Review

Metabolically healthy status and BMI in relation to depression: A systematic review of observational studies

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A R T I C L E   I N F O

A B S T R A C T

Aim: Findings of association between metabolically healthy status and BMI and risk of depression are controversial. This study aimed to assess the relation between metabolically healthy status and BMI and depression.
Methods: All published studies up to 25 June 2018 were searched by using the databases of PubMed, ISI Web of Science, SCOPUS and Google Scholar and following key words were used: metabolically AND (healthy OR unhealthy OR benign) AND (overweight OR obes* OR "over weight") AND phenotype AND (depression OR depress* OR "depressive disorder").
Results: After screening title and abstract and considering inclusion criteria, 5 studies were found to be included in our study. Metabolically unhealthy obesity was associated with 30%—83% increased risk of depression and metabolically unhealthy non-obesity was associated with 19%—60% increased risk of depression. Metabolically healthy obesity was not associated with the risk of depression in all studies.
Conclusions: In conclusion, metabolically health status and BMI are associated with risk of depression. Metabolically unhealthy situation increased risk of depression greater than metabolically healthy status.

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1. Introduction

Depression, the common mental disorder, is a major public health problem across the globe [1]. Depression affects more than 300 million people worldwide [2]. It is estimated that depression is responsible for 50—70% of suicides. The World Health Organization (WHO) predicts that depression will become the second most prevalent disorder (after ischemic heart disease) by the year 2020 [3]. On the other hand, the prevalence of overweight and obesity are also increasing in the world [4]. In 2016, more than 1.9 billion adults, 18 years and older, were overweight and of these over 650 million were obese [5]. Obesity is an established risk factor for mental disorders and depression [6]. Previous publications support an increased risk of depression among the obese people [6,7]. (Fig. 1).

Obesity in most of people associated with an increased risk of insulin resistance, type 2 diabetes, hypertension, dyslipidemia, cardiovascular disease, cancers and inflammatory diseases [8—10]. Nevertheless, "metabolically healthy obesity" (MHO) is a complicated condition that obesity does not produce disturbed metabolic status [11].

Some studies have examined MHO in relation to mental disorders. In The English Longitudinal Study of Ageing (ELSA), unhealthy metabolic obese people in comparison with metabolically healthy obese people had higher risk of depression [12]. In a cross-sectional study in Ireland, depression was greater among the metabolically unhealthy obese subjects [13]. Although, some of the previous studies have reported the increased risk of depression in metabolically unhealthy obese people, the findings of all studies did not confirm this association. In a cross-sectional study in Korea, the risk of depression was not associated with MHO [14]. Due to conflict findings of the previous publications, we aimed to conduct a

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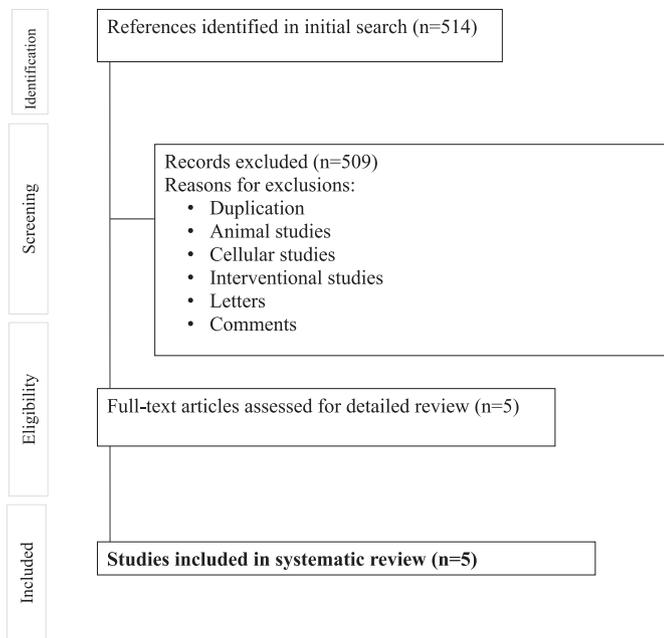
Fig. 1. PRISMA flowchart describing the study's systematic literature search and study selection.

comprehensive systematic review to summarize available data on the association between depression and metabolic healthy obesity.

2. Methods

This systematic review was performed based on the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement. Code of Pre-registration of systematic review protocols is 109371.

Search strategy: A computerized search strategy was implemented until 25 June 2018 using Pubmed, ISI Web of Science, SCOPUS and Google Scholar. The following key words were used in this search: metabolically AND (healthy OR unhealthy OR benign) AND (overweight OR obes* OR "over weight") AND phenotype AND (depression OR depress* OR "depressive disorder"). In Pubmed, keywords were searched through [tiab] and [MeSH] tags. No limitation was applied during the search. The reference lists of retrieved papers were also examined to avoid missing any published data.

Inclusion criteria: Two investigators independently selected the articles through mentioned search strategy. Publications that fulfilled the following criteria were eligible for inclusion: 1) all studies that have observational design (cross-sectional, case-control or cohort) and meta-analysis; 2) studies that examined the relationship between MHO and risk of depression; and 3) those that reported hazards ratios (HRs) or relative risk (RRs) or odds ratios (ORs) along with 95% confidence intervals (CIs) for MHO and risk of depression.

Data extraction: From each eligible study, we extracted the following information: first author, year of publication, study design, name of study, country, age range or mean age, gender, sample size, number of cases, exposure, exposure assessment tool, outcome, outcome assessment tool, relevant effect sizes (OR, HR,RR) and 95% CIs and covariates adjusted for.

Quality assessment of studies: The quality of included studies was examined by using the STROBE (Strengthening The Reporting of Observational Studies in Epidemiology) Checklist [15]. The STROBE assigns a maximum of 22 points to each study: 1 for title and abstract, 2 for introduction, 9 for methods, 5 for results, 4 for discussion and one for other information. The quality score was ranged from 12 to 18 in this study, with the median of 15. In the current analysis, when a study got more than median stars ($\geq$15), it was considered as relatively high quality; otherwise it was deemed to have low quality. Any discrepancies were resolved by discussion.

3. Results

In total, 514 articles were found in our initial search. We excluded duplicated studies, letters, comments and animal studies from the analysis. After screening the title and abstract, 5 papers remained for systematic review in the current study. The characteristics of 5 studies in this systematic review are presented in Table 1. One meta-analysis was found in our search that included due to lack of access to assessed original studies.

Descriptive of studies: The studies were published between 2012 and 2017. Among included studies, two had cross-sectional design [13,14], two had cohort design [12,16], and the reminding study was a meta-analysis [17]. Four publication were reported from European and American countries [12,13,16,17]; and one study from Asia [14]. All publications were done in adult populations and in both genders. Sample sizes ranged from 2040 people in cross-sectional studies to 30337 in meta-analysis. In total 65163 participants were studied. Duration of studies varied from 1 year in a cross-sectional study [13] to 16 year in a cohort study [16].

Exposure assessment: Participants in all studies were categorized based on metabolically health situation (healthy or unhealthy) and BMI (obese or non-obese) to 4 groups [12–14,17]. Metabolically healthy non-obese (MHNO), metabolically unhealthy non-obese (MUHNO), metabolically healthy obese (MHO) and metabolically unhealthy obese (MUHO) were the four status that considered in these studies. In one cross-sectional study, BMI was categorized to normal, overweight and obese situation [16]. Metabolically health normal weight (MHNW), metabolically healthy overweight (MHOW), metabolically healthy obesity (MHO), metabolically unhealthy normal weight (MUHNW), metabolically unhealthy overweight (MUHOW), metabolically unhealthy obesity (MUHO) were six conditions in this study. Metabolically healthy status was defined as having less than 2 risk factors in 3 studies [12,13,17], less than 3 risk factors in one study [14] and less than 1 risk factor in one reminding study [16]. Metabolically health risk factors were assessed by National Cholesterol Education Program Adult Treatment panel III (NCEP ATP III) [1-Abdominal obesity: Men: > 40 inches, Women: > 35 inches, 2-Elevated triglycerides> 150 mg/dl or drug treatment for elevated triglycerides, 3-Reduced HDL-Cholesterol (HDL-C):Men: < 40 mg/dl, Women: < 50 mg/dl, 4-Elevated blood pressure > 130/85 mm Hg or drug treatment for elevated blood pressure, 5-Elevated fasting glucose> 100 mg/dl or drug treatment for elevated glucose] in 2 studies [13,14], insulin resistance criteria [1- BMI $\geq$ 25 kg/m^2, 2- Triglyceride level of 150 mg/dl or higher, 3- HDL level <40 mg/dl in men or <50 mg/dl in women, 4-Blood pressure of 130/85 mm Hg or higher, 5-Glucose level of more than 140 mg/dl 2 h after administration of 75 g of glucose, 6- fasting glucose level of 110–126 mg/dl] in 1 study [13] and Wildman criteria [1- Elevated blood pressure> 130/85 mm Hg, 2-Elevated triglycerides $\geq$ 150 mg/dl, 3-Decreased HDL-cholesterol: Men: < 40 mg/dl, Women: < 50 mg/dl, 4-Elevated glucose level $\geq$ 100 mg/dl, 5-Insulin resistance: HOMA-IR>5.13, 6-Systemic inflammation: hsCRP level>0.1 mg/l] in 1 study [13]. Metabolically health status was assessed by having hypertension, impaired glycemic control, systemic inflammation, adverse HDL cholesterol and adverse TG were assessed in 2 studies [12,17]. Also, having hypertension, type 2 diabetes and dyslipidemia was

Table 1
Characteristics of studies that reported the relationship between metabolically healthy status and BMI and depression.

First Author (Year)	Study design	Duration of follow up	Country	Mean Age	Gender	Sample size	Cases	Exposure	Exposure assessment	Outcome	Outcome assessment	Comparison	OR/RR (95%CI)	Quality score	Adjustments
Hamer (2012)	cohort	5 y	UK	63	F,M	3851 1822 972 362 695	426 160 123 41 105	MH<2 MUH> = 2	Hypertension/impaired glycemic control/systemic inflammation/adverse HDL cholesterol/adverse TG	Depression	CES_D score ≥ 4	MHNO MUHNO MHO MUHO	1.00 1.44(1.08−1.92) 1.38(0.88−2.17) 1.50(1.05−2.15)	12	Age, sex, baseline CESD score, smoking, physical activity, alcohol, cardiovascular disease, central obesity.
Jokela (2013)	Meta-analysis of 8 cross-sectional studies	−	European & American countries	46	F,M	30337 16386 6278 3055 4618	3314	MH<2 MUH> = 2	Hypertension/impaired glycemic control/systemic inflammation/adverse HDL cholesterol/adverse TG	Depression	CED_D GDS CIS-R DIS PHQ	MHNO MUHNO MHO MUHO	1.00 1.19(1.06−1.33) 1.32(1.13−1.54) 1.59(1.28−1.96)		
Philips (2015)	Cross-sectional	−	Ireland	58.71	F,M	2040		MH<2 MUH> = 2	NCEP ATP3	Depression	CES-D	MUHNO MHO MUHO	1.36(0.83−2.22) 1.05(0.53−2.05) 1.83(1.14−2.92)	17	antidepressant medication use, history of anxiety and depression, age, gender, smoking, physical activity, dietary quality and alcohol intake
				59.38		2040			Insulin resistance			MUHNO MHO MUHO	1.23(0.71−2.11) 1.18(0.64−2.18) 1.55(0.95−2.52)		
				58.51		2040			Wildman			MUHNO MHO MUHO	1.60(1.02−2.50) 1.32(0.63−2.72) 1.82(1.12−2.96)		
Yang (2015)	Cross-sectional	−	Korea	46.8 ± 0.3 F 62.8 ± 0.5 48.8 ± 0.5 56.5 ± 0.4 48.9 ± 0.3 M 56.3 ± 0.5 45.5 ± 0.4 49.0 ± 0.4		4524 1145 994 1580 3185 786 1005 1241	570 199 168 287 251 73 62 87	MH<3 MUH> = 3	NCEP ATP3	Depression	EQ-5D	MHNO MUHNO MHO MUHO MHNO MUHNO MHO MUHO	1.00 0.85(0.66−1.09) 1.18(0.94−1.50) 0.96(0.77−1.21) 1.00 1.18(0.80−1.75) 1.03(0.72−1.47) 0.99(0.70−1.41)	18	age, monthly household income, marriage status, education, smoking, drinking, physical activities, hypertension, diabetes, cardiovascular,disease, muscular skeletal disease, cancer, lung disease, menopause

MHNW: Metabolically healthy normal weight, MHO: Metabolically healthy obese, MHOW: Metabolically healthy over-weight, MUHNW: Metabolically unhealthy normal weight, MUHO: Metabolically unhealthy obese, MUHOW: Metabolically unhealthy over-weight, BMI; Body mass index.

considered as metabolically unhealthy status in one reminding study [16].

Outcome assessment: Depression is the outcome in all studies and was assessed by different tools: the Center for Epidemiologic Studies Depression scale (CES-D) in four studies [12,13,16,17], Generalized Estimating Equations (GEE) in one study [16], and EuroQol-5 dimension questionnaire (EQ-5D) in one study [14]. Also, depression was assessed by Geriatric Depression Scale (GDS), Clinical Interview Schedule (CIS-R), Diagnostic Interview Schedule (DIS), Depression Screening Questionnaire based on the Patient Health Questionnaire (PHQ) and CES-D in meta-analysis study [17].

Statistical analysis and adjustments: In all studies OR, RR and HR with 95% confidence interval (95%CI) were reported. Metabolically healthy non-obese group was considered as reference group in all studies. Most studies had adjustment for age [12–14,16], sex [12,13,16], smoking [12–14,16], physical activity [12–14,16], alcohol [12–14,16], marital status [14,16], cardiovascular disease [12,14]. Some studies had also controlled for socioeconomic status [16], fruit and vegetable consumption [16], dietary quality [13], income [14], education [14], baseline CESD score [12], central obesity [12], antidepressant medication use [13], history of anxiety and depression [13], hypertension [14], diabetes [14], muscular skeletal disease [14], cancer [14], lung disease [14], and menopause [14]. Three of studies had high quality score [higher than median stars] [13,14,16].

Findings: MUHO participants had an increased risk of depression compared with MHNO participants in almost all studies [Hamer: RR = 1.50(95%CI: 1.05, 2.15); Jakela: RR = 1.59(1.28, 1.96); Hinnouho:RR = 1.30(1.10, 1.54)] [13,16,17]. In Philips et al. study, risk of depression was associated with MUHO by NCEP ATP3 [OR = 1.83(1.14, 2.92)] and Wildman criteria [OR = 1.82(1.12, 2.96)] [13]. In one cross-sectional study no significant relation between risk of depression and MUHO was reported [female: OR = 0.96(0.77, 1.21); male: 0.99(0.70, 1.41)] [14].

Risk of depression was greater in MHO only in a meta-analysis study [RR = 1.32(1.28, 1.96)] [17]. Other studies could not find significant association between MHO and depression [Hamer: RR = 1.38(0.88, 2.17); Philips: OR = 1.05(0.53, 2.05)/OR = 1.18(0.64, 2.18)/OR = 1.32(0.63, 2.72); Yang: male: OR = 1.03(0.72, 1.47)/female: OR = 1.18(0.94, 1.50); Hinnouho: RR = 1.04(0.81, 1.32)] [12–14,16].

MUHNO people had an increased risk of depression in four studies [Hamer: RR = 1.44(1.08, 1.92); Jakela: RR = 1.19(1.06, 1.33); Hinnouho: RR = 1.37(1.25, 1.51)][12,16,17]. In Philips et al. study, risk of depression was associated with MUHNO only by Wildman criteria [OR = 1.60(1.02, 2.50)] [13]. In one remaining study, no association was found between risk of depression and MUHNO [male: OR = 1.18(0.80, 1.75); female: OR = 0.85(0.66, 1.09)] [14].

4. Discussion

Findings from all observational studies assessed the association between metabolically healthy status and BMI and risk of depression did not confirm this relation. Some publications had reported significantly greater risk of depression in MUHO, MHO, MUHNO groups compared with MHNO. Other ones did not find any association.

Metabolically healthy obesity was reported up to 35% of obese people in previous publication [18]. Although, lower risk of chronic diseases was reported in MHO people, but MHO is not a static condition. Nearly 30% of individuals with MHO converted to MUHO status after following for 5–10 years [11]. Therefore, considering to variables that predict metabolic deterioration is important. Depression causes metabolic syndrome and obesity and vice versa [19,20]. In most studies, MHO status was not significantly associated with the risk of depression [12–14,16]. Only the meta-analysis

of 8 observational studies had reported 32% increased risk of depression in MHO people compared with MHNO group [17]. However findings of meta-analysis are often more reliable, two large cohort studies did not confirm these conclusions. Different assessment tools of exposure and outcome, different location and ethnicity might explain differences in all studies.

In metabolically unhealthy obese people, risk of depression was greater 30% and 50% in cohort studies [12,16], 83% in one cross-sectional study [13], and 59% in meta-analysis study [17]. Only one cross-sectional study (Yong 2015) was reported a non-significant decreased risk of depression [14]. In this study, 6217 men and 8243 women over age of 30 years old were assessed. Cross-sectional design, different exposure criteria, different outcome tool assessment, different location and ethnicity might explain the discrepant findings of different studies.

Metabolically unhealthy non-obese individuals had greater risk of depression compared with MHNO group. Increased risk of depression was reported 19% in meta-analysis study [17], 44% and 37% in cohort studies [12,16] and 60% in one cross-sectional study by Wildman criteria [13]. Yang et al. [14] and Philips et al. [13] [metabolically health assessment tools: NCEP ATP III and Insulin Resistance criteria] did not reported any significant association between depression and metabolically health status. Different exposure assessment tool, different outcome assessment tool, cross-sectional design and different location and ethnicity could explain the controversial results in studies.

Depression and obesity are linked by genetics, hypothalamic–pituitary–adrenal (HPA) axis, immune-inflammatory activation, neuroendocrine regulators of energy metabolism including leptin and insulin, and microbiome. Genetic factors influence both depression and obesity. Hyper activation of HPA axis leads long-term exposure to cortisol and might influence mood and weight management. Obesity is a chronic inflammation condition that changed cytokine levels and mood neurotransmitters as a result. Levels of Leptin and insulin are affected by body fat and affect psychological condition. Microbiota of gastro-intestinal tract could change neurotransmitters levels and brain activities [19]. Also, depression and metabolic syndrome are associated by biological rhythms [21], serum lipid fractions [22], and insulin resistance [23].

The present study has some strengths and limitations. It is the first study that systematically reviews the association between metabolically health status, BMI and depression. A comprehensive search strategy was performed and no limitation was applied during the search. These are the most strengths of our study. Due to low number of included studies, we could not perform meta-analysis methods to summarize all study's findings. Also, we systematically review online published previous articles in this regard. Lack of access to unpublished articles might affect our findings.

In conclusion, metabolically health status and BMI are associated with risk of depression. Metabolically unhealthy situation increased risk of depression greater than metabolically healthy status in obese participants.

Implications for behavioral health

Metabolically health status and BMI are associated with risk of depression. Metabolically unhealthy obesity was associated with 30%–83% increased risk of depression and metabolically unhealthy non-obesity was associated with 19%–60% increased risk of depression. Metabolically healthy obesity was not associated with the risk of depression in all studies.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.dsx.2019.01.027.

References

[1] Jacka FN, Mykletun A, Berk M. Moving towards a population health approach to the primary prevention of common mental disorders. BMC Med 2012;10: 149.

[2] Chocano-Bedoya PO, O'Reilly EJ, Lucas M, et al. Prospective study on long-term dietary patterns and incident depression in middle-aged and older women. Am J Clin Nutr 2013;98(3):813–20.

[3] Reddy MS. Depression: the disorder and the burden. Indian J Psychol Med 2010;32(1):1–2.

[4] The GBDOC, Ng M, Fleming T, et al. Global, regional and national prevalence of overweight and obesity in children and adults 1980-2013: a systematic analysis. Lancet (London, England) 2014;384(9945):766–81.

[5] Obesity and overweight. fact sheet. 2018. 2018, http://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight.

[6] Luppino FS, de Wit LM, Bouvy PF, et al. Overweight, obesity, and depression: a systematic review and meta-analysis of longitudinal studies. Arch Gen Psychiatr 2010;67(3):220–9.

[7] de Wit L, Luppino F, van Straten A, Penninx B, Zitman F, Cuijpers P. Depression and obesity: a meta-analysis of community-based studies. Psychiatr Res 2010;178(2):230–5.

[8] Gallagher EJ, LeRoith D. Obesity and diabetes: the increased risk of cancer and cancer-related mortality. Physiol Rev 2015;95(3):727–48.

[9] Lavie CJ, Milani RV, Ventura HO. Obesity and cardiovascular disease: risk factor, paradox, and impact of weight loss. J Am Coll Cardiol 2009;53(21): 1925–32.

[10] Reaven G, Abbasi F, McLaughlin T. Obesity, insulin resistance, and cardio-vascular disease. Recent Prog Horm Res 2004;59:207–23.

[11] Jung CH, Lee WJ, Song K-H. Metabolically healthy obesity: a friend or foe? Kor J Intern Med 2017;32(4):611–21.

[12] Hamer M, Batty GD, Kivimaki M. Risk of future depression in people who are obese but metabolically healthy: the English longitudinal study of ageing. Mol Psychiatr 2012;17(9):940–5.

[13] Phillips CM, Perry IJ. Depressive symptoms, anxiety and well-being among metabolic health obese subtypes. Psychoneuroendocrinology 2015;62:47–53.

[14] Yang Y, Herting JR, Choi J. Obesity, metabolic abnormality, and health-related quality of life by gender: a cross-sectional study in Korean adults. Qual Life Res : Int J Qual Life Aspects Treat Care Rehabil 2016;25(6):1537–48.

[15] Christen Myriam Cevallos. STROBE (strengthening The Reporting of OBservational Studies in Epidemiology) checklist. 2010. https://www.strobe-statement.org/index.php?id=available-checklists.

[16] Hinnouho GM, Singh-Manoux A, Gueguen A, et al. Metabolically healthy obesity and depressive symptoms: 16-year follow-up of the Gazel cohort study. PLoS One 2017;12(4), e0174678.

[17] Jokela M, Hamer M, Singh-Manoux A, Batty GD, Kivimaki M. Association of metabolically healthy obesity with depressive symptoms: pooled analysis of eight studies. Mol Psychiatr 2014;19(8):910–4.

[18] Nordqvist J. Metabolically healthy obesity: all you need to know. Medical News Today; 2017. 2018, https://www.medicalnewstoday.com/articles/265405.php.

[19] Milaneschi Y, Simmons WK, van Rossum EFC, Penninx BWJH. Depression and obesity: evidence of shared biological mechanisms. Mol Psychiatr 2018:1.

[20] Ghanei Gheshlagh R, Parizad N, Sayehmiri K. The relationship between depression and metabolic syndrome: systematic review and meta-analysis study. Iran Red Crescent Med J 2016;18(6):e26523.

[21] Moreira FP, Jansen K, Mondin TC, et al. Biological rhythms, metabolic syndrome and current depressive episode in a community sample. Psychoneuroendocrinology 2016;72:34–9.

[22] Igna CV, Julkunen J, Vanhanen H, Keskivaara P, Verkasalo M. Depressive symptoms and serum lipid fractions in middle-aged men: physiologic and health behavior links. Psychosom Med 2008;70(9):960–6.

[23] Skilton MR, Moulin P, Terra J-L, Bonnet F. Associations between anxiety, depression, and the metabolic syndrome. Biol Psychiatry 2007;62(11): 1251–7.