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Bidirectional Association Between Depression and Metabolic Syndrome

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Bidirectional Association Between Depression and Metabolic Syndrome

A systematic review and meta-analysis of epidemiological studies

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OBJECTIVE—Epidemiological studies have repeatedly investigated the association between depression and metabolic syndrome (MetS). However, the results have been inconsistent. This meta-analysis aimed to summarize the current evidence from cross-sectional and prospective cohort studies that evaluated this association.

RESEARCH DESIGN AND METHODS—MEDLINE, EMBASE, and PsycINFO databases were searched for articles published up to January 2012. Cross-sectional and cohort studies that reported an association between the two conditions in adults were included. Data on prevalence, incidence, unadjusted or adjusted odds ratio (OR), and 95% CI were extracted or provided by the authors. The pooled OR was calculated separately for cross-sectional and cohort studies using random-effects models. The I^2 statistic was used to assess heterogeneity.

RESULTS—The search yielded 29 cross-sectional studies ($n = 155,333$): 27 studies reported unadjusted OR with a pooled estimate of 1.42 (95% CI 1.28–1.57; $I^2 = 55.1\%$); 11 studies reported adjusted OR with depression as the outcome (1.27 [1.07–1.57]; $I^2 = 60.9\%$), and 12 studies reported adjusted OR with MetS as the outcome (1.34 [1.18–1.51]; $I^2 = 0\%$). Eleven cohort studies were found (2 studies reported both directions): 9 studies ($n = 26,936$ with 2,316 new-onset depression case subjects) reported adjusted OR with depression as the outcome (1.49 [1.19–1.87]; $I^2 = 56.8\%$), 4 studies ($n = 3,834$ with 350 MetS case subjects) reported adjusted OR with MetS as the outcome (1.52 [1.20–1.91]; $I^2 = 0\%$).

CONCLUSIONS—Our results indicate a bidirectional association between depression and MetS. These results support early detection and management of depression among patients with MetS and vice versa.

Depression is one of the most common psychiatric illnesses affecting adults and is a major public health problem in the U.S. (1). A growing body of evidence shows that depression is related to an increased risk of diabetes (2) and cardiovascular disease (CVD) (3). Metabolic syndrome (MetS) is a cluster of several CVD risk factors, including central obesity, hyperglycemia, elevated blood pressure, hypertriglyceridemia, and decreased HDL cholesterol (4). MetS is also prevalent in the general population (5) and is associated with an increased risk of diabetes and CVD (6). Because both depression and MetS confer significant public health challenges, the association between the two conditions has attracted attention recently.

A number of epidemiological studies have been conducted to investigate this association with inconsistent results reported. In particular, the temporal direction of this association remains unclear. We therefore summarized here the available data from both cross-sectional and prospective cohort studies and performed meta-analyses to investigate the cross-sectional correlation and longitudinal relation between depression and MetS.

RESEARCH DESIGN AND METHODS

Data sources

We conducted a systematic literature search (from the index date of the database up to January 2012) of MEDLINE, EMBASE, and PsycINFO for studies describing the association between depression and MetS. Two search themes were combined using the Boolean operator "and." The first theme, depression, combined exploded versions of Medical Subject Headings (MeSH in MEDLINE) "depression," "depressive disorder," or "antidepressive agents" and corresponding key words in titles and/or abstracts. The second theme, MetS, combined exploded versions of MeSH terms (in MEDLINE) "insulin resistance" or "metabolic syndrome X" and corresponding key words in titles and/or abstracts. Appropriate modifications were used for searches in EMBASE and PsycINFO. No restrictions in the search strategy were inserted. The detailed search strategy is available upon request. In addition, we searched the reference lists of all identified relevant publications and reviews. Experts in this area were also contacted for potential unpublished data.

Study selection

Two authors (A.P. and N.K.) independently assessed literature eligibility, and discrepancies were resolved by consensus or determined by a third author (F.B.H.). Articles were considered for inclusion in the systematic review if *1*) the authors reported data from an original, peer-reviewed study (i.e., not case reports, comments, letters, meeting abstracts, or review articles);

Table 1—Characteristics of cross-sectional studies in the meta-analysis*

Reference	Study name, country	N	Sample composition	Depression measures	MetS measures†	Depression case subjects/total MetS case subjects (prevalence [%])	Depression case subjects/total non-MetS case subjects (prevalence [%])	Note
Capuron et al. 2008	Twins Heart Study, U.S.	323	Age range: 47–60; 100% M	DSM-IV MDD	NCEP ATP-III	39/147 (26.5)	34/176 (19.3)	Only in crude OR meta
Carroll et al. 2009	Vietnam Experience Study, U.S.	4,256	Age mean (SD): 38 (2.5); 100% M	DSM-III MDD	Modified NCEP ATP-III	57/773 (7.0)	220/3,483 (6.0)	Only in crude OR meta
Demirci et al. 2011	Turkey	205	Age range: 18–70; 48% M	BDI-21 ≥17	NCEP ATP-III	28/121 (23.1)	24/129 (18.6)	Only in crude OR meta
Dunbar et al. 2008	Australia	1,345	Age range: 25–84; 49% M	HADS-D ≥8	NCEP ATP-III	41/409 (10.0)	65/936 (6.9)	
Fekedulegn et al. 2010	Buffalo Cardio-Metabolic Occupational Police Stress study, U.S.	96	Age mean (SD): 40 (7.7); 58% M	CESD-20 ≥16	NCEP ATP-III	3/15 (20.0)	5/81 (6.2)	
Foley et al. 2010	Australian Twin Registry, Australia	2,525	Age range: 26–90; 31% M	DSM-IV MDD	Modified NCEP ATP-III	30/145 (20.7)	456/2,380 (19.2)	
Gil et al 2006	SOPKARD Project, Poland	795	Age range: 50–60; 40% M	BDI ≥10	NCEP ATP-III	103/253 (40.7)	191/542 (35.2)	Only in crude OR meta
Grimaldi et al. 2009	Health 2000 Study, Finland	5,460	Age range: ≥30; 45% M	DSM-IV MDD	NCEP ATP-III	73/1,643 (4.4)	200/3,817 (5.2)	
Goldbacher et al. 2009	Study of Women's Health Across the Nation, U.S.	429	Age mean: 45.6; 0% M	DSM-IV MDD	NCEP ATP-III	37/88 (42.0)	114/341 (33.4)	Bidirectional
Herva et al. 2006	Northern Finland 1966 Birth Cohort Study, Finland	5,691	Age: all 31 years old; 50% M	HSCL-25 ≥1.74	NCEP ATP-III	39/325 (12.0)	729/5,366 (13.6)	Only in crude OR meta
Hildrum et al. 2009	Norwegian HUNT study, Norway	9,571	Age range: 20–89; 50% M	HADS-D ≥8	IDF	187/2,716 (6.9)	281/6,855 (4.1)	
Kimura et al. 2011	Japan	458	Age range: 21–67; 62% M	CESD-20 ≥16	Modified NCEP ATP-III	24/68 (35.3)	145/390 (37.2)	
Kinder et al. 2004	NHANES III, U.S.	6,189	Age range: 17–39; 52% M	DSM-III-R MDD	NCEP ATP-III	66/478 (13.8)	479/5,711 (8.4)	
Kobrosly et al. 2010	2005–2006 NHANES, U.S.	1,126	Age range: ≥40; 53% M	PHQ-9 ≥10	NCEP ATP-III	6/77 (7.8)	59/1,049 (5.6)	
Miettola et al. 2008	Lapinlahti 2005 study, Finland	416	Age mean: 50.4; 47% M	BDI-21 ≥15	NCEP ATP-III	20/153 (13.1)	23/263 (8.8)	
Muhtz et al. 2009	Stress, Atherosclerosis, and ECG Study, Germany	215	Age range: 30–70; 50% M	PHQ-9 >10	IDF	3/35 (8.6)	20/180 (11.1)	
Nishina et al. 2011	Japan	1,613	Age range: 30–79; 51% M	GHQ, top quartile	Modified NCEP ATP-III			Only in adjusted OR meta

Table 1—Continued

Reference	Study name, country	N	Sample composition	Depression measures	MetS measures†	Depression case subjects/total MetS case subjects (prevalence [%])	Depression case subjects/total non-MetS case subjects (prevalence [%])	Note
Pannier et al. 2006	SYMFONIE study, France	101,667	Age range: 18–80; 65% M	Le Questionnaire QD-2 >6	NCEP ATP-III	658/8,266 (8.0)	6,217/9,3401 (6.7)	
Petrlova et al. 2004	Post-MONICA study, Czech Republic	116	Age range: 35–65; 46% M	HADS-D ≥8	NCEP ATP-III	22/40 (55.0)	16/74 (21.6)	Only in crude OR meta
Roriz-Cruz et al. 2007	Brazil	422	Age range: 60–91; 37% M	DSM-IV MDD	Modified NCEP ATP-III			Only in adjusted OR meta
Seppala et al. 2011	Finnish type 2 diabetes (FIN-D2D) survey, Finland	2,820	Age range: 45–74; mean 60; 48% M	BDI-21 ≥10	NCEP ATP-III	278/1,533 (18.1)	154/1,287 (12.0)	Only in crude OR meta
Skilton et al. 2007	France	1,598	Age range: 30–80; 63% M	HADS-D ≥8	NCEP ATP-III	276/983 (28.1)	116/615 (18.9)	
Takeuchi et al. 2009(a)	Japan	1,215	Age range: 20–67; 100% M	POMS score ≥20	IDF-2006	15/148 (10.1)	77/1,067 (7.2)	
Tziallas et al. 2011	Greece	359	Age mean: 54.9; 49% M	HADS-D >11	Modified IDF	67/206 (33.0)	22/153 (14.0)	
Vaccarino et al. 2008	Women's Ischemia Syndrome Evaluation (WISE) study, U.S.	652	Age mean: 57.9; 0% M	BDI-21 ≥10 and/or physician diagnosis	NCEP ATP-III	228/391 (58.3)	119/261 (45.6)	
van Reedt Dortland et al. 2010	Netherlands Study of Depression and Anxiety, the Netherlands	890	Age range: 18–65; 39% M	DSM-IV MDD	NCEP ATP-III	57/179 (31.8)	204/711 (28.7)	
Vogelzangs et al. 2007	InCHIANTI Study, Italy	867	Age range: ≥65; 45% M	CESD-20 ≥20	Modified NCEP ATP-III	55/212 (25.9)	124/655 (18.9)	
Vogelzangs et al. 2007	Health, Aging, and Body Composition study, U.S.	2,917	Age range: 70–79; 49% M	CESD-20 ≥16	NCEP ATP-III	60/1,125 (5.3)	75/1,792 (4.2)	
Vogelzangs et al. 2009	Longitudinal Aging Study Amsterdam, the Netherlands	1,060	Age range: 65–85; 49% M	CESD-20 ≥16 and DSM-III MDD	Modified NCEP ATP-III	14/395 (3.5)	17/665 (2.6)	Participants with subthreshold depression were not included

M, male; GHQ, general health questionnaire; HADS-D, Hospital Anxiety and Depression Scale–Depression subscale; HSCL, Hopkins Symptom Checklist; MDD, major depressive disorder; POMS, Profile of Mood States. *A complete list of the references is available in Supplementary References. †Modifications of the MetS diagnosis criteria are as follows: in the Carroll et al. study, BMI ≥25 kg/m² was considered as the MetS component instead of waist; in the Foley et al. study, BMI ≥30 kg/m² was considered as the MetS component instead of waist, the blood samples were collected in nonfasting status, and the glucose and lipids were modified to account for the nonfasting status; in the Kimura et al. study, BMI ≥25 kg/m² was considered as the MetS component instead of waist, and in women, high triglyceride level was not counted as a component because few women had high triglyceride; in the Nishina et al. study, BMI ≥25 kg/m² was considered as the MetS component instead of waist; in the Roriz-Cruz et al. study, BMI ≥30 kg/m² was considered as the MetS component instead of waist, and the cutoff point for high blood pressure was 140/90 mmHg instead of 130/85 mmHg; in the Tziallas et al. study, BMI ≥30 kg/m² was considered as the MetS component instead of waist; in the Vogelzangs et al. 2007 InCHIANTI Study, the cutoff point for high blood pressure was 160/90 mmHg instead of 130/85 mmHg; and in the Vogelzangs et al. Longitudinal Aging Study Amsterdam, the cutoff point for high blood pressure was 160/90 mmHg instead of 130/85 mmHg, and the fructosamine level of ≥247 μmol/L was used instead of glucose level of ≥6.1 mmol/L.

2) the study was a cross-sectional or prospective cohort study with a noninstitutional adult population (age >18 years); 3) the authors reported an association between the two conditions (prevalence, incidence, unadjusted or adjusted odds ratio [OR], and its 95% CI); and 4) the study was published in English. We used broad inclusion criteria for studies, including all definitions of MetS (National Cholesterol Education Program Adult Treatment Panel III [NCEP ATP-III], International Diabetes Federation [IDF], and definitions from other organizations or modified versions) (4,7) and depression status (assessed by self-reported symptom scales, physician/clinician diagnosis, or structured clinical diagnostic interview). In the case of multiple publications from the same study, only the most recent paper or article with a longer follow-up was included. We evaluated eligible articles by first screening titles or abstracts followed by a full-text review.

Data extraction
Two authors (A.P. and N.K.) independently extracted the following information from each study using a predesigned collection form: study characteristics (study name, authors, publication year and journal, study site, number of participants, and follow-up years for cohort studies), participants' characteristics (age range or mean age and sex composition), depression and MetS measures, analysis strategy (statistical models and covariates adjusted in the models), and results (prevalence, incidence, unadjusted or adjusted OR, and 95% CI). We evaluated the study quality by allocating 1 score for each of the following aspects: selection bias, standard measures of exposure and outcome, participation rate in cross-sectional studies or follow-up rate in cohort studies, adjustment for important confounding factors (socioeconomic status and lifestyle variables), and generalizability. The scores were summed up and studies were classified as high versus low quality based on the median value.

Data synthesis
Separate meta-analyses were conducted to determine *1*) the crude OR of this association in cross-sectional studies (since there is no explicit direction in cross-sectional studies), *2*) the adjusted OR with MetS as the independent variable in the original reports of cross-sectional studies, *3*) the adjusted OR with depression as the independent variable in the original reports of cross-sectional studies,

4) the OR of baseline MetS status and risk of incident depression in cohort studies, and *5*) the OR of baseline depression status and risk of future MetS in cohort studies.

The OR was used as the common measure of association across articles in both cross-sectional and cohort studies. If the study reported effect size other than OR, transformation was performed and the corresponding author was contacted for unpublished data if possible. To be consistent across studies, we used binary variables (yes/no) for both MetS and depression. We did not include studies using depressive scale as a continuous variable because the risk estimates were not comparable with studies using categorized depression measures.

The ORs were pooled using the random-effects model that included between-study heterogeneity, and forest plots were produced. Heterogeneity was evaluated by the I^2 statistic, and values of 25, 50, and 75% are considered to represent low, medium, and high heterogeneity, respectively (8). The possibility of publication bias was evaluated using the Begg test and visual inspection of a funnel plot (9). Stratified analyses were performed to evaluate the influences of selected study quality and participant characteristics on study results (10): sex, mean age at baseline, different definitions of MetS, depression measure, continent of origin, and study quality. All statistical analyses were performed with Stata statistical software version 11.0 (StataCorp, College Station, TX). P values were two-sided with a significance level of 0.05.

RESULTS

Literature search and study selection
A total of 4,231 articles were found from the three electronic databases. The title and abstract screening based on the aforementioned criteria left us with 422 articles. After examining those articles in full text, 375 articles were excluded (Supplementary Fig. 1). Among the remaining 47 articles, 5 articles used continuous variables for depression scales and 1 article (11) used an extremely low score (Center for Epidemiologic Studies–Depression Scale [CESD]-10 score = 0) to define the reference group (the conventional cutoff is <10). Because the risk estimates might be overestimated in this study, it was not included in the main analysis. However, a sensitivity analysis of including this article did not change the results. Two articles (12,13) used the same samples as the

other two studies (14,15), and articles with longer follow-up and more detailed information were retained (14,15). Finally, 39 articles were included (for the complete references of the 39 articles, please see references in Supplementary Data). One cohort study (16) reported the baseline cross-sectional association between depression and MetS and was included in both cross-sectional and cohort analyses. One cross-sectional study (14) and 2 cohort studies (16,17) reported results in both directions. Therefore, 29 cross-sectional studies and 11 cohort studies were included in the meta-analysis. One cohort study (17) is still ongoing, and the authors provided the most recent unpublished results for our meta-analysis.

Cross-sectional studies of the association between depression and MetS
In the 29 cross-sectional studies shown in Table 1, 8 studies used structured or semistructured diagnostic interviews to diagnose major depressive disorder according to the DSM. Nineteen studies assessed depression using self-report symptom scales (e.g., the Beck Depression Inventory [BDI], the CESD, or the Patient Health Questionnaire [PHQ]). Two studies used both measures to identify depression case subjects; however, 1 study required meeting both criteria, and the other study required meeting either criterion. In the studies that used the self-report symptom scales, the threshold score for a depression case subject varied across studies (e.g., BDI score ≥10, ≥15, ≥17, or ≥19 in various studies). MetS was identified based on the NCEP ATP-III or modified versions in most studies, while 4 studies adopted IDF criteria or a modified version. Three studies were conducted in men, 2 in women, and the remaining in both sexes. Most studies were implemented in the U.S. (*n* = 8) or European countries (*n* = 14), with 3 in Japan, 2 in Australia, 1 in Brazil, and 1 in Turkey.

A total of 27 studies (*n* = 153,298) provided data on the prevalence of depression in adults with and without MetS (another 2 studies provided only adjusted OR and, therefore, were not included here). The pooled crude OR between depression and MetS was 1.42 (95% CI 1.28–1.57) with a moderate heterogeneity detected (I^2 = 55.1%) (Fig. 1). No significant publication bias was detected (*P* = 0.72) (Supplementary Fig. 2*A*). Subgroup analyses (Supplementary Table 1) showed significant differences by
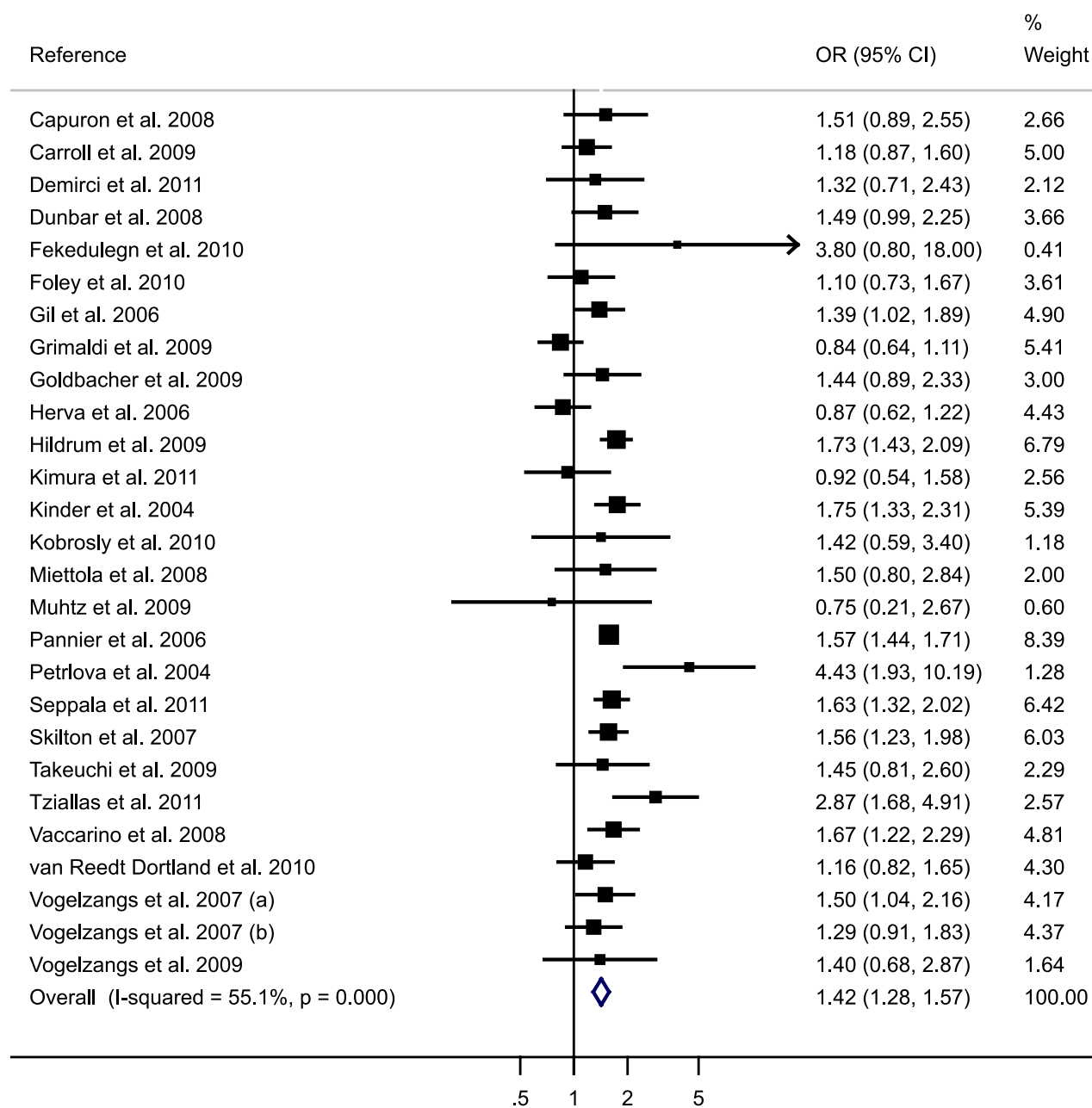
Reference		OR (95% CI)	% Weight
Capuron et al. 2008		1.51 (0.89, 2.55)	2.66
Carroll et al. 2009		1.18 (0.87, 1.60)	5.00
Demirci et al. 2011		1.32 (0.71, 2.43)	2.12
Dunbar et al. 2008		1.49 (0.99, 2.25)	3.66
Fekedulegn et al. 2010		3.80 (0.80, 18.00)	0.41
Foley et al. 2010		1.10 (0.73, 1.67)	3.61
Gil et al. 2006		1.39 (1.02, 1.89)	4.90
Grimaldi et al. 2009		0.84 (0.64, 1.11)	5.41
Goldbacher et al. 2009		1.44 (0.89, 2.33)	3.00
Herva et al. 2006		0.87 (0.62, 1.22)	4.43
Hildrum et al. 2009		1.73 (1.43, 2.09)	6.79
Kimura et al. 2011		0.92 (0.54, 1.58)	2.56
Kinder et al. 2004		1.75 (1.33, 2.31)	5.39
Kobrosly et al. 2010		1.42 (0.59, 3.40)	1.18
Miettola et al. 2008		1.50 (0.80, 2.84)	2.00
Muhtz et al. 2009		0.75 (0.21, 2.67)	0.60
Pannier et al. 2006		1.57 (1.44, 1.71)	8.39
Petrlova et al. 2004		4.43 (1.93, 10.19)	1.28
Seppala et al. 2011		1.63 (1.32, 2.02)	6.42
Skilton et al. 2007		1.56 (1.23, 1.98)	6.03
Takeuchi et al. 2009		1.45 (0.81, 2.60)	2.29
Tziallas et al. 2011		2.87 (1.68, 4.91)	2.57
Vaccarino et al. 2008		1.67 (1.22, 2.29)	4.81
van Reedt Dortland et al. 2010		1.16 (0.82, 1.65)	4.30
Vogelzangs et al. 2007 (a)		1.50 (1.04, 2.16)	4.17
Vogelzangs et al. 2007 (b)		1.29 (0.91, 1.83)	4.37
Vogelzangs et al. 2009		1.40 (0.68, 2.87)	1.64
Overall (I-squared = 55.1%, p = 0.000)		1.42 (1.28, 1.57)	100.00

.5 1 2 5

Figure 1—*Forest plot of cross-sectional studies of the crude association between depression and MetS.*

depression measures (*P* for between-group difference = 0.005) and MetS definitions (*P* for between-group difference = 0.04). The association was slightly weaker when depression was assessed by a diagnostic interview rather than a self-reported symptom scale (OR = 1.29 vs. 1.51) and was notably weaker when MetS was defined according to the NECP ATP-III criterion compared with other criteria (OR = 1.38 vs. 1.78). No significant between-group difference was found for continent of residence, study quality, age category, and sex.

Most of the studies performed multivariate logistic regression to adjust for potential confounders (Supplementary Table 2). A total of 11 studies (12 reports because 1 study reported results separately for men and women) ran the regression models using depression as the dependent variable, and the pooled OR was 1.27 (95% CI 1.07–1.51) with a moderate to high heterogeneity detected (I^2 = 60.9%) (Supplementary Fig. 3). Twelve studies (14 reports because 2 studies reported results separately for men and women) used MetS as the dependent variable. The pooled OR was

1.34 (1.18–1.51) with no heterogeneity detected (I^2 = 0%) (Supplementary Fig. 3).

Three studies were excluded because depressive symptoms score was used as a continuous variable rather than a binary variable. Prescott et al. (18) reported that both men (adjusted OR 1.08 [95% CI 1.05–1.10]) and women (1.04 [1.02–1.07]) had an elevated risk of MetS for 1-unit increase of 17-item Vital Exhaustion sum score. Toker et al. (19) reported that women were at an elevated risk of MetS for 1-unit increase of PHQ-9 (1.94 [1.22–3.07]) but not men (1.19 [0.79–1.80]).

Table 2—Characteristics of cohort studies included in the meta-analysis*

Reference	Study name, country	Incident case subjects/N	Follow-up (years)	Sample composition	Depression measures	MetS measures†	Note
MetS predicting depression							
Akbaraly et al. 2009	Whitehall II study, U.K.	428/5,232	6	Age range: 41–61; 72% M	GHQ-4 ≥4	NCEP ATP-III	Participants with current depression at baseline were excluded
Akbaraly et al. 2011	Three-City Study, France	827/4,446	4	Age range: 65–91; 45% M	CESD-20 ≥16 or ADM use	NCEP ATP-III	Unpublished data; participants with lifetime depression at baseline were excluded
Almeida et al. 2009	Health in Men Study, Australia	481/12,066	10	Age range: 65–84; 100% M	ICD-10 coded MDD and dysthymia from a linked hospital data system	Modified version because no biochemistry measures were available	Participants with current depression at baseline were excluded
Goldbacher et al. 2009	Study of Women's Health Across the Nation, U.S.	45/278	7	Age range: 42–52; 0% M	MDD of Structured Clinical Interview based on DSM-IV	NCEP ATP-III	Unpublished data; participants with lifetime depression at baseline were excluded
Koponen et al. 2008	Finland	777/604	7	Age mean: 54.1; 44% M	BDI-21 ≥10	NCEP ATP-III	Participants with current depression at baseline were excluded
Mast et al. 2008	Health, Aging, and Body Composition study, U.S.	135/1,769	2	Age range: 70–79; 52% M	CESD-10 >8	NCEP ATP-III	Participants with current depression at baseline were excluded
Pulkki-Råback et al. 2009	Cardiovascular Risk in Young Finns Study, Finland	126/996	6	Age mean: 33; 42% M	BDI-21 ≥10	NCEP ATP-III	Unpublished data; participants with current depression at baseline were excluded
Takeuchi et al. 2009(b)	Japan	66/890	1	Age range: 20–66; 100% M	POMS score >20	IDF	Participants with current depression at baseline were excluded
Vogelzangs et al. 2011	InCHIANTI Study, Italy	170/655	6	Age range: ≥65; 49% M	CESD-20 ≥20	NCEP ATP-III	Participants with current depression at baseline were excluded
Depression predicting MetS							
Gaysina et al. 2011	British 1946 birth cohort, U.K.	132/2,105	17	Age: all 36 years old; 48% M	PSE ≥5	Modified NCEP ATP-III	Unpublished data for multivariate-adjusted model; participants with baseline MetS were not excluded
Goldbacher et al. 2009	Study of Women's Health Across the Nation, U.S.	56/341	7	Age range: 42–52; 0% M	DSM-IV MDD	NCEP ATP-III	Participants with baseline MetS were excluded

Table 2—Continued

Reference	Study name, country	Incident case subjects/N	Follow-up (years)	Sample composition	Depression measures	MetS measures†	Note
Pulkki-Råback et al. 2009	Cardiovascular Risk in Young Finns Study, Finland	87/1,094	6	Age mean: 33; 43% M	Modified BDI-21, top quintile	NCEP ATP-III	Unpublished data; participants with baseline MetS were excluded
Vanhala 2009	Finland	75/294	7	Age mean: 46; 0% M	BDI ≥10	NCEP ATP-III	Results from men not shown; participants with baseline MetS were excluded

M, male; ADM, antidepressant medication; GHQ, General Health Questionnaire; MDD, major depressive disorder; POMS, Profile of Mood States; PSE, Present State Examination. *A complete list of the references is available in Supplementary References. †Modifications of the MetS diagnosis criteria are as follows: in the Almeida et al. study, no biochemistry measures were available; therefore, self-reported history or treatment of hypertension, diabetes, high cholesterol, and high triglycerides were used as the components of MetS; and in the Gaysina et al. study, fasting HbA_{1c} level of ≥5.8% was used instead of fasting glucose level of ≥6.1 mmol/L.

Laudisio et al. (20) reported that MetS was associated with the Geriatric Depression Scale score in a multivariate linear regression analysis in women (β = 2.14 [95% CI 0.14–4.14]) but not in men (β = −0.84 [−3.17 to 1.49]). Therefore, even if these studies were included, the significant association between depression and MetS would not change.

Cohort studies of MetS predicting depression risk

Nine cohort studies investigated the association between baseline MetS status and incident depression with a total sample size of 26,936 and 2,316 depression case subjects. Characteristics of the studies are shown in Table 2. Of the nine studies, MetS was identified by the NECP ATP-III criteria in seven studies, by the IDF criteria in one study, and by the modified NECP ATP-III criteria in one study as a result of the unavailability of biomarker data. In defining depression, six studies used a self-reported symptom scale, two studies used clinical diagnosis–based indicators for depression (one study used a physician diagnosis from ICD-10 codes and one used a structured clinical diagnostic interview), and one study used a self-reported symptom scale and/or antidepressant medication use. Participants with depression at baseline were excluded in all nine studies, with two studies excluding lifetime depression case subjects and the other seven studies excluding the current depression case subjects. Two studies were conducted exclusively in men, one study in women, and six studies were in both sexes with one study reporting results separately for men and women. Four studies enrolled participants aged >65 years; the other five studies enrolled young to middle-aged groups. Five studies were implemented in European countries, two in the U.S., one in Japan, and one in Australia. The follow-up ranged from 1 to 10 years. The statistical models, adjusted covariates, and results from each study are shown in Supplementary Table 3.

One study reported the results stratified by sex; therefore, there were 10 reports from nine studies. A moderate heterogeneity was detected (I^2 = 56.8%), and the pooled adjusted OR was 1.49 (95% CI 1.19–1.89) (Fig. 2). No publication bias was detected (P = 0.25) (Supplementary Fig. 2B). Furthermore, when the diagnostic components of MetS were analyzed separately (Supplementary Table 4), significant positive association was found between central obesity (1.20 [1.07–1.35]),

hypertriglyceridemia (1.20 [1.05–1.38]), and low HDL concentrations (1.39 [1.19–1.62]) with risk of depression but not for hyperglycemia (1.05 [0.78–1.42]) and high blood pressure (0.96 [0.72–1.29]) with risk of depression.

The subgroup analyses are shown in Supplementary Table 4. We found that the association was more pronounced in men (OR = 2.15 vs. 1.66), in non-European residents (1.69 vs. 1.25), in studies using diagnostic interview to diagnose depression (2.18 vs. 1.36), and in studies not using NECP ATP-III criteria for MetS definition (2.31 vs. 1.28) compared with their counterparts. However, because of the limited numbers of studies within several subgroups, the results should be interpreted cautiously.

Cohort studies of depression predicting MetS risk

Four cohort studies investigated the association between baseline depression and future risk of MetS with a total sample size of 3,834 and 350 MetS case subjects. In one study, MetS at baseline was not assessed, but the results did not change when baseline obesity or diabetic case subjects were excluded as specified in that study. The characteristics of the studies are shown in Table 2. Of the four studies, depression was defined by a self-reported symptom scale in three studies and by diagnostic interview in one study. All of the four studies used the NECP ATP-III criterion or its modified version to determine MetS status. Two studies were conducted in women and two in both sexes with total and sex-specific results reported. All four studies enrolled participants aged <60 years. Three studies were implemented in European countries and one in the U.S. The follow-up ranged from 6 to 17 years.

The pooled adjusted OR was 1.52 (95% CI 1.20–1.91) (Fig. 2) with no heterogeneity detected (I^2 = 0%). No publication bias was detected (P = 0.50) (Supplementary Fig. 2C). For the subgroup analyses (Supplementary Table 5), the association was stronger in women (1.72 [1.33–2.23]) but not significant in men (1.03 [0.62–1.69]). No significant differences were found for other stratified variables. Two studies reported results for each component of MetS, and the OR by baseline depression was marginally significant only for central obesity (1.31 [0.99–1.73]) and hypertriglyceridemia (1.28 [0.98–1.67]).

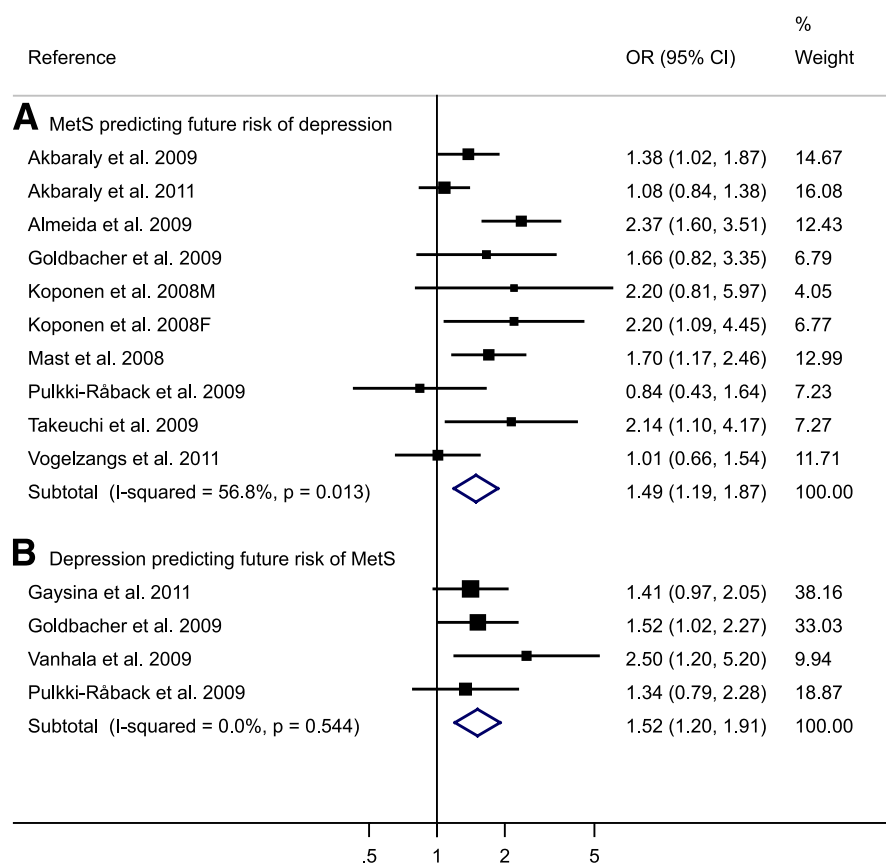Of note, two articles (21,22) from the same cohort study were excluded from

Figure 2—*Forest plot of prospective studies of the adjusted OR between depression and MetS: baseline MetS predicting incident depression and baseline depression predicting incident MetS.*

the meta-analysis because depressive symptoms score (BDI score) was used as a continuous variable. In the article with longer follow-up (22), the authors reported that 1-SD increment in the BDI score was associated with 29% increased odds of MetS (OR 1.29 [95% CI 1.04–1.60]). Thus, our results would not change if we included this study.

CONCLUSIONS—To the best of our knowledge, this is the first meta-analysis that examines the association between depression and MetS, using data from both cross-sectional and cohort studies. We found that depression and MetS were significantly correlated in cross-sectional studies, and a bidirectional association was observed in prospective cohort studies.

Most of the cross-sectional studies reported a higher prevalence of depression in participants with MetS compared with those without. However, the prevalence varied significantly by sex, study design, subject sources, and assessment methods of depression and MetS. Therefore, we did not pool the prevalence; instead, we

pooled the OR, a measure of association that was more consistent across studies. Our estimated crude OR was 1.42 (95% CI 1.28–1.57), suggesting that MetS and depression are significantly related. The effect size remained significant in the pooled ORs of studies adjusting for potential confounders, such as sociodemographic factors and lifestyle factors: the pooled adjusted OR of depression by MetS status was 1.27 (1.07–1.51), and the pooled adjusted OR of MetS by depression status was 1.34 (1.18–1.51).

We found that the association was somewhat stronger in cross-sectional studies that identified depression using a self-reported symptom scale rather than a structured clinical diagnostic interview or clinician diagnosis. One possible explanation is that estimates may differ depending on the use of dimensionally versus categorically based depression assessment tools (23). Categorically based tools—particularly structured psychiatric interviews—would explicitly exclude individuals with subsyndromal depressive symptoms from case status. By contrast,

use of self-reported symptom cutoff scores would allow inclusion of many people with clinically significant depressive symptoms who would not meet formal criteria for DSM diagnosis, yet abundant evidence indicates that subsyndromal depressive symptoms, like clinical syndromes, are significantly associated with morbidity, adverse functional outcomes, and excess health care use (24). Thus, inclusion of people with subsyndromal depression in the reference category may have weakened estimates of studies using categorically based depression definitions. However, this is in opposition to cohort studies of MetS predicting depression: participants with MetS were more likely to develop clinical diagnosed depression than self-reported symptoms (OR = 2.18 vs. 1.36). Nevertheless, only two studies used clinical diagnosed depression (16,25), and the definition of MetS in the Almeida et al. (25) study was stringent (meeting all four criteria of high waist circumference and self-reported treatment of dyslipidemia, diabetes, and hypertension). Thus, this result should be interpreted cautiously. We also found that the association was stronger in studies that defined MetS using the IDF criterion instead of the NCEP ATP-III criterion. The major distinction between the two criteria is that the IDF criterion specifies an obligatory component of central obesity, which is optional in the NCEP ATP-III criterion. Depression was significantly associated with central obesity (26), which might explain why the association was stronger when the IDF definition was used.

Cross-sectional studies do not provide the temporal relationship between depression and MetS. We thus conducted a further meta-analysis to investigate the association between depression and MetS in prospective cohort studies. This observed bidirectional association between depression and MetS was consistent with results from the cross-sectional studies and also in agreement with two recent meta-analyses that show a reciprocal association between depression and diabetes (2) and between depression and obesity (27).

The interplay between depression and MetS is likely to be mediated through multiple mechanisms. First, depression has been positively associated with central obesity (26), chronic inflammation (28), and insulin resistance (29), which are underlying etiological mechanisms for MetS (2). Second, depression has known neuroendocrine effects (e.g., dysregulation of the hypothalamic-pituitary-adrenocortical axis and sympathetic nervous

system activation) (3), which could influence MetS risk by affecting abdominal fat accumulation, glucose metabolism, and blood pressure regulation (30). Third, depressed individuals tend to have poor diet and sleep disturbance and engage in less physical activity (31), and these behaviors are known risk factors for the development of MetS. Fourth, conventional medication treatment for depression may exert direct effects on various components of MetS and partially explain the observed association (32). In the opposite direction, individuals with MetS have increased levels of inflammatory cytokines (e.g., C-reactive protein and interleukin 6) (5) and leptin resistance (33), which may also be involved in depressive mood (34,35). Other metabolic disturbances, such as insulin-glucose homeostasis and mitochondrial respiration, are also indicated in the pathophysiology of depression (36). Another potential explanation is that vascular damage in the brain might predispose to depression in the elderly according to the vascular depression hypothesis (37). MetS, as a cluster of vascular risk factors, could lead to subclinical vascular damage (38), which in turn may produce depressive symptoms. Furthermore, MetS is associated with a sedentary lifestyle and a negative self-perception due to stigmatization of obesity (a component of MetS), which can lead to an increased risk of depression (27,39). Taken together, the potential mechanisms are complex and may involve several shared physiological pathways, such as obesity and inflammation. Certainly, more studies are needed to explore the mechanisms underlying this reciprocal relation, which will be crucial for the prevention and treatment of both conditions.

This meta-analysis has strengths and limitations. The primary strength is that this is the first meta-analysis that explicitly examines the bidirectionality of the depression-MetS relationship on the basis of a comprehensive literature search. We contacted authors for unpublished data and found no indication of publication bias in all the analyses. However, the meta-analysis was limited to English-language publications, and we may have missed some articles of other languages. We also observed robust and consistent associations across different subgroups via sensitivity analyses and subgroup analyses. Yet as a major limitation, there was evidence of heterogeneity across the studies used for the analysis of association between MetS and risk of depression in both study designs. This heterogeneity

may be attributable to the differences in study design, sample size, analysis strategies, participants' characteristics, and diagnostic criteria of depression and MetS definition criteria. To account for the heterogeneity, we chose random-effects models for the meta-analyses, but the results were not materially changed when we used fixed-effect models. Furthermore, few cohort studies examine the association between baseline depression and future risk of MetS and, thus, more investigations along this line are needed.

In spite of these limitations, our results have significant implications for both clinical care and public health. Mounting evidence suggests that depression is associated with increased risks of diabetes (2) and CVD (3). MetS is regarded as an intermediate condition that frequently proceeds to the clinical manifestations of diabetes and CVD, although MetS is not usually diagnosed in clinical settings. Our results suggest that the association between depression and diabetes/CVD might start at an early stage before individuals meet the diagnostic criteria of diabetes or CVD. Therefore, we argue that in patients with depression, the cardiometabolic risk factors and MetS status should be carefully monitored, and proper treatment and lifestyle changes could be advised if the patients are at a higher risk of diabetes/CVD. On the other hand, for people with MetS who are already susceptible to diabetes/CVD, early detection of depression may inform appropriate preventive strategies. Collaborative care for patients with depression and diabetes/CVD recently has been demonstrated to be effective in control of both depression and comorbidities (40). Certainly, more studies are still needed to evaluate whether early screening and collaborative care for patients with depression and MetS (or its components) could reduce the future risk of diabetes and vascular diseases.

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