; adjustment for age, sex, baseline CESD score.

Model 2; adjustment for age, sex, baseline CESD score, BMI, and mutually for all presented risk factors.