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Metabolic Syndrome and Depression: A Systematic Review of the Association

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METABOLIC SYNDROME AND DEPRESSION: A SYSTEMATIC REVIEW
OF THE ASSOCIAITON

by

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This scholarly paper has been read by this faculty member and
has been found to be satisfactory.

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ABSTRACT

METABOLIC SYNDROME AND DEPRESSION: A SYSTEMATIC REVIEW
OF THE ASSOCIAITON

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Purpose
To explore whether there is an association between metabolic syndrome (MetS) and depression, the nature of the relationship, and implications for practicing health care professionals.

Data Sources
Peer reviewed articles obtained through electronic database search in: CINAHL, The Cochrane Library, MEDLINE, and PsychINFO between the years of 2006 and 2013.

Results
MetS and depression have a bidirectional association; MetS leads to depression and vice-versa. More severe depression has a stronger association with MetS. Increased waist circumference (AKA: abdominal obesity, body mass index [BMI]), elevated triglycerides, and low HDL cholesterol are the MetS components most commonly/strongly associated depression. Though not thoroughly evaluated, gender, age, and race were not found to impact this association.

Implications for Practice
As patients with MetS are at higher risk for developing depression, and vice-versa, practitioners should evaluate patients with either condition for the presence of the other. Presence/severity of depression should be assessed with a screening instrument. In the reviewed articles no suggested treatment is given; MetS components and depression should each be treated independently. Caution should be exercised with TCA antidepressants as they are associated with abdominal obesity.

Keywords:
Association, depression, major depressive disorder (MDD), metabolic syndrome, waist circumference, abdominal obesity, body mass index (BMI), high density lipoprotein (HDL), hypoalphalipoproteinemia, hypertriglyceridemia, diabetes mellitus (DM), blood glucose, hyperinsulinemia, insulin resistance, hypertension (HTN).

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Metabolic syndrome and depression: A systematic review of the association

MetS is a constellation of symptoms found concurrently in a patient. The most widely used criteria are the ATP-III and the IDF; diagnoses of MetS using these criteria are explained in Table 1.

The prevalence of Metabolic Syndrome (MetS) in the United States is currently 35% as defined by the National Cholesterol Education Program Adult Treatment Plan-III criterion (ATP-III) and 39% using the International Diabetes Federation (IDF) criterion (McCullough, 2011). Prevalence of MetS from 1988-1994, according to the ATP-III criteria, was found to be 21.8% (Ford, Giles, & Dietz, 2002). The average yearly health care cost for a patient with MetS is 1.6-times that of a non-MetS patient with the overall cost increasing by an average of 24% per additional risk factor (Boudreau et al., 2009). These figures underscore the importance of detection and treatment of MetS.

Because of the significant effects of this syndrome on morbidity and mortality, and the dramatic increase in prevalence of the syndrome, much research is being done to determine other factors that may impact the syndrome. Depression is one disease entity that is presently being explored as either a causal factor or a result of MetS (Almeida, Calver, Jamrozik, Hankey, & Flicker, 2009; Pyykkönen et al., 2012; Skilton, Moulin, Terra, & Bonnet, 2007).

Depression is the most common mental disorder in the US (McLaughlin, 2011). Nearly 1 in 5 adults in the US (about 42.1 million Americans) screen positive for at least mild depressive symptoms (Shim, Baltrus, Ye, & Rust, 2011). Estimated cost of major depression in the US is $83.1-billion per year (McLaughlin, 2011).

Depression is a cluster of symptoms manifesting in a patient. *The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5; American Psychiatric Association, 2013) provides the definition of the various types of mood disorders. The current

criterion for the diagnosis of Major Depressive Disorder (MDD) is shown in Table 2. The prevalence and serious nature of these two conditions prompts us to ask whether MetS and depression are associated. Evidence suggests an association between these conditions (Almeida et al, 2009; Seppälä et al., 2011; Takeuchi et al., 2009). What seems unclear is whether depression is a contributing factor to MetS or occurs because of MetS. The purpose of this systematic review is to explore whether there is an association between MetS and depression, the nature of the relationship, and implications for practice.

Methods

An electronic database search was conducted in CINAHL, The Cochrane Library, MEDLINE, and PsychINFO between the years of 2006 and 2013. Article titles were searched for the key terms metabolic syndrome and depression. Accepted articles described the relationship between metabolic syndrome and depression in an adult population (age ≥ 18 years-old). Inclusion criteria for selected articles included peer-reviewed, outpatient populations, written in the English language, and included only human subjects. Articles suggested by experts, as well as articles identified from reference lists of accepted articles, that fit the inclusion criteria, were also included. Rigor of articles was assessed using Melnyk and Fineout-Overhold's (2011) levels of evidence; the strongest being level-I and weakest level-VII. All articles included were at level-IV. A total of 21 articles were included in the review..

Results

Association of MetS and Depression

Results concerning the association of MetS and depression are mixed, though most (15 out of 21) studies report an association between MetS and depression as shown in Table 3.

Nature of the Association. The exact nature of the association between MetS and depression is unknown. It is unclear whether depression is a risk factor for MetS or vice-versa. Evidence supports both premises. Multiple studies suggest that depression is a risk factor for MetS, though the exact mechanism is unknown. For example, subjects with depression have anywhere from 1.11-10.10 greater odds of developing MetS, p-value range <0.0001 to 0.004. Similarly, those with MetS have 1.47-2.37 greater odds of developing depression than those who do not have MetS (p-value range <0.001 to ≤0.05); five of the seven studies that reported MetS as a risk for developing depression studied new-onset depression specifically. One study reported MetS is a risk factor for new-onset depression HR 2.37, 95% CI 1.60-3.51, p<0.001 (Almeida et al., 2009) and another reported higher mean depression scores of those with MetS when compared to those without those without (3.14 vs. 2.95; 95% CI 3.12-3.70 vs. 2.76-3.13; p=0.013; Dunbar et al., 2008).

No Association Reported. Six studies found no significant association between MetS and depression. Though the overall relationship was not significant, the majority of these studies report that one, or more, individual components of MetS have a significant association with depression (Foley et al., 2010; Herva et al., 2006; Hildrum, Mykletun, Midthjell, Ismail, & Dahl, 2009; Vogelzangs et al., 2009). Tsai and Tsai (2012) suggests that it is any functional impairment, not MetS, that is associated with greater risk for depression (OR 5.13, 95% CI 2.13-12.36, p<0.001).

Components of MetS and their Association with Depression

Many components of MetS were found to be significantly associated with depression, whether in combination with another or individually. Large waist circumference (WC), elevated triglycerides, low HDL cholesterol, and elevated glucose were the most commonly associated

components of MetS and depression. Major findings will be discussed in this section, for more detail see Table 3.

Waist circumference (also discussed in the literature as increased BMI or abdominal/central obesity) was the MetS component most commonly associated with depression. Twelve of the studies found increased waist circumference was associated with depression. Results from seven of those studies showed OR range 1.02-2.37 (p-value range 0.002 to < 0.008) and β-range 0.038-0.070 (p-value range <0.0001-0.003). Almeida et al. (2009) reports that depression is associated with elevated BMI, HR 1.31, 95% CI 1.05-1.64, p=0.018. Hildrum et al. (2009) reports that depression is associated with central obesity, OR per standard deviation (SD) increase in depression 1.07, 95% CI 1.02-1.11, p<0.05. Three studies indicate that increase waist circumference is associated with depression by using means of comparison (p-value range <0.0001 to <0.05). One study reported an inverse association between depression and waist circumference (β= -0.063, p=0.03) and sub-threshold depression and waist circumference (β= -0.085, p=0.002; Vogelzangs et al., 2009).

Elevated triglyceride levels were found to be associated with depression in ten studies. Results from nine of those studies showed OR range 1.36-7.73 (p-value range from 0.001 to <0.05) and β-range 0.042-2.073 (p-value range <0.001-0.003). Three studies indicate that hypertriglyceridemia is associated with depression by using means of comparison (p-value range 0.015 to <0.05). Hildrum et al. (2009) reports that depression is associated with elevated triglycerides, OR per SD increase in depression 1.08, 95% CI 1.03-1.13, p<0.05.

Low HDL cholesterol levels were found to be associated with depression in eleven studies. Most studies reported this association between depression and low HDL cholesterol; OR range 1.33-1.81 (p-value range 0.03 to ≤0.05), β-range 0.074-0.089 (p-value range 0.003-0.009).

Some studies reported an inverse relationship between HDL cholesterol and depression (showing an association between depression and low HDL cholesterol), OR range -1.22 to -2.89 (p-value range 0.001-0.002), β-range -0.056 to -0.063 (p-value range 0.002-0.01). Two studies indicate that low HDL cholesterol is associated with depression by using means of comparison (p-value range 0.003 to <0.05). Hildrum et al. (2009) report low HDL cholesterol grows in associated with increasing depression, OR per SD increase depression 1.05, 95% CI 1.01-1.10, p<0.05.

High blood glucose (also referred to as diabetes mellitus [DM in the literature]) was found to be associated with depression in eight studies; OR range 1.80-4.14 (p-value range 0.001-0.02). Three studies indicate that high glucose is associated with depression by using means of comparison (all p-values <0.05). One study reported β=0.079, p<0.001 (Luppino et al., 2011) and another reported HR 1.57, 95% CI 1.22-2.03 (Almeida et al., 2009).

HTN was associated with depression in a total of four studies; results from three of the studies show OR range 1.34-2.26 (all p-values ≤0.05) and Luppino et al. (2011) report somatic arousal (SA; β=0.069, p<0.001) and positive affect (PA; β=0.076, p<0.001) depression associated with HTN. East et al. (2010) report that in three models HTN is associated with depression by means of comparison (all p-values<0.05) and in one model systolic blood pressure was inversely associated with depression (p<0.05). A total of four studies report that HTN was inversely associated with depression; results from three of the studies show OR range 0.63-0.75 (p-value range 0.02 to <0.05) and Hildrum et al. (2009) report an inverse relationship per standard deviation increase in depression OR 0.91, 95% CI 0.87-0.96, p<0.05.

Five studies reported that increased numbers of MetS components were associated with depression but did not give figures. Akbaraly et al. (2009) reported that the combination of large waist circumference, elevated triglycerides, and low HDL cholesterol were associated with new-

onset depression (OR 2.71, 95% CI 1.73-4.24). Luppino et al. (2011) reported that depression was associated with increasing number of MetS components (SA: β=0.098, p<0.001, p-trend=0.001; PA: β=0.107, p<0.001). Interestingly, Almeida et al. (2009) reported that depression was not associated with any combination of 3 of the 4 MetS components; this finding is likely explained by the combination of triglycerides and low HDL cholesterol into a single component (which alters MetS criteria).

Discussion

In this review of 21 articles, fifteen report that MetS and depression are associated. Six report they are not; though some of these found that individual MetS components are associated with depression. This association is bidirectional, which is consistent with the findings of a similar review (Pan et al., 2012). Gender was not found to be a significant influence on the relationship; six report an association in both genders, three in only males, and three in females only. Similarly, age does not seem a significant influence on the relationship; subject's ages varied in most studies and were usually not discussed. Foley et al. (2010) reported risk of MetS in depressed patients increased with age (OR 1.04, 95% CI 1.03-1.05, p<0.001). None of the articles reported on race.

Implications on Practice

Patients with MetS should be screened for depression, and vice-versa, and close follow-up is suggested. Implications largely fall into assessment and treatment.

Assessment. Careful assessment of patients with either MetS or depression to determine whether the other disease is present is important in designing effective treatments, since there appears to be a bidirectional relationship. Treating one disease without determining if the other

disease is present may minimize the effectiveness of the treatment for either disease. Screening should be done using established criteria and/or instruments.

Assessing for MetS using either ATP-III or IDF criteria is acceptable as these criteria are comparable. The three most frequently associated components of MetS with depression are increased waist circumference (AKA: abdominal obesity, body mass index [BMI]), elevated triglycerides, and low HDL cholesterol. The combination of large waist circumference, elevated triglycerides, and low HDL cholesterol is strongly associated with depression (Akbaraly et al., 2009). If the patient screens positive for one of the MetS components, or depression, than the practitioner should screen for depression and presence of other MetS components; especially depression, large waist circumference, elevated triglycerides, and low HDL cholesterol.

It is also important to use a screening instrument to determine the presence, type, and severity of the depression (as these may all affect the strength of the relationship). A variety of screening instruments for depression were used in the articles reviewed. None of the articles discussed the different instruments in terms of effectiveness. The most frequently used methods/instruments for assessing depression in the reviewed articles were: clinical interview using the current DSM criteria, *Center for Epidemiologic Studies Depression Scale* (CES-D), *Beck Depression Inventory* (BDI), *Hospital Anxiety and Depression Scale – Depression* (HADS-D), *Patient Health Questionnaire* (PHQ), and *Inventory of Depressive Symptoms – Self Report* (IDS-SR), among others. Though many different types of depression are associated with MetS (non-melancholic, somatic arousal SA, positive affect [PA], and high mental status [HMS]), severity of depression – no matter the type – more strongly affects the association between MetS and depression. Pyykkönen et al. (2012) illustrate this point in their reporting that the odds for having MetS increase by 10% for each SD increase in depressive symptoms. Close follow-up is

important as the development of one disease may follow the diagnosis of the other disease. For example those with MetS are more likely to have the development of first-time depression.

In addition, screening for cardiovascular disease (CVD), stroke risk, sleep disturbances, and preeclampsia in pregnant women should be central to the care of patients with MetS (and to some extent) depression, as their risk for these complications are higher.

Suggested Treatment. Treatment of depression and MetS, including each of its components, should address individual entities. If both diseases are present and only one disease is diagnosed and treated, the effectiveness of the treatment could be impaired; generally the treatment of both diseases will improve the outcomes of each disease. Assisting patients to make life-style modification and improve cardiovascular fitness is strongly suggested; close follow-up, education, and continued patient encouragement are also suggested. In treating depression, it is recommended that tricyclic antidepressants (TCAs) be avoided as they are associated with MetS, abdominal obesity, elevated triglyceride levels, and HTN (van Reedt Dortland et al., 2010). Because of the complex nature of these disease processes, a general principal to follow would be consultation with a clinical pharmacologist when prescribing medications to treat comorbid MetS and depression. This is to ensure that prescribed treatments will not worsen any of the concurrent disease entities.

Suggestions for further research

The designs of the reviewed studies cannot establish causality; further longitudinal studies should be done in order to determine the causal relationship. Research should be conducted to determine if treatment of depression leads to resolution/improvement in MetS, and vice-versa. Paramount would be research that would determine the pathophysiology of this

association, in order to develop an evidence-based treatment protocol that ensures best outcomes for patients with MetS and depression.

Limitations

This integrative literature review illustrates a number of limitations in current research. First, the majority of data were taken from cohort and cross-sectional design studies. There was a lack of information coming from longitudinal designs and, because of the research question, there is an inability to gain information from randomized control trials. Second, because of individual research designs controlling for all possible confounding variables did not occur. For example, patient use of antidepressant medication and life-style factors (other than smoking status, alcohol use, or physical activity) was rarely discussed. Third, many of the included studies relied on self-reported data. Although self-reported data is useful, it may be unreliable. Fourth, very few studies included race as a variable in their studies. Studies that included race did not report on it.

This review had some limitation in its ability to directly compare data due to the use of different depression scales and the use of different MetS criteria (some studies even altered accepted criteria to be able to analyze data retrospectively); some might argue that the displayed relationship under such a wide variety of measures strengthens the association. Finally, only studies written in English and available on electronic databases were reviewed.

Conclusion

The purpose of this review was to explore whether there is an association between MetS and depression, the nature of the relationship, and implications for practice. Results of individual studies are mixed, yet these data suggest that there is a bidirectional association between MetS and depression. Multiple MetS components are also found to be independently

associated with depression. Patients with MetS should be screened for depression and those with depression should be screened for MetS; use of established MetS criteria and depression screening instruments is strongly encouraged. In addition, screening for cardiovascular disease (CVD), stroke risk, sleep disturbances, and preeclampsia in pregnant women should be central to the care of patients with MetS (and to some extent) depression, as their risk for these complications are increased. The comorbid presence of these conditions requires sensitive yet aggressive management. Patient understanding of needed lifestyle changes, adherence to medical therapies, and assistance to make these changes is paramount for best outcomes.

The individual components of MetS and depression should be treated individually. Generally the treatment of both diseases will improve the outcomes of each disease. Close follow-up, education, and continued encouragement are also suggested. TCAs should be avoided in the treatment of depression as they are associated with MetS, abdominal obesity, elevated triglyceride levels, and HTN. Consultation with a clinical pharmacologist to ensure that prescribed treatments do not worsen either disease entity is suggested.

Though the association of these conditions is clear, the question remains as to the exact cause. Further studies to determine the cause of this association is suggested. Researchers should focus their efforts on determining a treatment protocol for comorbid MetS and depression to assist practitioners in obtaining the best patient outcomes possible.

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TABLES

Table 1: ATP-III and IDF criteria for MetS diagnosis

Criteria	ATP-III	IDF
How MetS is diagnosed with the criteria	Presence of ≥3 of the above components	Increased waist circumference and presence of ≥2 of the above components
Abdominal obesity (waist circumference)	Male: ≥40 in/102 cm Female: ≥35 in/88 cm	Uses a scale based on race and gender. (i.e.: Europids: Male: ≥94 cm, Female: ≥80 cm)
Elevated Triglyceride levels	≥150 mg/dL (1.7 mmol/L) or current drug treatment for elevated levels	
low high density lipoprotein (HDL) levels	Male: < 40 mg/dL (1.03 mmol/L), Female: < 50 mg/dL (1.29 mmol/L) or current drug treatment for low HDL	
Hypertension (HTN)	≥130/85,	>135 / >85
	or current treatment for HTN	
Elevated fasting glucose (also referred to as hyperglycemia, insulin resistance, or diabetes mellitus [DM])	≥ 100 mg/dL (5.6 mmol/L) or previous diagnosis of DM or current drug treatment for elevated blood glucose	

(Grundy et al., 2005; International Diabetes federation, 2006)

Table 2: DSM-5 criteria for diagnosis of depression

MDD is diagnosed when a combination of five, or more, of the following symptoms are present for most of the day, nearly every day, for a period of at least two-week. (Note: At least one symptom must be either of the shaded symptoms. Symptoms should not be counted if they can be clearly attributed to another medical condition.)
Depressed mood Loss of interest/pleasure in most, or all, activities
Insomnia/hypersomnia Change in appetite/weight (e.g., a change of ≥5% body weight in one month) Psychomotor retardation/agitation Fatigue/low energy Poor concentration/mentation or indecisiveness Thoughts/feelings of worthlessness/guilt Recurrent thoughts about death/suicide

(American Psychiatric Association, 2013)

Table 3: Association of MetS and MetS Components with Depression - Major Findings

Author/Year Design/Location	Characteristics Measures	Major Findings: Association	Major Findings: Components MetS

Akbaraly et al., 2009
 	
Prospective, cohort
 	
Britain
	n=5,232
	Male and Female
	Age: 41-61 yo
	
	MetS: ATP-III
	Depression: GHQ
		MetS associated with new-onset depression (OR 1.47, 95% CI 1.09-1.99, p=0.01), adjusted for sex, age, and ethnicity; remained significant after further adjustment.
		No association with depression and new-onset MetS (OR 0.89, 95% CI 0.60-1.33, p=0.57), adjusted for sex, age, and ethnicity; remained insignificant after further adjustment.
			New-onset depression associated with the following, after adjusted for sex, age, and ethnicity:
			   Central obesity (OR 1.50, 95% CI 1.11-2.01, p=0.007); remained significant after further adjustment.
			   Elevated triglycerides (OR 1.36, 95% CI 1.09-1.71, p=0.007); remained significant after further adjustment.
			   Low HDL cholesterol (OR 1.33, 95% CI 1.04-1.69, p=0.02); remained significant after further adjustment.
			   Combination of WC, elevated triglycerides, and low HDL cholesterol (OR 2.71, 95% CI 1.73-4.24).

Akbaraly et al., 2011
 	
Prospective, cohort
 	
France
	n=4,446
	Male (45.3%) and Female (54.7%)
	Age: 65-91 yo
	
	MetS: ATP-III
	Depression: CES-D, antidepressant use at follow-up
		MetS associated with new-onset depression in 65-69.4 yo age group (OR 1.73, 95% CI 1.02-2.95, p=0.04), adjusted for age, sex, study center, education, MetS treatment, marital status, smoking and alcohol use, cognitive deficit, disability, BMI, and CVD; remained significant after further adjustment.	New-onset depression associated with the following, after adjusted for age, sex, study center, MetS treatment, education, marital status, smoking and alcohol use, cognitive deficit, disability, BMI, and CVD:
			   Low HDL cholesterol in the 65-69.4 yo group (OR 1.81, 95% CI 1.04-3.17, p=0.03).
			   High glucose in the 69.4-72.8 yo group (OR 1.80, 95% CI 1.10-2.96, p=0.02).
			   HTN inversely associated with MetS in the 72.8-76.8 yo group (OR 0.63, 95% CI 0.43-0.92, p=0.02).

Almeida et al., 2009
 	
Population-based, prospective, cohort
 	
Australia
	n=12,066
	Male (100%)
	Age: 65-84 yo; mean 72.1 yo, SD 4.4
	
	MetS: ATP-III with self-report
	Depression: ICD-9, ICD-10 diagnosis
		Cumulative Proportion of older men with MetS experienced new-onset depression (HR 2.37, 95% CI 1.60-3.5, p<0.001), adjusted for age, marital status, education, socioeconomic status, smoking and alcohol use, diet, and physical activity.	Cumulative Proportion of older men with depression associated with the following after adjusted for age, marital status, education, social disadvantage, smoking and alcohol use, diet, and physical activity:
			   High BMI (HR 1.31, 95% CI 1.05-1.64, p=0.018)
			   DM (HR 1.57, 95% CI 1.22-2.03, no p-value given)
			Depression not associated with any combination of 3 of the 4 MetS components (hypertriglyceridemia and low HDL cholesterol combined; HR 1.10, 95% CI 0.88-1.39, p = 0.403).

Dunbar et al., 2008	n=1,345 Male and Female	Those with MetS had higher mean depression scores [3.41 (95% CI 3.12-	High HADS-D score associated with the following, compared to those without depression, after adjusted for sex, smoking and

Cross-sectional, non-experimental, correlative Turkey	Age: 25-84 yo MetS: ATP-III, IDF Depression: HADS-D	3.70) vs. 2.95 (95% CI 2.76-3.13), p=0.013], adjusted for sex, smoking and alcohol use, and physical activity; remained significant after further adjustment.	alcohol use, and physical activity: Large WC (mean score 3.38 vs. 2.86, 95% CI 3.14-3.63 vs. 2.66-3.06, p=0.002); remained significant after adjustment. Low HDL cholesterol (mean score 3.75 vs. 2.93, 95% CI 3.37-4.13 vs. 2.76-3.10, p=0.003); remained significant after adjustment.
East et al., 2010 Cross-sectional, cohort USA	n=5,125 Male (67%) and Female (33%) Age: 20-88 yo Male: average 49.3 yo (SD 10.2 yrs) Female: average 47.6 yo (SD 10.3 yrs) MetS: ATP-III Depression: CES-D 10, Self-reported history	Depression associated with MetS in men (OR 1.56, 95% CI 1.33-1.84, p<0.0001) and women (OR 2.35, 95% CI 1.71-3.24, p<0.0001); remained significant after all adjustments in women, lost significance after final adjustment in men.	Depression associated with the following, compared to those without depression: Men: BMI (mean 28.4 vs. 27.3, p<0.05). Large WC (mean 96. vs. 94.2, p<0.05). Elevated triglycerides (median 119 vs. 104, p<0.05). Low HDL cholesterol (mean 46.8 vs. 49.5, p<0.05). History DM (2.7% vs. 1.6%, p<0.05). Elevated SBP, inversely (mean in mmHg 123 vs. 125, p<0.05). Elevated DBP (mean in mmHg 83.7 vs. 83.4, p<0.05). History HTN (25% vs. 14.4%, p<0.05). Women: High BMI (mean 25.6 vs. 23.6, p<0.05). Large WC (mean 79.7 vs. 74.8, p<0.05). Elevated triglycerides (median 89 vs. 80, p<0.05). Low HDL cholesterol (mean 64.2 vs. 68.3, p<0.05) High glucose (mean 93.1 vs. 91.2, p<0.05). History of HTN (18% vs. 9.6%, p<0.05).
Foley et al., 2010 Non-experimental, correlative Australia	n=3,389 Male (33.7%) and Female (66.3%) Age: Male: 30-85 yo; average 44 yo. Female: 26-90 yo; average 45 yo. MetS: Modified	No association between MetS and depression. MetS component associated with depression (see table 4).	Life-time history major depression associated with low HDL cholesterol (OR 1.33, 95% CI 1.33-1.72, no p-value given); remained significant after adjustment.

	ATP-III (BMI used in place of waist circumference) Depression: DSM-IV MDD		
Herva et al., 2006 Cross-sectional, quantitative, non-experimental, retrospective Finland	n=5,698 Male (49.7%) and Female (50.3%) Age: Mean 31 yo MetS: ATP-III Depression: HSCL	No association between MetS and depression. MetS components associated with depression (see table 4).	Large WC associated with depression (OR 1.30, 95% CI 1.05-1.61); lost significance after adjusted. HTN inversely associated with depression (OR 0.74, 95% CI 0.63-0.88); remained significant after adjustment.

Hildrum et al., 2009
 	
Quantitative, non-experimental, cross-sectional
 	
Norway
	n=9,571
	Male and Female
	Age: 20-89 yo
	MetS: IDF
	Depression: HADS-D
		Authors report no association between depression and MetS. Initial association between MetS and depression as a continuous measures (OR 1.07 per SD increase in symptom load, 95% CI 1.02-1.12, p=0.007), adjusted for age and gender; lost significance after final adjustments.
		
		MetS components associated with depression (see table 4).
			Continuous depression associated with the following, after adjusted for age and gender:
			  Central obesity (OR per SD increase in depression 1.07, 95% CI 1.02-1.11, p<0.05); remained significant after further adjustment.
			  Elevated triglycerides (OR per SD increase in depression 1.08, 95% CI 1.03-1.13, p<0.05); loses significance after further adjustment.
			  Low HDL cholesterol (OR per SD increase in depression 1.05, 95% CI 1.01-1.10, p<0.05); loses significance after further adjustment.
			  HTN inversely (OR 0.75, 95% CI 0.59-0.96, p<0.05 and OR per SD increase in depression 0.91, 95% CI 0.87-0.96, p<0.05); remained significant after further adjustment.

Kinder et al., 2004 Cross-sectional, non-experimental, correlative	n=6,189 Male (87.3%) and Female (69.3%) Age: 17-39 yo MetS: ATP-III Depression:	Depression, life-time history, associated with MetS in women (OR 2.09, 95% CI 1.20-3.65, p≤ 0.01); remained significance after adjustment. No association found in men, though direction of relationship similar.	Depression in women associated with the following, after adjusted for age, race, education, smoking and alcohol use, physical activity, and diet. HTN (OR 2.26, 95% CI 1.38-3.72; p≤0.001). Depression and number of MetS components reported to have a significant graded association.

USA	Interview with DSM-III-revised		
Kobrosly et al., 2010	n=1,126 Male (52.6%) and Female (47.4%) Age: ≥ 40 yo	No association between MetS and depression.	No clear association between MetS (or any of its components) and depression.
Cross-sectional, non-experimental, correlative	MetS: ATP-III Depression: PHQ		
USA			
Koponen et al., 2008	n=1,611 - 923 in 1998 - 688 in 2005 Male and Female Age: approx 42-62	MetS associated with new-onset depression (OR 2.1, 95% CI 1.20-3.80, p≤0.05), adjusted for age, BMI, education, physical activity, smoking and alcohol use, marital status, use of antidepressants; after additionally adjusting for gender only found to be significant in women (OR 2.20, 95% CI 1.10-4.50, p≤0.05).	Depression in women associated with low HDL cholesterol (OR 2.0, 95% CI 1.0-3.9, p≤0.05), adjusted for age, education, smoking and alcohol use, physical activity, BMI, marital status, and antidepressant use.
Population-based, longitudinal	MetS: ATP-III Depression: BDI		
Finland			
Luppino et al., 2011	n=2,433 Male (33.1%) and Female (66.9%) Age: 18-65 yo, mean = 42.3 yo	**Somatic Arousal depression (SA)**: hyperarousal; anxiety symptoms, shortness of breath, palpitations, dizziness, etc. Associated with MetS (β=0.098, p<0.001); remained significant after adjustment. MetS associated with continuous score MASQ-SA dimensions (OR per SD increase MASQ 1.19, 95% CI 1.08-1.31, p<0.001); remained significant after adjustment. **Positive Affect depression (PA)**: anhedonic depression.	**SA depression** (hyperarousal; anxiety symptoms, shortness of breath, palpitations, dizziness, etc) associated with: Large WC (β=0.061, p=0.003); remained significant after adjustments. Elevated triglycerides (β=0.077, p<0.001); remained significant after adjustments. HDL cholesterol, inversely (β= -0.056, p=0.01); remained significant until final adjustment. HTN (β=0.069, p<0.001); remained significant after adjustments. Number of MetS components (β=0.098, p<0.001); remained significant after adjustments. An adjusted (geometric) means across quartiles of the MASQ-D30 was performed for individual components, adjusted for
Non-experimental, correlative, cohort, dimensional	MetS: ATP-III Depression: IDS-SR, MASQ-30D		
Netherlands			

		Associated with MetS (β=0.107, p<0.001), lost significance after adjustment. MetS associated with continuous score MASQ-PA dimensions (OR per SD increase MASQ 1.16, 95% CI 1.05-1.28, p=0.004), lost significance after adjustment. **Negative Affect depression (NA)**: typical depression and anxiety symptoms; i.e. lack of concentration, pessimism. 　No association between NA and MetS.	age, sex, education, smoking and alcohol use, and physical activity. Significant values included: Large WC (p-trend=0.027), elevated triglycerides (p-trend=0.006), HTN (p-trend<0.001), and number of MetS components (p-trend=0.001). **PA depression** (anhedonic depression) associated with: 　Large WC (β=0.070, p=0.001); loses significance after adjustments. 　Elevated triglycerides (β=0.097, p=<0.001); remained significant until final adjustment. 　HDL cholesterol, inversely (β= -0.063, p=0.002); remained significant until final adjustment. 　High glucose (β=0.079, p<0.001); lost significance after adjustments. 　HTN (β=0.076, p<0.001); lost significance after adjustments. 　Number of MetS components (β=0.107, p<0.001); lost significant after adjustments. **NA depression** (typical depression and anxiety symptoms; i.e. lack of concentration, pessimism) associated with elevated triglycerides (became significant after adjusting for age, sex, and years of education [β=0.042, p=0.03]); lost significance after further adjustment.
Pyykkönen et al., 2012<hr>Population-based, cohort Finland	n=4,967 Male (47%) and Female (53%) Age: 18-75 yo<hr>MetS: Harmonized clinical criteria Depression: SF-36	Depression associated with MetS (OR 1.11, 95% CI 1.04-1.19, p=0.002), after adjustment for age and sex; remained significant after further adjustment. Odds for having MetS increased over 10% for each SD increase in depressive symptoms.	Depression associated with the following, after adjusted for age and sex: 　Elevated triglycerides (OR 3.49, 95% CI 2.06-4.92, p=0.001); remained significant through further adjustment. 　HDL cholesterol, inversely (OR -1.22, 95% CI -2.00 to -0.44, p=0.002; remained significant through further adjustment. Severe depression associated with the following, after adjusted for age and sex: 　Elevated triglycerides (OR 7.37, 95% CI 4.14-10.60, p=0.001); remained significant after further adjustment. 　HDL cholesterol, inversely (OR -2.89, 95% CI -4.66 to -1.13, p=0.001); remained significant after further adjustment.

			High glucose (OR 4.14, 95% CI 2.06-6.23, p=0.001); remained significant after further adjustment.

Seppälä et al., 2011
 	
 Population-based, cohort, cross-sectional, non-experimental
 	
 Finland
	n=2,820
	 Male (48%) and Female (52%)
	 Age:52-68 yo, mean 60 yo
	
	 MetS: ATP-III
	 Depression: BDI
		Non-melancholic depression associated with MetS (OR 2.10, 95% CI 1.62-2.73, p<0.001); remained significant after adjustments.
		 Melancholic depression and MetS not associated.
			Non-Melancholic depression associated with:
			   High BMI (women: 16% vs. 13%, men: 14% vs. 11%; both p<0.001).
			   Elevated triglycerides (132 vs. 120.5, p=0.015).
			   High glucose (114.4 vs. 111.0, p=0.048).

Skilton et al., 2007
 	
 Cross-sectional, quantitative, non-experimental, retrospective
 	
 France
	n=1,598
	 Male (62.9%) and Female (37.1%)
	 Age: 30-80 yo
	
	 MetS: ATP-III
	 Depression: HADS-D
		MetS associated with depression in both men (OR 1.57, 95% CI 1.11-2.22, p=0.01) and women (OR 2.25, 95% CI 1.53-3.31, p<0.0001), after adjustment for age, CVD, employment status, and marital status; remained significant after further adjustments.	Depression in women associated with the following, adjusted for age, history CVD, employment status, marital status, smoking, diet, and physical activity:
			   Large WC (OR 1.02, 95% CI 1.01-1.04, p=0.0003).
			   Elevated triglycerides (OR 3.58, 95% CI 1.50-8.52, p=0.004).
			 High HADS-D score associated with the following, adjusted for age, history CVD, employment status, marital status, smoking, diet, and physical activity:
			   Large WC (β[SE] = 0.038[0.01], p<0.0001)
			   Elevated triglycerides (β[SE] = 2.073[.69], p=0.003)
			 Depression associated with increased number of MetS components (p-trend=0.003) and with increased levels of HADS-D score (p-trend=0.002) in men and women.

Takeuchi et al., 2009
 	
 Prospective, cohort
 	
 Japan
	n=956
	 Male (100%)
	 Age: mean 42.7 yo (SD 10.2 yrs; range 20-66 yo; SD 10.2 yrs)
	
	 MetS: IDF
	 Depression: POMS Score, DSM-IV
		MetS associated with new-onset depression in men (OR 2.00, 95% CI 1.05-3.81); remained significant after adjustment.	New-onset depression associated with:
			   Large WC (OR 2.10, 95% CI 1.26-3.50, no p-value given); remained significant after adjustment.
			   Number of MetS components (p-trend<0.01).

Toker et al.,	n=3,880	Depression associated with MetS in	Depression associated with the following in women:

2008 Cross-sectional, quantitative, non-experimental, retrospective Israel	Male (60.1%) and Female (39.9%) Age: 20-75 yo MetS: ATP-III Depression: PHQ	women (OR 1.72, 95% CI 1.21-2.46, p<0.008); remained significant after adjustments. No association found in men.	Large WC (OR 2.06, 95% CI 1.57-2.73, p<0.008); remained significant after adjustment. Elevated triglycerides (OR 1.53, 95% CI 1.10-211, p<0.05) Low HDL cholesterol (OR 1.41, 95% CI 1.03-1.93, p<0.05); lost significance after adjustment. High glucose (OR 2.07, 95% CI 1.30-3.28, p<0.008); remained significant after adjustments. HTN (OR 1.34, 95% CI 1.05-1.85, p<0.05); lost significance after adjustments. Depression associated with the following in men: Large WC (OR 1.58, 95% CI 1.14-2.18, p<0.008); remained significant in the most adjusted model. Elevated triglycerides (OR 1.42, 95% CI 1.04-1.94, p<0.05); lost significance after adjustments.
Tsai et al., 2000 Cross-sectional, quantitative, retrospective, non-experimental Taiwan	n=1,023 Male (57.6%) and Female (42.4%) Age: ≥ 54 yo MetS: ATP II Depression: CES-D	No association between MetS and depression.	MetS components not discussed; authors reported no association between MetS and depression.
van Reedt Dortland et al., 2010 Cross-sectional, quantitative, non-experimental, cohort Netherlands	n=1,846 Male (35.5%) and Female (65.5%) Age: 18-65 yo MetS: ATP-III Depression: DSM-IV, IDS-SR	Moderate (OR 2.48, 95% CI 1.36-4.53, p=0.003) and severe (OR 3.27, 95% CI 1.68-6.38, p<0.001) depression associated with MetS; moderate depression lost significance after adjustments, severe depression remained significant after further adjustments.	MDD (DSM-IV) associated with large WC (OR 1.44, 95% CI 1.15-1.82, p=0.002), lost significant after adjustment. Very severe depression associated with the following, adjusted for age, sex, education, clinic site, and oral contraceptive use: Large WC (OR 2.37, 95% CI 1.27-4.41, p=0.007); remained significant after further adjustment. Elevated triglycerides (OR 2.11, 95% CI 1.05-4.24, p=0.04); lost significance after further adjustment. Increased depression severity (IDS-SR) associated with increased number of MetS components (p<0.001).
Viinamäki et al., 2009	n=1,347 Male and Female	Severe depression associated with MetS (OR 1.14, 95% CI 1.03-1.27). Only	HMS depression associated with Elevated triglycerides in men (71.4% vs. 46.6%, p<0.05).

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Longitudinal, population-based
 	
Finland
	Age: 25-65 yo
	MetS: ATP-III
	Depression: BDI, HDRS, TAS, LS score, DSM-IV
		found to be significant in men (OR 1.31, 95% CI 1.04-1.64) after adjusted for age and gender.
		HMS depression associated with MetS (OR 3.03, 95% CI 1.22-7.53. Only found to be significant in men (OR 10.10, 95% CI 1.99-51.30) after adjusted for age and gender.
		MDD not found to be associated with MetS.
			High glucose in women (54% vs. 34.8%, p<0.05).
			High mean BDI score in men associated with:
			  Elevated triglycerides (11.1 vs. 5.9, p<0.05).
			  High glucose (8.4% vs. 4.6%, p<0.05).
			MDD in men associated with high glucose (26.2% vs. 9.1%, p<0.05).

Vogelzangs et al., 2009
 	
Non-experimental, cross-sectional, correlative, longitudinal, cohort
 	
Netherlands
	n=1,212
	Male (48.5%) and Female (51.5%).
	Age: ≥ 65 yo, mean 75.5 yo ± SD 6.5
	MetS: Modified ATP-III [BP ≥160/90, fructosamine used level in place of glucose(≥247 mmol/L – equal to 6.1 mmol/L glucose)]
	Depression: CES-D (20), DSM-III MDD
		No association between MetS and depression.
		Sub-threshold depression associated with decreased odds of MetS (OR 0.55, 95% CI 0.37-0.82).
		
		MetS component associated with depression (see table 4).
			Depression associated with the following, adjusted for age, sex, education, smoking and alcohol use, physical activity, DM, CVD, and "a number of other chronic diseases":
			  WC, inversely (β= -0.063, p=0.03).
			  Low HDL cholesterol (β=0.089, p=0.003).
			Subthreshold depression associated with the following, adjusted for age, sex, education, smoking and alcohol use, physical activity, DM, CVD, and "a number of other chronic diseases":
			  WC, inversely (β= -0.085, p=0.002).
			  Low HDL cholesterol (β=0.074, p=0.009).

Abbreviations: ATP-III, National Cholesterol Education Program Adult Treatment Plan-III; BDI, Beck Depression Inventory; CES-D, Center for Epidemiologic Studies Depression Scale; CES-D 10, Center for Epidemiologic Studies Depression Scale 10 questions (short form); CI, confidence interval; CVD, cardiovascular disease; DM, diabetes mellitus; DSM-III, Diagnostic and Statistical Manual 3rd edition; DSM-IV, Diagnostic and Statistical Manual 4th edition; GHQ, General Health Questionnaire; HADS-D, Hospital Anxiety and Depression Scale-Depression; HDL cholesterol, high density lipoprotein; HDRS, Hamilton Rating Scale for Depression; HMS, high mental symptoms; HR, hazard ratio; HSCL, Hopkins Symptom Checklist; HTN, hypertension; IDF, International Diabetes Federation; IDS-SR, Inventory of Depressive Symptoms Self-Report; LS score, Life

Dissatisfaction Scale; MDD, Major Depressive Disorder; MASQ-30D, Mood and Anxiety Symptom Questionnaire – 30 question Adaptation; NA, negative affect depression; OR, Odds Ratio; PA, positive affect depression; PHQ, Patient Health Questionnaire Depression Screen; POMS, Profile of Mood States; SA, somatic arousal depression; SE, standard error; SF-36/RAND-36, 36-Item Short Form Health Survey; TAS, Toronto Alexithymia Scale; TCA, tricyclic antidepressants; WC, waist circumference; yo, years old.