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Abstract

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 8 studies and pooled for individual-participant meta-analysis with 30,337 men and women aged 15 to 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 7,673 (25%) obese participants (body mass index$\geq$30kg/m^2). Compared to all non-obese individuals, the odds ratio for depressive symptoms was higher in metabolically unhealthy obese individuals with 2 or more metabolic risk factors (1.45; 95%CI=1.30, 1.61) and for metabolically healthy obese with $\leq$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 (odds ratio=1.23, 95%CI=1.05, 1.45) compared to 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.

Keywords: Obesity; Depression; Metabolic health; Meta-analysis; Inflammation

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 (ELSA),[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 8 studies with over 30,000 men and women aged 15 to 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.

Methods

Participants

We searched the data collections of the Inter-University Consortium for Political and Social Research (ICPSR; http://www.icpsr.umich.edu/icpsrweb/ICPSR/) and the Economic and Social Data Service (ESDS; 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 CRP inflammation), and depressive symptoms, and had a sufficiently large sample size (n>1000). We located 7 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 2004-2009;[20] the British National Child Development Study (NCDS; n=7237) biomedical sub-study from 2002-2004;[21] the National Health and Nutrition Examination Survey III (NHANES III; n=7790) from 1988-1994; the three more recent continuous National Health and Nutrition Examination Surveys (NHANES) from 2005-2006 (n=1998), 2007-2008 (n=2238), and 2009-2010 (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 available in Online 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/(height in m)^2. Obesity was defined as BMI ≥ 30kg/m^2 and overweight as BMI≥25kg/m^2 but below 30kg/m^2. Metabolic risk markers included high blood pressure (>130mmHg systolic or >85mmHg diastolic), high triglycerides (>1.7mmol/L), low HDL cholesterol (<1.03mmol/L in men, <1.29mmol/L in women), impaired glucose metabolism (glycated hemoglobin HA1c > 6%), and high C-reactive protein (CRP>3.0mg/dL), 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 ≥ 30kg/m^2 and 2 or more metabolic risk factors (high blood pressure, high triglycerides, low HDL cholesterol, impaired glucose metabolism, high CRP). 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 3 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≥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≤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 25kg/m^2 but below 30kg/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 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, SD=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% to 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 (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 odds ratios 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 25kg/m^2 and 30kg/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 confidence intervals 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 1SD difference, CI=0.76, 0.90), higher waist circumference (OR=1.27 per 5cm, CI=1.21, 1.33), and lower education (OR=0.81 per 1SD 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 Figures 1** to **11**.

Comment

Results from 8 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 datasets 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 robustly 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 suggest 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 ELSA,[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 (HPA) 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 to 105 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. The findings suggest that metabolically healthy obesity is not a completely benign condition in relation to mental health risk.

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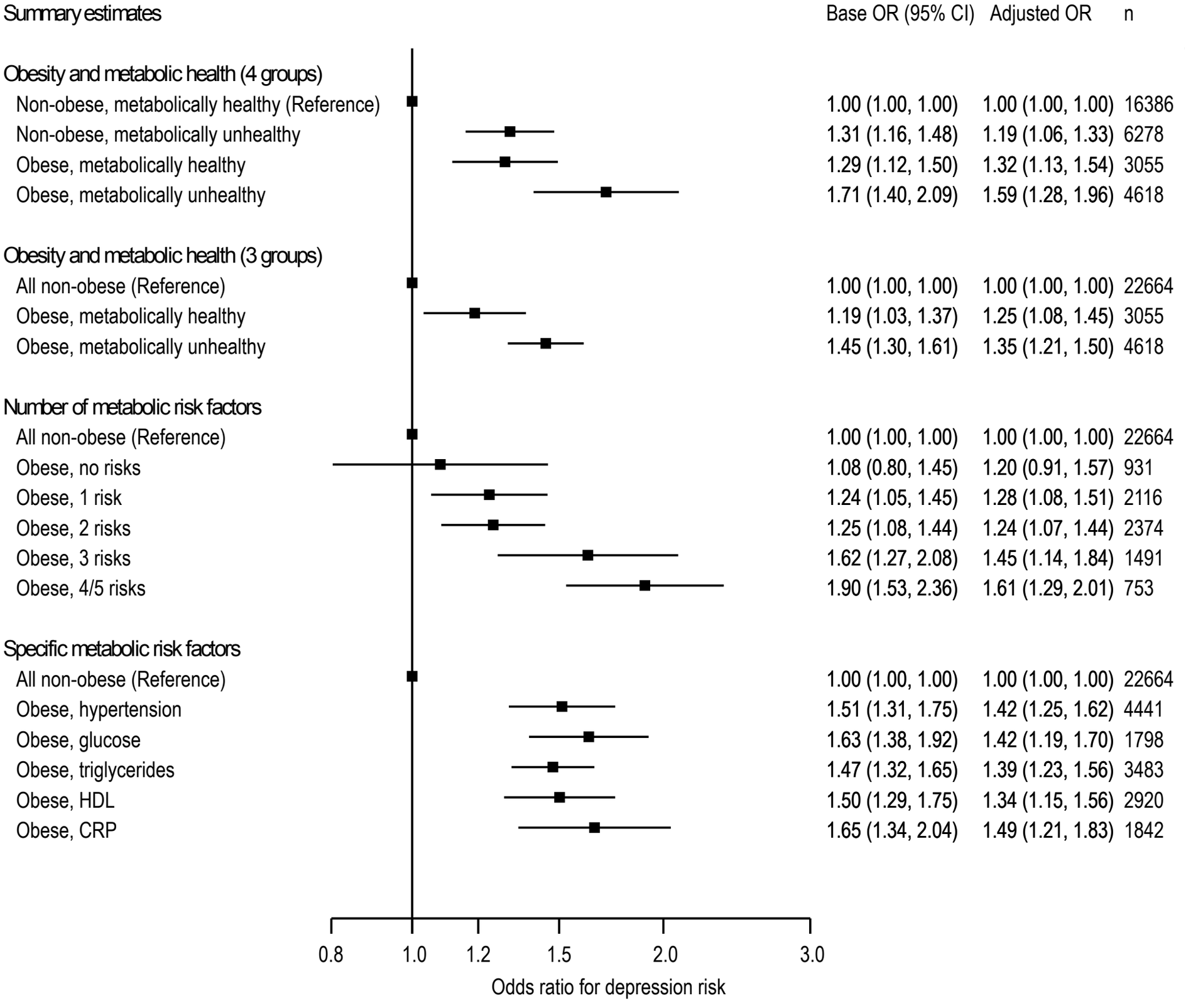
Table 1. Characteristics of the included cohorts

	CRELES	MIDUS	NCDS	NHANES III	NHANES 2005	NHANES 2007	NHANES 2009	Whitehall II
Participants (n)	1,731	1,214	7,237	7,790	1,998	2,238	2,406	5,723
Age (Years, SD)	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 (3,594)	53.7 (4,187)	50.8 (1,014)	49.7 (1,112)	51.4 (1,236)	28.1 (1,606)
Ethnic background								
White/Caucasian	-	93.6 (934)	-	28.2 (2,193)	48.5 (969)	47.9 (1,072)	47.8 (1,150)	92.4 (5,284)
Black/African	-	2.7 (27)	-	32.9 (2,566)	22.9 (458)	18.7 (419)	16.4 (394)	4.8 (272)
Other	-	3.7 (37)	-	38.9 (3,031)	28.6 (571)	33.4 (747)	35.8 (862)	2.9 (163)
Depressive symptoms	9.7 (168)	16.1 (195)	16.5 (1,195)	4.9 (383)	5.9 (118)	8.4 (188)	8.6 (206)	15.0 (861)
Body mass index (kg/m2, SD)	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 (2,502)	51.0 (3,976)	31.2 (623)	28.7 (643)	28.0 (673)	36.1 (2,066)
Overweight	40.9 (708)	35.7 (433)	41.9 (3,030)	28.4 (2,213)	32.7 (654)	35.7 (798)	34.5 (831)	45.2 (2,584)
Obese	22.0 (380)	40.7 (494)	23.6 (1,705)	20.6 (1,601)	36.1 (721)	35.6 (797)	37.5 (902)	18.7 (1,073)
Hypertension	81.2 (1,406)	67.1 (814)	41.6 (3,007)	20.0 (1,560)	41.7 (834)	45.5 (1,018)	44.0 (1,058)	54.7 (3,128)
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 (1,013)	29.7 (361)	11.0 (793)	34.6 (2,699)	21.8 (435)	28.6 (641)	30.7 (739)	10.7 (614)
High triglycerides	44.2 (765)	27.5 (334)	49.6 (3,589)	20.1 (1,563)	30.1 (601)	29.8 (667)	26.5 (638)	25.8 (1,478)
Metabolic risk factors								
None	5.8 (100)	14.4 (175)	29.0 (2,096)	45.5 (3,541)	31.5 (630)	28.9 (647)	29.7 (714)	29.4 (1,683)
One	22.2 (385)	27.8 (338)	32.3 (2,337)	33.7 (2,629)	33.0 (659)	30.1 (674)	30.8 (742)	36.5 (2,091)
Two	29.6 (513)	25.0 (304)	26.7 (1,931)	15.6 (1,217)	22.0 (439)	23.1 (516)	21.8 (525)	21.8 (1,246)
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 (%) *	14.8	22.1	32.4	52.9	43.8	43.1	44.8	37.3

Note: Values are unweighted percentages (and numbers) of participants unless otherwise indicated. Data are shown for participants included in the main analyses. CRELES=Costa Rican Longevity and Healthy Aging Study, MIDUS=Midlife in the United States, NCDS=British National Child Development Study, NHANES=National Health and Nutrition Examination Survey. * Percentage of obese (BMI≥30) participants.

Figure legends

Figure 1. Pooled estimates across 8 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 online supplementary material for study-specific results.


Summary estimates
Base OR (95% CI)
Adjusted OR
n
Obesity and metabolic health (4 groups)
Non-obese, metabolically healthy (Reference)
1.00 (1.00, 1.00)
1.00 (1.00, 1.00)
16386
Non-obese, metabolically unhealthy
1.31 (1.16, 1.48)
1.19 (1.06, 1.33)
6278
Obese, metabolically healthy
1.29 (1.12, 1.50)
1.32 (1.13, 1.54)
3055
Obese, metabolically unhealthy
1.71 (1.40, 2.09)
1.59 (1.28, 1.96)
4618
Obesity and metabolic health (3 groups)
All non-obese (Reference)
1.00 (1.00, 1.00)
1.00 (1.00, 1.00)
22664
Obese, metabolically healthy
1.19 (1.03, 1.37)
1.25 (1.08, 1.45)
3055
Obese, metabolically unhealthy
1.45 (1.30, 1.61)
1.35 (1.21, 1.50)
4618
Number of metabolic risk factors
All non-obese (Reference)
1.00 (1.00, 1.00)
1.00 (1.00, 1.00)
22664
Obese, no risks
1.08 (0.80, 1.45)
1.20 (0.91, 1.57)
931
Obese, 1 risk
1.24 (1.05, 1.45)
1.28 (1.08, 1.51)
2116
Obese, 2 risks
1.25 (1.08, 1.44)
1.24 (1.07, 1.44)
2374
Obese, 3 risks
1.62 (1.27, 2.08)
1.45 (1.14, 1.84)
1491
Obese, 4/5 risks
1.90 (1.53, 2.36)
1.61 (1.29, 2.01)
753
Specific metabolic risk factors
All non-obese (Reference)
1.00 (1.00, 1.00)
1.00 (1.00, 1.00)
22664
Obese, hypertension
1.51 (1.31, 1.75)
1.42 (1.25, 1.62)
4441
Obese, glucose
1.63 (1.38, 1.92)
1.42 (1.19, 1.70)
1798
Obese, triglycerides
1.47 (1.32, 1.65)
1.39 (1.23, 1.56)
3483
Obese, HDL
1.50 (1.29, 1.75)
1.34 (1.15, 1.56)
2920
Obese, CRP
1.65 (1.34, 2.04)
1.49 (1.21, 1.83)
1842
0.8
1.0
1.2
1.5
2.0
3.0
Odds ratio for depression risk

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

Online Supplementary Material

- **Cohort descriptions**
- **Supplementary Figures 1–11**
- **Acknoweldgements**
- **References**

Abbreviations

CRELES=Costa Rican Longevity and Healthy Aging Study; MIDUS=Midlife in the United States; NCDS=British National Child Development Study; NHANES=National Health and Nutrition Examination Survey; HDL=high-density lipoprotein cholesterol; CRP=C-reactive protein; HA1c=glycated hemoglobin

Costa Rican Longevity and Healthy Aging Study (CRELES)
Costa Rica Estudio de Longevidad y Envejecimiento Saludable

The Costa Rican Longevity and Healthy Aging Study (CRELES, or *Costa Rica Estudio de Longevidad y Envejecimiento Saludable*) is a nationally representative longitudinal survey of health and lifecourse experiences of 2,827 Costa Ricans ages 60 and over in 2005.[1] Baseline household interviews were conducted between November 2004 and September 2006, with two-year follow-up interviews. The sample was drawn from Costa Rican residents in the 2000 population census who were born in 1945 or before, with an over-sample of the oldest-old (ages 95 and over). The main study objective was to determine the length and quality of life, and its contributing factors in the elderly of Costa Rica – a country with unusually high life expectancy for a middle-income country. Information have been collected on a broad range of topics including self-reported physical health, psychological health, living conditions, health behaviors, health care utilization, social support, and socioeconomic status. Objective health indicators include anthropometrics, observed mobility, and biomarkers from fasting blood and overnight urine collection (such as cholesterol, glycosylated hemoglobin, C-reactive protein, cortisol, and other components of integrative allostatic load measures).

Height and **weight** were measured in medical examination, and BMI was calculated from these data ($BMI=weight_{kg}/height_{m}^{2}$).

Metabolic risk markers included high triglyceride (>1.7mmol/L), high blood pressure (>130mmHg systolic or >85mmHg diastolic), low HDL (<1.03mmol/L in men, <1.29mmol/L in women), high blood glucose (glycated hemoglobin HA1c > 6.0%), and high CRP inflammation (CRP>3.0mg/dL). High blood pressure was assigned also to individuals using hypertensive medication, and high blood glucose was assigned to individuals using diabetic medication.

Depressive symptoms were assessed using a 15-items of the Geriatric Depression Scale with dichotomous yes/no response scales for each item. A sum score was calculated, and dichotomous depression indicator was determined as 0=score of 0-7, 1=score of 8-15.[2] **Smoking** status and history was self-reported and coded as non-smoker, ex-smoker, and current smoker. **Physical activity** was assessed with the question *"In the last 12 months, did you exercise regularly or do other physically rigorous activities like sports, jogging, dancing, or heavy work, three times a week?"* with a dichotomous no/yes response scale. **Alcohol consumption** was determined as the frequency of drinking beer and liquer (both items coded as 0=never or less than once a month, 1=1-3 times per month, 2=once per week or more often), and summing these two items together.

Study website:
http://ccp.ucr.ac.cr/creles/

Midlife in the United States (MIDUS)

The MacArthur Foundation Survey of Midlife Development in the United States (MIDUS) is based on a nationally representative random-digit-dial sample of non-institutionalized, English-speaking adults, aged 25 to 74 years, in 1995-1996 United States.[3] The total original sample (n=7108) includes main respondents (n=3487), their siblings (n=950), a city oversample (n=757), and a twin subsample (n=1914). Data were collected in a telephone interview and with a mail questionnaire. A follow-up study of the original sample was carried out in 2004-5, and the Biomarker Project from which the present data are derived was carried out in 2004-2009. [4] The Biomarker Project of MIDUS II contains data from 1,255 respondents from two distinct subsamples: the longitudinal survey sample of 1,054 participants, and the Milwaukee sample of 201 participants who participated in the baseline MIDUS Milwaukee study initiated in 2005.

Height and **weight** were measured in medical examination, and BMI was calculated from these data ($BMI=weight_{kg} / height_{m}^2$).

Metabolic risk markers included high triglycerides (>1.7mmol/L), high blood pressure (>130mmHg systolic or >85mmHg diastolic), low HDL (<1.03mmol/L in men, <1.29mmol/L in women), high blood glucose (glycated hemoglobin HA1c > 6.0%), and high CRP inflammation (CRP>3.0mg/dL). High blood pressure was assigned also to individuals using hypertensive medication, and high blood glucose was assigned to individuals using diabetic medication.

Depressive symptoms were assessed using the 20-item CES-D questionnaire with each item reponded on a 4-point scale, and a cut-off score of 16 or more determining depression.[5]

Data on **race/ethnicity** was based on participants' self-reports and was coded as a dichotomous variable (0=white, non-Hispanic; 1=other). **Smoking** was coded as a 3-category variable (0=never smoked, 1=ex-smoker, 2=current smoker). **Alcohol consumption** was reported as the frequency of drinking alcoholic beverages last month (0=never/inapp, 1=less than 1wk, 2=1-2 per week, 3=3-4 per week, 4=5-6 per week, 5=everyday). **Physical activity** was assessed by the question "Do you engage in regular exercise, or activity, of any type for 20 minutes or more at least 3 times/week?" with a dichotomous yes/no response options. **Educational level** was determined on the basis of the highest achieved grade (0=primary education, 1=secondary education, 3=tertiary education).

Study website:
http://www.midus.wisc.edu/

National Child Development Study (NCDS)

The British National Child Development Study (also known as the 1958 British Birth Cohort Study) is a nationally representative multidisciplinary study.[6] The original participants were 17,634 individuals born in England, Wales, and Scotland during one week in March 1958. Data have been collected in follow-up phases at ages 7, 11, 16, 23, 33, 42, 46, and 50. Written informed consent was obtained from the parents for childhood measurements and ethical approval for the study was obtained from the South East Multi-Centre Research Ethics Committee.

The data for the present study come from the Biomedical Survey conducted in 2002-2004. The survey was designed to obtain objective measures of ill-health and biomedical risk factors in order to address a wide range of specific hypotheses relating to anthropometry; cardiovascular, respiratory and allergic diseases; visual and hearing impairment; and mental ill-health. The target sample for the biomedical survey was all cohort members (excluding permanent refusals) currently living in England, Scotland or Wales (n=14,737 cohort members in August 2002). This target sample definition was subsequently refined, and some cohort members excluded for various reasons, so that the sample issued to field (i.e. cohort members invited to take part in the study) comprised 12,037 cohort members, who had responded to NCDS 4, 5 or 6. The biomedical survey involved nurse-interviewers taking a number of biomedical measurements, including: near, distance and stereo vision; hearing; lung function; blood pressure and pulse, height and weight; and waist and hip. A short mental health interview was also administered, and samples of blood and saliva were taken. Fieldwork began in September 2002 and was completed at the end of March 2004. Levels of co-operation with the survey were high, with some 9,400 cohort members taking part, and only a minority declining to provide samples of blood and saliva.

Height and **weight** were measured in medical examination, and BMI was calculated from these data ($BMI=weight_{kg}/height_{m}^{2}$).

Metabolic risk markers included high triglyceride (>1.7mmol/L), high blood pressure (>130mmHg systolic or >85mmHg diastolic), low HDL (<1.03mmol/L in men, <1.29mmol/L in women), high blood glucose (glycated hemoglobin HA1c > 6%), and high CRP inflammation (CRP>3.0mg/dL).

Depressive symptoms were assessed in the Clinical Interview Schedule (CIS-R) mental health interview with 8 items, and dichotomous depression was determined as 0=no symptoms, 1=one or more symptoms.[7]

Data on **race/ethnicity** was based on participants' self-reports and was coded as a dichotomous variable (0=white, non-Hispanic; 1=other). **Educational level** was determined on the basis of the highest achieved grade (0=primary education, 1=secondary education, 3=tertiary education). **Alcohol consumption** was assessed with the questions "How often do you have a drink containing alcohol?" (0=Not in the last 12 months, 1=Once a month or less, 2=Two to four times a month, 4=Two or three times a week, 5=Four or more times a week) and "How many standard drinks do you have on a typical day, when you are drinking?" (1=one or two, 2=three or four, 3=five or six, or more), and total alcohol consumption was determined by multiplying these two variables. **Physical activity** was determined on the basis of 28 items on the frequency of various leisure-time physical activities (each reported on a scale recoded as 0=not done last year, or less than once a month, 1=1-3 times per month, 2=once a week, 3=2-3 times per week, 4=4-5 times per week or more often), and physical activity variable was created as a sum of these 28 items.

Study website:
http://www.cls.ioe.ac.uk/default.aspx

National Health and Nutrition Examination Surveys (NHANES) III, 2005-2006, 2007-2008, and 2009-2010

The National Health and Nutrition Examination Surveys (NHANES) is a program of studies designed to obtain nationally representative information on the health and nutritional status of adults and children of the United States. [8] The NHANES combines personal interviews and physical examinations, which focus on different population groups or health topics. These surveys have been conducted by the National Center for Health Statistics (NCHS) on a periodic basis from 1971 to 1994. NHANES III was conducted in 1988-1994. In 1999 the NHANES became a continuous program with a changing focus on a variety of health and nutrition measurements, which were designed to meet current and emerging concerns. These more recent surveys examine a nationally representative sample of approximately 5,000 persons each year. The sample for the survey is selected to represent the U.S. population of all ages. To produce reliable statistics, NHANES over-samples persons 60 and older, African Americans, Asians, and Hispanics. These persons are located in counties across the United States, 15 of which are visited each year.

For NHANES III, there were 39,695 persons selected for the sample, 33,994 of those were interviewed (86 percent) and 30,818 (78 percent) were examined in the mobile examination centers. For NHANES 2005-2006, there were 10,348 persons selected for the sample, 10,122 of those were interviewed (79%) and 9,643 (76%) were examined in the mobile examination centers. For NHANES 2007-2008, there were 12,946 persons selected for the sample, 10,149 of those were interviewed (78%) and 9,762 (75%) were examined in the mobile examination centers. For NHANES 2009-2010, there were 13,272 persons selected for the sample, 10,537 of those were interviewed (79%) and 10,253 were examined in the mobile examination centers (77%).

Height and **weight** were measured in medical examination, and BMI was calculated from these data ($BMI=weight_{kg} / height_{m}^2$).

Metabolic risk markers included high triglyceride (>1.7mmol/L), high blood pressure (>130mmHg systolic or >85mmHg diastolic), low HDL (<1.03mmol/L in men, <1.29mmol/L in women), high blood glucose (glycated hemoglobin HA1c > 6.0%), and high CRP inflammation (CRP>3.0mg/dL). In the continuous NHANES studies, the number of participants included in the present study was limited by information on triglyseride levels, which was available only for about half of the participants with measurements on other biomarkers; triglyceride levels were measured on examinees that were examined in the morning session only. In NHANES III, high blood pressure was assigned also to individuals who reported having been diagnosed with hypertension by a doctor, and high blood glucose was assigned to individuals who reported having been diagnosed with diabetes by a doctor. In the continuous NHANES studies, high blood pressure was assigned also to individuals using hypertensive medication, and high blood glucose was assigned to individuals using diabetic medication.

In NHANES III, **depressive symptoms** were assessed in participants aged 15–39 using the Diagnostic Interview Schedule (DIS), and depression was determined on the basis of having had an episode of depression within 6 months of the interview.[9] **Physical activity** was determined as the sum of 9 items on the frequency of various leisure-time physical activities, weighted by MET-scores determined for each activity. **Alcohol consumption** was calculated by multiplying the response to question "Number of days drank alcohol in past 12 months" by the response to another question of "Number of drinks per day on average drinking day." **Smoking** status was categorized as non-smoker, ex-smoker, and current smoker.

In the three continuous NHANES studies, **depressive symptoms** were assessed using a 9-item Depression Screener Questionnaire (DPQ) for which questions were selected from the Patient Health Questionnaire, a version of the Prime-MD diagnostic instrument. [10] They are a self-reported assessment of the past 2 weeks, based on nine DSM-IV signs and symptoms from depression. The nine symptom questions are scored from "0" (not at all) to "3" (nearly every day). **Alcohol consumption** was calculated by multiplying the response to question "Number of days drank alcohol in past 12 months" by the response to another question of "Number of drinks per day on average drinking day." **Physical activity** was determined on the basis of responses to questions of whether or not the participant had participated in moderate or vigorous physical activities, or muscle strengthening activities in the past month (each reported as 0=no, or not able, 1=yes), the final variable coded as 0=no physical activities, 1=moderate activities, 2=vigorous or muscle-strengthening activities. **Smoking** status was categorized as non-smoker, ex-smoker, and current smoker.

Study website:
http://www.cdc.gov/nchs/nhanes.htm

Whitehall II

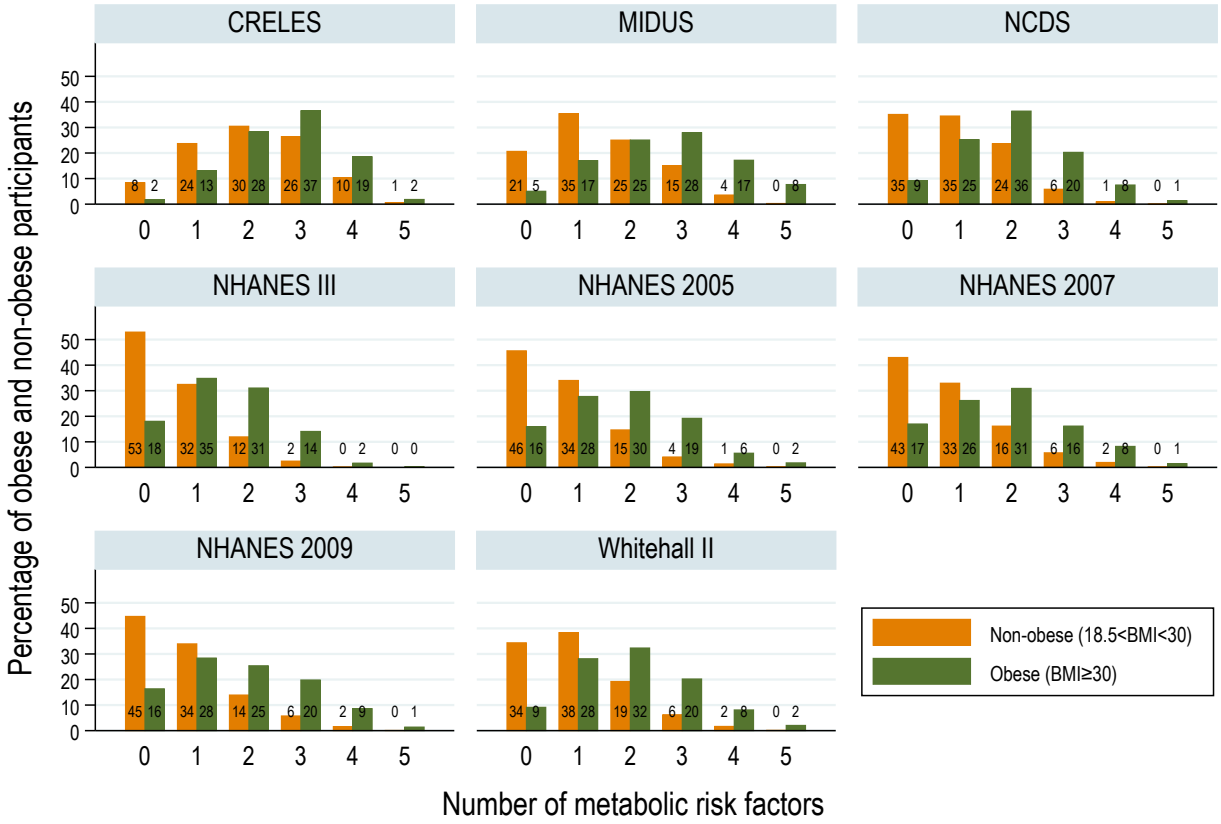
The Whitehall II prospective cohort study of British civil servants was set up in 1985 with the intention of examining reasons for the social gradient in health and disease in men and women.[11] The target population for the Whitehall II study was all civil servants (men and women) aged 35–55 years working in the London offices of 20 Whitehall departments in 1985–88. The achieved sample size was 10 308 people: 3413 women and 6895 men. The participants, who were from clerical and office support grades, middle-ranking executive grades, and senior administrative grades, differ widely in salary. Some have remained in the civil service. Many have retired, and others have taken employment elsewhere; some are unemployed. The whole cohort has been invited to the research clinic at 5-year intervals for medical examinations, and a postal questionnaire is sent to participants between clinic phases. The 7 data collection phases have been carried out in 1985-1988, 1989-1990, 1991-1993, 1997-1999, 2001, 2002-2004, and 2006. Home visits by nurses were offered for the first time to participants unwilling or unable to travel to the Phase 7 clinic. A brief telephone questionnaire is administered to those who decline clinic and full questionnaire participation at each phase. Data for the present study were taken from the 7th study wave in 2006.

Height and **weight** were measured in medical examination, and BMI was calculated from these data (BMI=$weight_{kg}$ /$height_{m}^{2}$). Repeatability of the weight and height measurements over 1 month (ie between-subject variability/total (between + within subject) variability), undertaken on 306 participants, was 0.99 at the Phase 7 screening.

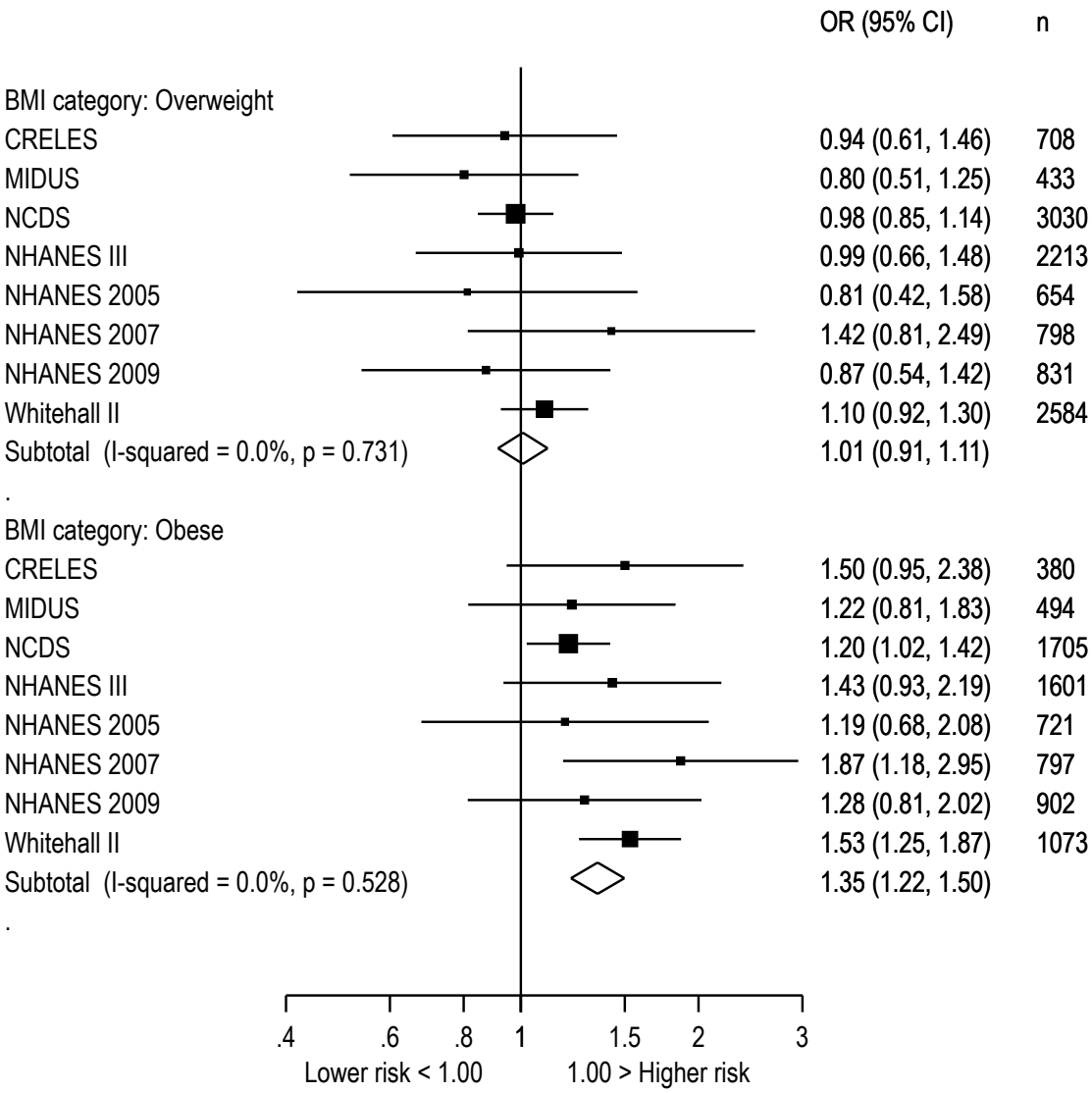
Metabolic risk markers included high triglyceride (>1.7mmol/L), high blood pressure (>130mmHg systolic or >85mmHg diastolic), low HDL (<1.03mmol/L in men, <1.29mmol/L in women), high blood glucose (glycated hemoglobin HA1c > 6.0%), and high CRP inflammation (CRP>3.0mg/dL). High blood pressure was assigned also to individuals using hypertensive medication, and high blood glucose was assigned to individuals using diabetic medication.

Depressive symptoms were assessed using the 20-item CES-D questionnaire with each item reponded on a 4-point scale, and a cut-off score of 16 or more determining depression.[5] **Alcohol consumption** was determined as the frequency of drinking alcohol in the last 12 months (6-point scale). **Physical activity** was determined on the basis of self-reported hours of weekly moderate and vigorous physical activity, coded as 0=no moderate or vigorous activity, 1=less than 2.5 hours of moderate activity, 2=more than 2.5 hours of moderate activity, 3=more than 1 hour of vigorous activity. **Smoking** status was categorized as non-smoker, ex-smoker, and current smoker.

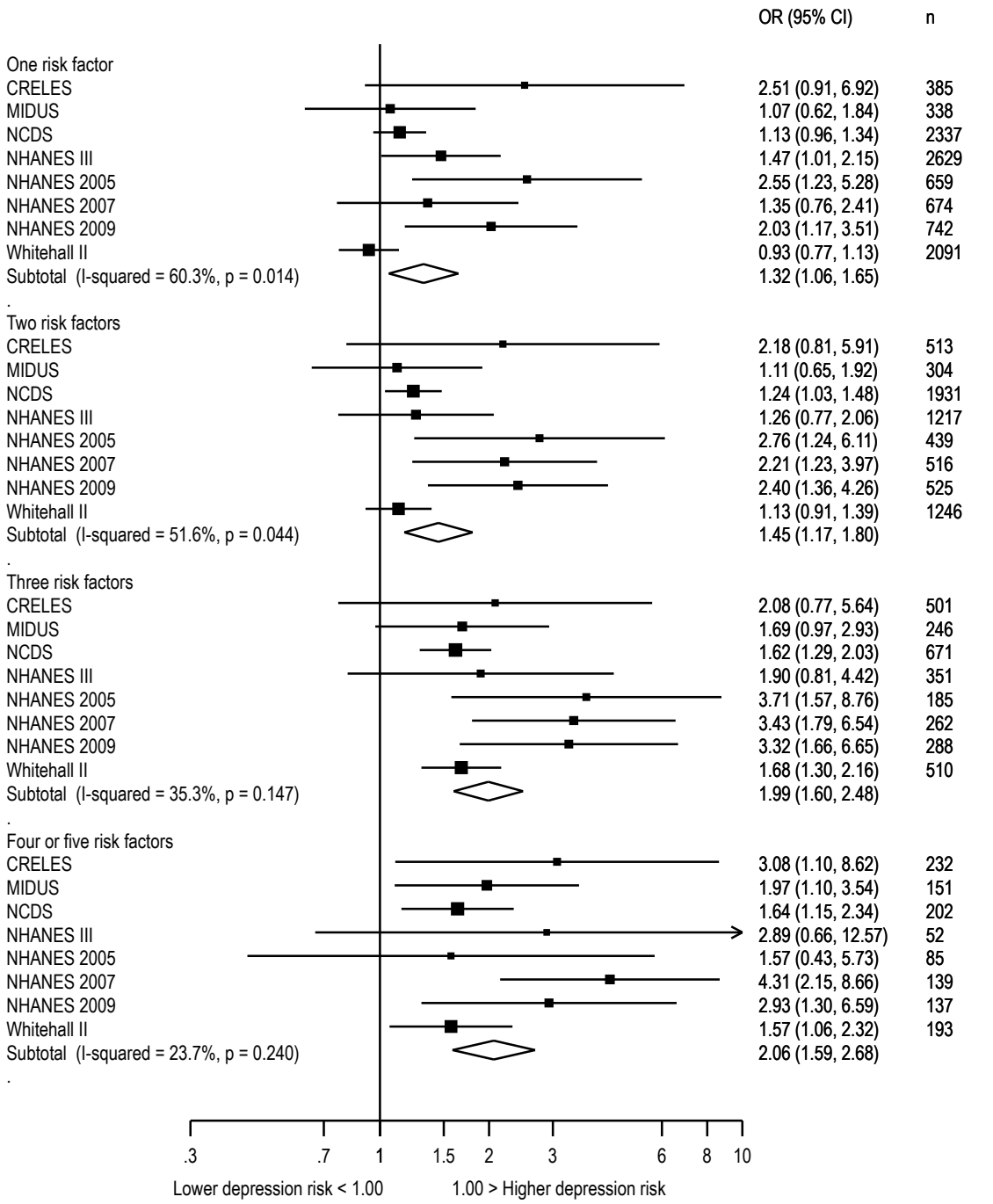
Website:
http://www.ucl.ac.uk/whitehallII



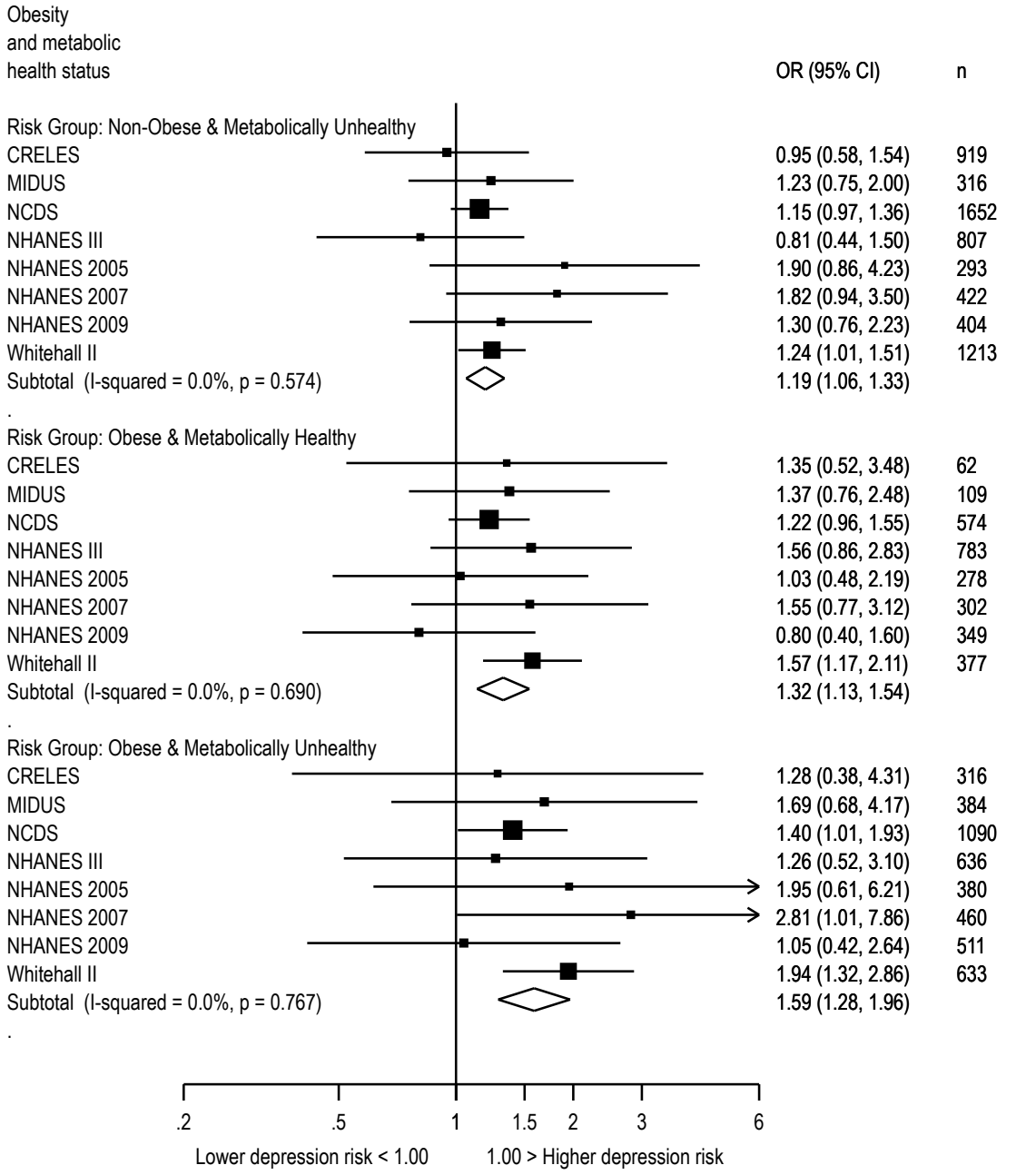
Supplementary Figure 1. Distribution of the number of metabolic risk factors (hypertension, low HDL, high triglyserides, high glycated haemoglobin, and C-reactive protein inflammation) within obese and non-obese participants. Proportions calculated using sampling weights in CRELES and all the NHANES cohorts.



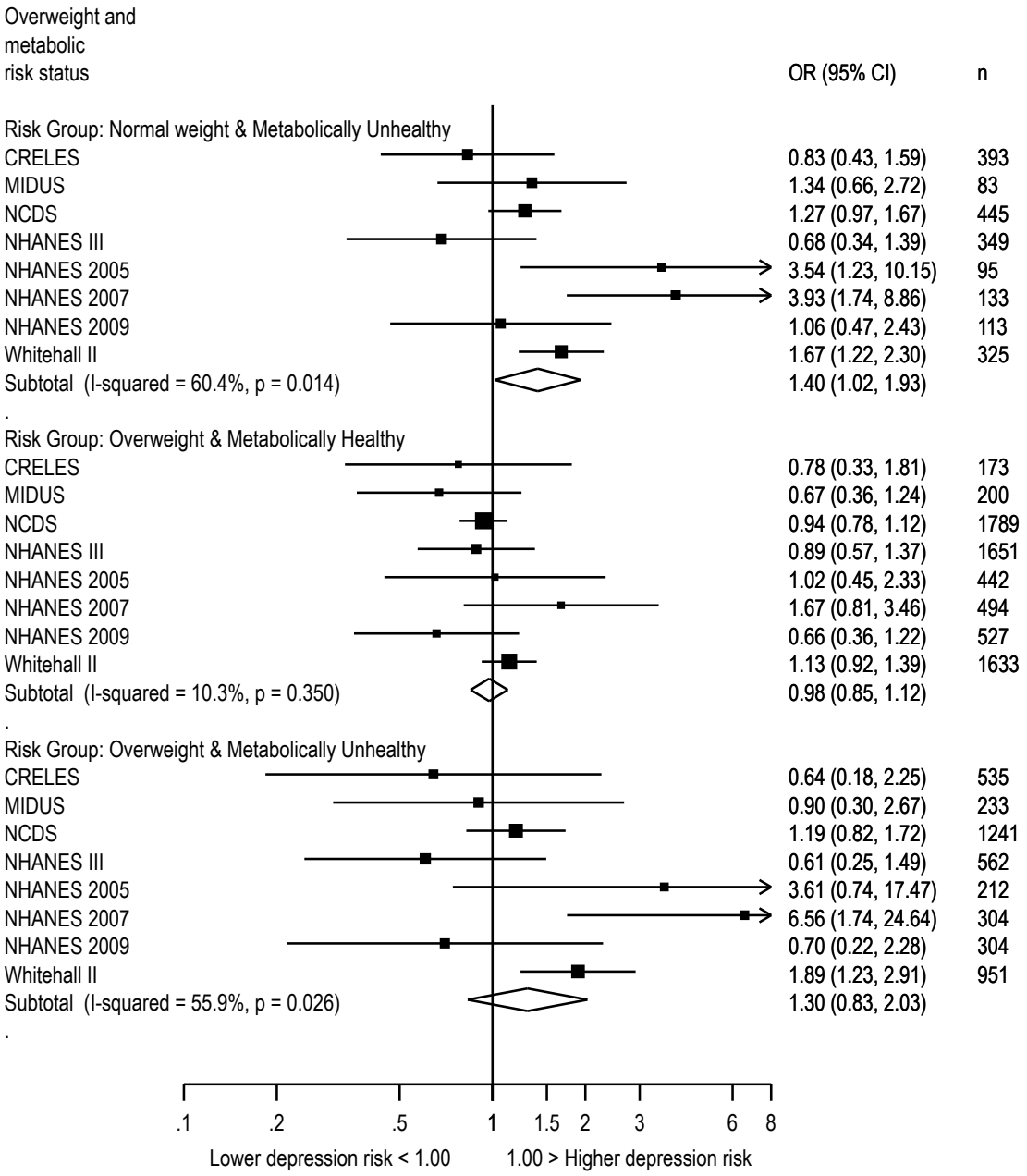
Supplementary Figure 2. Risk of depressive symptoms associated with overweight (BMI above 25kg/m^2 but below 30kg/m^2) and obesity (BMI over 30kg/m^2), with normal weight participants (BMI above 18.5kg/m^2 and below 25kg/m^2) as the reference group (n=11,413 normal weights in total), adjusted for sex, age, and race/ethnicity. Estimates are odds ratios and 95% confidence intervals. N=30,337 participants in total sample.



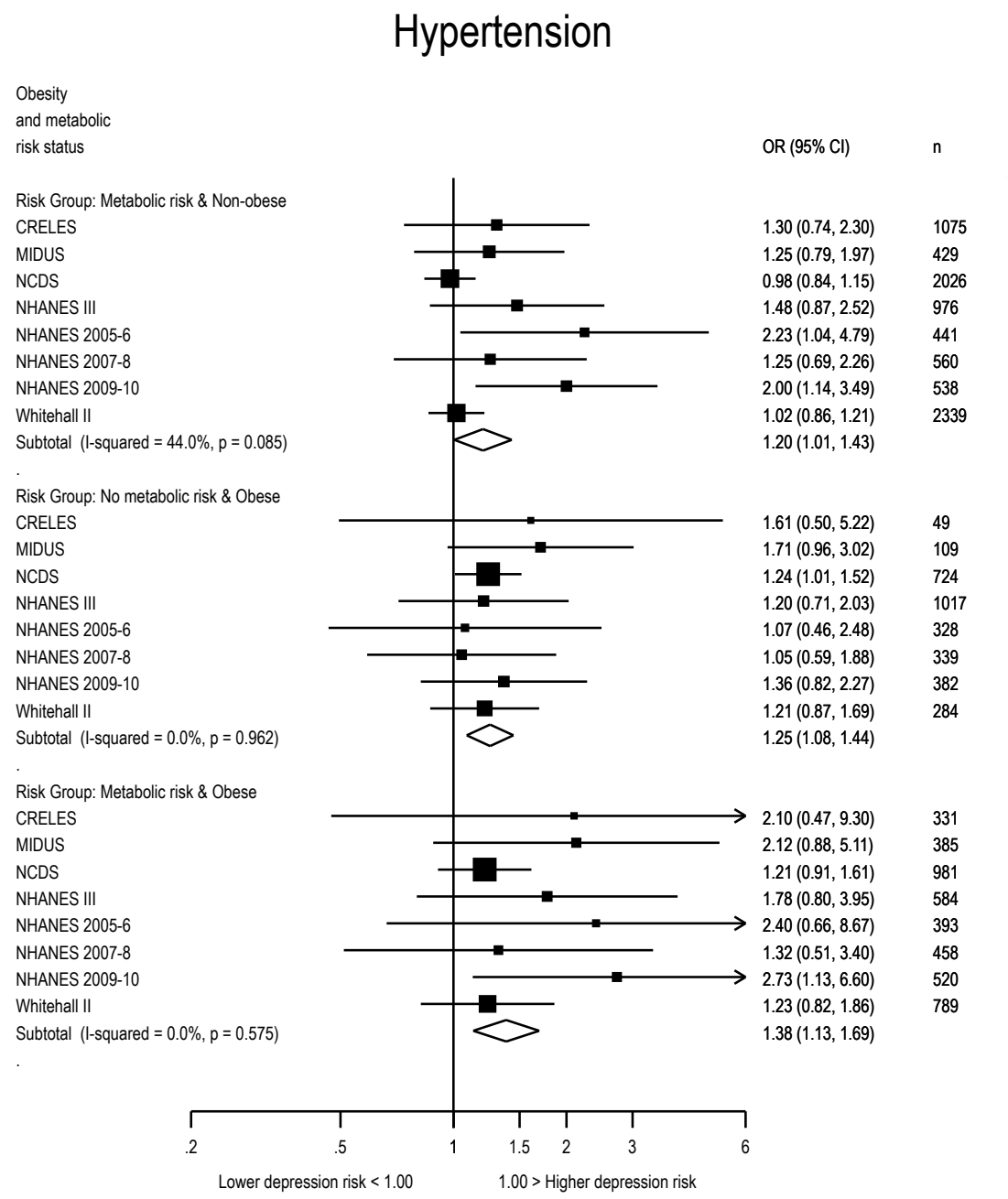
Supplementary Figure 3. Risk of depressive symptoms associated with the number of metabolic risk factors (hypertension, low HDL, high triglyserides, glycated haemoglobin, and C-reactive protein inflammation), with participants with no metabolic risk factors as the reference group (n=9,586 participants in the reference group) adjusted for sex, age, and race/ethnicity. Values are odds ratios and 95% confidence intervals. N=30,337 participants in the total sample.



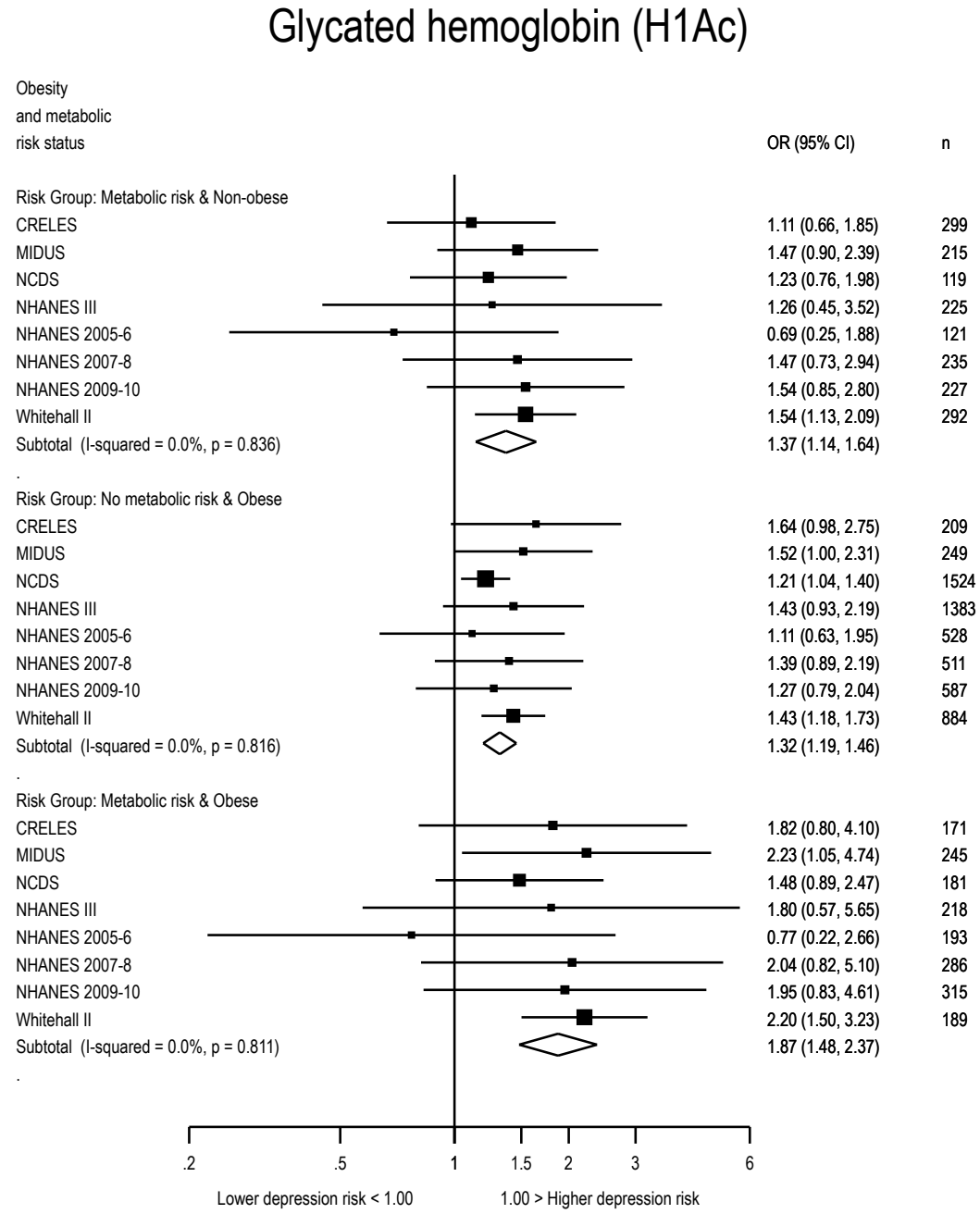
Supplementary Figure 4. Risk of depressive symptoms associated with obesity status and metabolic risk profile, adjusted for sex, age and race/ethnicity (odds ratios and 95% confidence intervals) with metabolically healthy non-obese (BMI<30kg/m^2) as the reference group (n=16,455 in the reference group). Obesity was defined as BMI≥30, and "metabolically unhealthy" as having more than 1 metabolic risk factors of high blood pressure, low HDL, high triglycerides, high blood glucose, and high C-reactive protein. N=30,337 participants in the total sample.



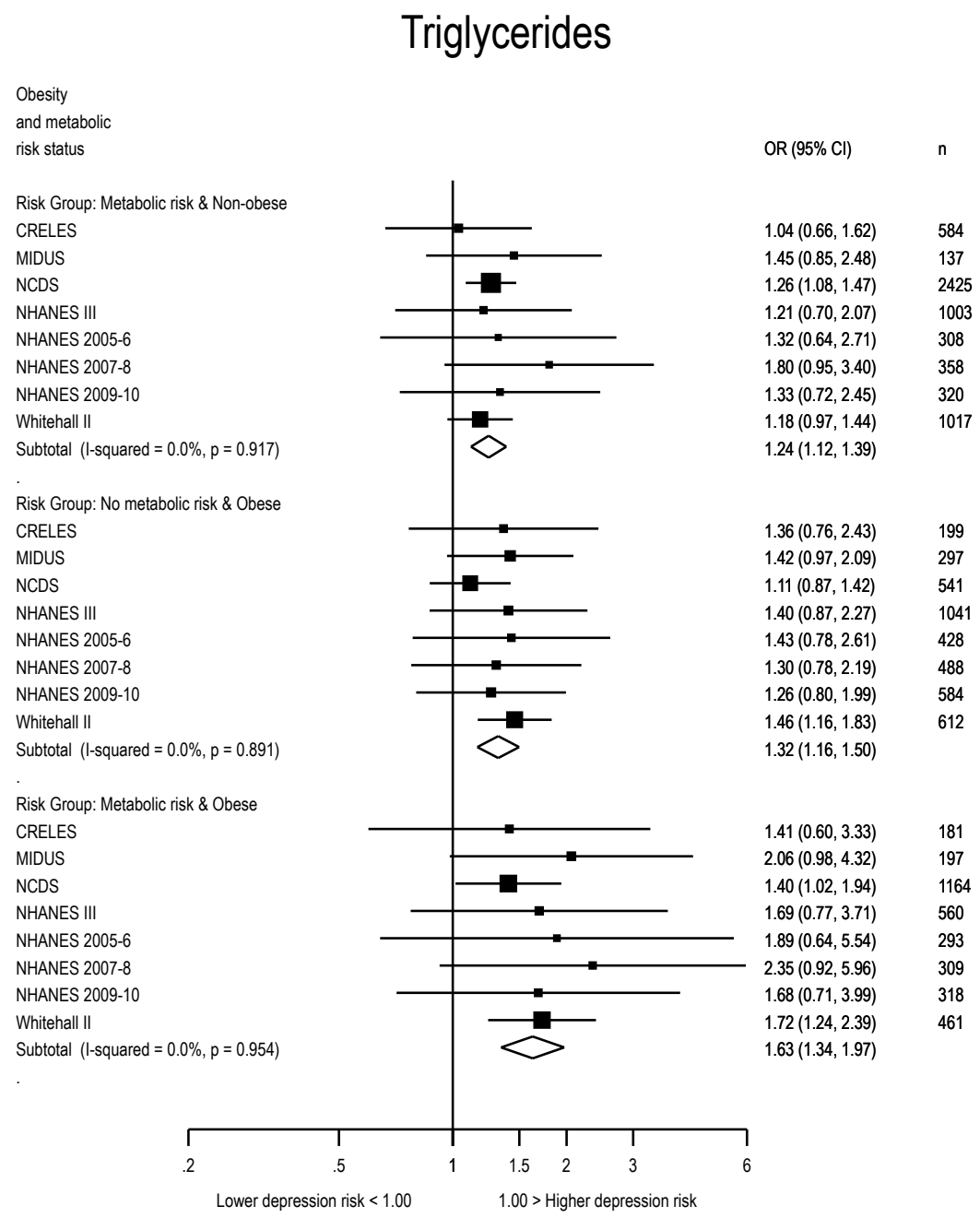
Supplementary Figure 5. Risk of depressive symptoms associated with metabolically healthy and unhealthy overweight, with normal weight (BMI above 18.5kg/m^2 and below 25kg/m^2) as the reference group (n=9,477 normal weights in total), and excluding obese participants from the analysis, adjusted for sex, age and race/ethnicity (odds ratios and 95% confidence intervals). Overweight is defined as BMI above 25kg/m^2 but below 30kg/m^2, and metabolically unhealthy as having more than 1 metabolic risks of hypertension, low HDL, high triglyserides, glycated haemoglobin, and C-reactive protein inflammation. N=22,664 in the total sample of non-obese participants.



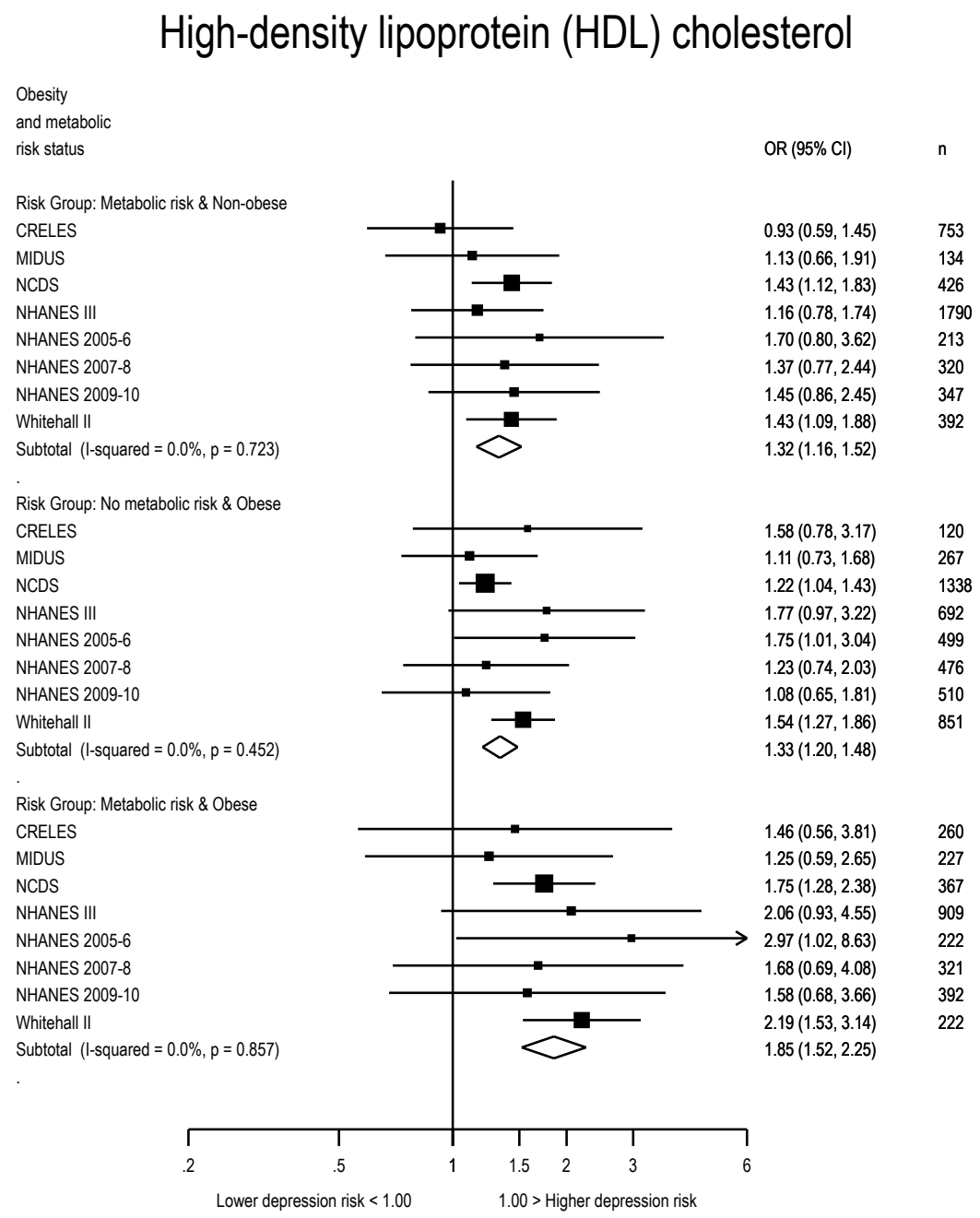
Supplementary Figure 6. Risk of depressive symptoms associated with obesity status and hypertension status (metabolic risk=>130mmHg systolic or >85mmHg diastolic), adjusted for sex, age and race/ethnicity (odds ratios and 95% confidence intervals) with non-hypertensive non-obese (BMI<30kg/m^2) as the reference group. N=30,337 participants in the total sample.



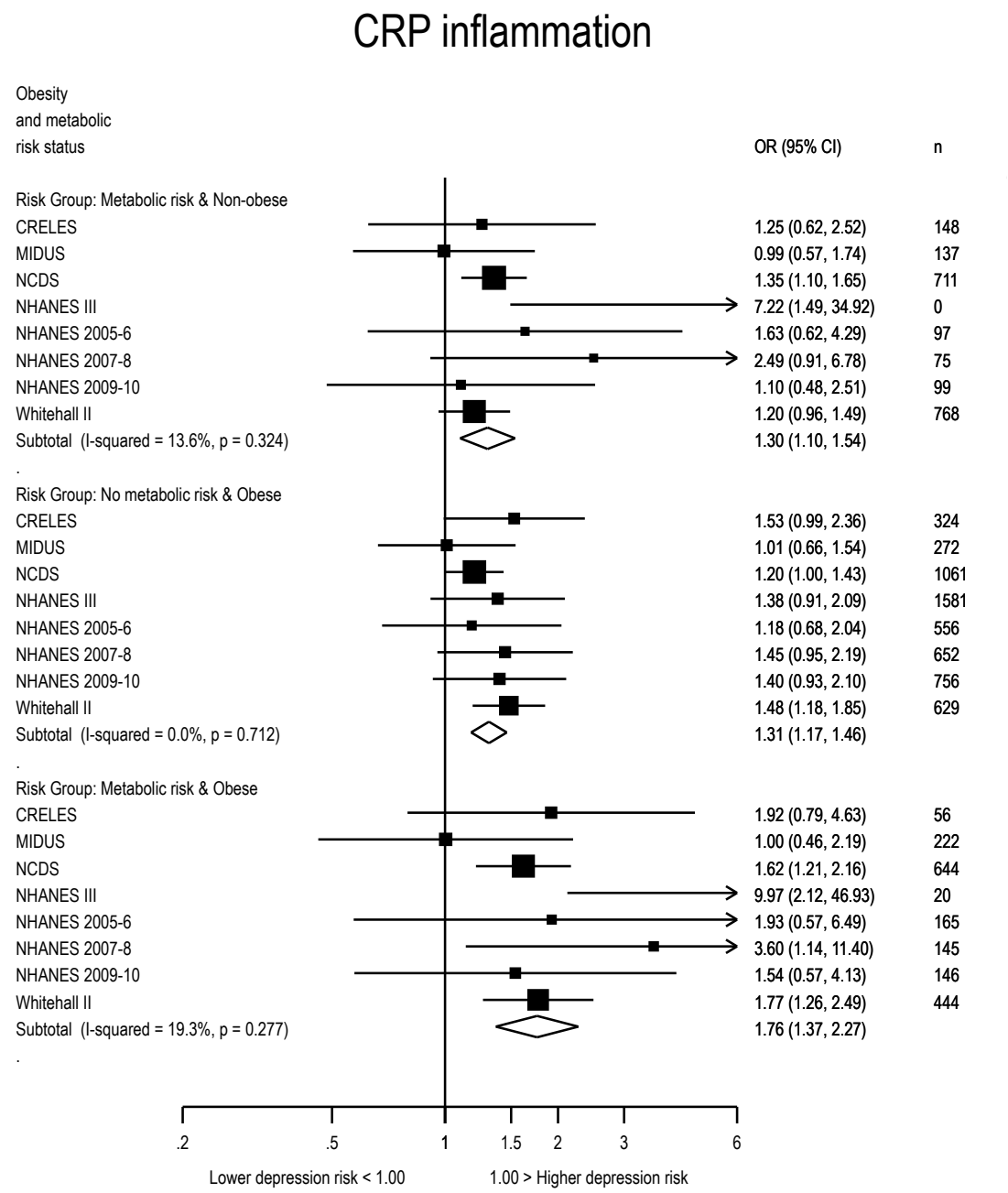
Supplementary Figure 7. Risk of depressive symptoms associated with obesity status and blood glucose level (metabolic risk= glycated hemoglobin HA1c above 6%), adjusted for sex, age and race/ethnicity (odds ratios and 95% confidence intervals) with non-hypertensive non-obese (BMI<30kg/m^2) as the reference group. N=30,337 participants in the total sample.



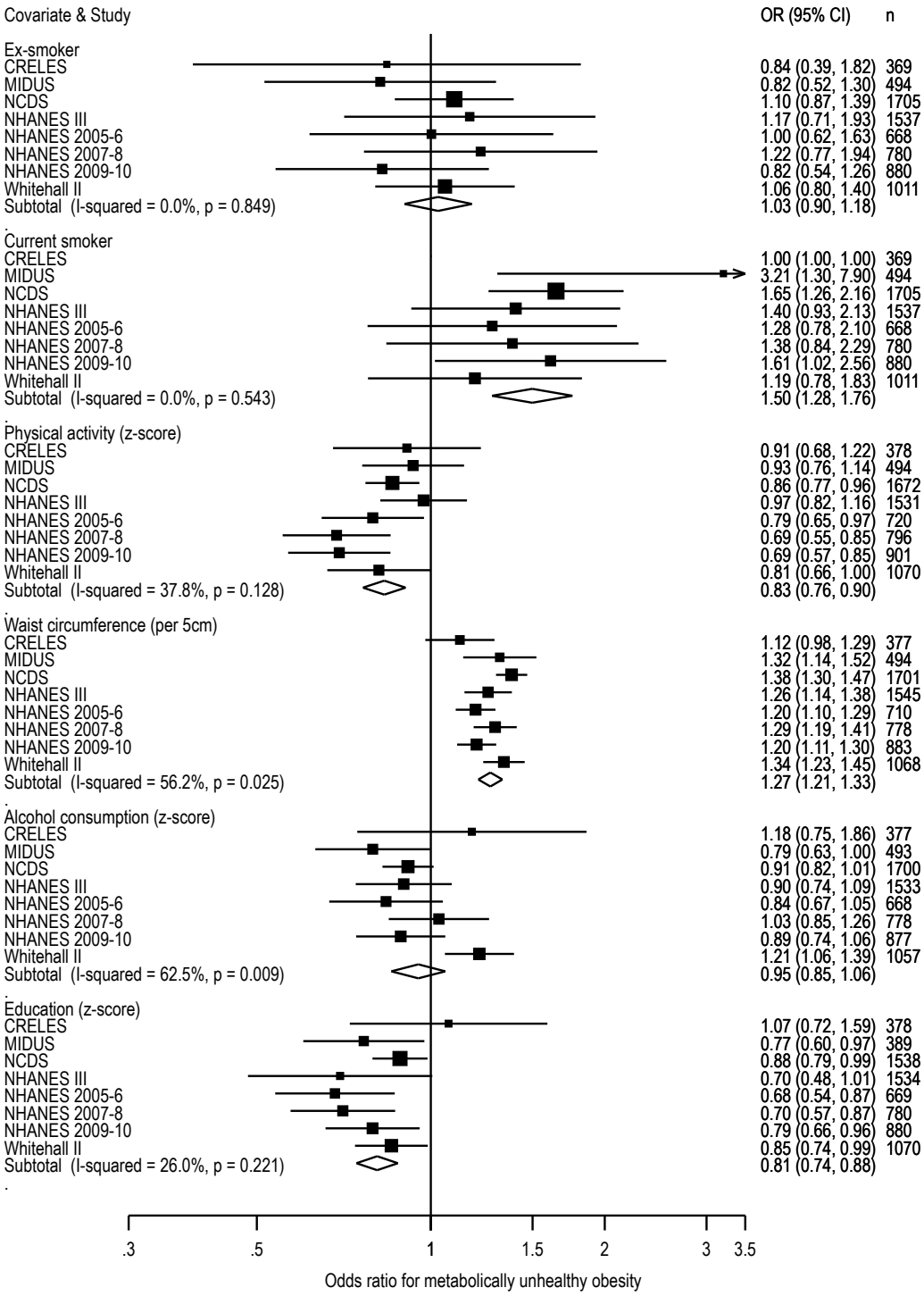
Supplementary Figure 8. Risk of depressive symptoms associated with obesity status and triglyserides level (metabolic risk=triglyserides above 1.7mmol/L), adjusted for sex, age and race/ethnicity (odds ratios and 95% confidence intervals) with non-hypertensive non-obese (BMI<30kg/m^2) as the reference group. N=30,337 participants in the total sample.



Supplementary Figure 9. Risk of depressive symptoms associated with obesity status and HDL level (metabolic risk=HDL below 1.03mmol/L in men or below 1.29mmol/L in women), adjusted for sex, age and race/ethnicity (odds ratios and 95% confidence intervals) with non-hypertensive non-obese (BMI<30kg/m^2) as the reference group. N=30,337 participants in the total sample.



Supplementary Figure 10. Risk of depressive symptoms associated with obesity status and CRP level (metabolic risk=CRP level above 3.0mg/dL), adjusted for sex, age and race/ethnicity (odds ratios and 95% confidence intervals) with non-hypertensive non-obese (BMI<30kg/m^2) as the reference group. N=30,337 participants in the total sample.



Suppleentary Figure 11. Risk of being metabolically unhealthy compared to metabolically healthy among obese individuals (BMI≥30). Participants with more than 1 risk factors of hypertension, low HDL, high triglyserides, glycated haemoglobin, and C-reactive protein inflammation, were defined as metabolically unhealthy. Total n=7,238 to n=7,562 obese participants depending on the covariate.

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