The prevalence and risk of metabolic syndrome and its components among people with posttraumatic stress disorder: A systematic review and meta-analysis

Simon Rosenbaum, Brendon Stubbs, Philip B. Ward, Zachary Steel, Oscar Lederman, Davy Vancampfort

PII: S0026-0495(15)00127-4
DOI: doi: 10.1016/j.metabol.2015.04.009
Reference: YMETA 53202

To appear in: *Metabolism*

Received date: 25 March 2015
Revised date: 8 April 2015
Accepted date: 29 April 2015

Please cite this article as: Rosenbaum Simon, Stubbs Brendon, Ward Philip B., Steel Zachary, Lederman Oscar, Vancampfort Davy, The prevalence and risk of metabolic syndrome and its components among people with posttraumatic stress disorder: A systematic review and meta-analysis, *Metabolism* (2015), doi: 10.1016/j.metabol.2015.04.009

METABOLISM: CLINICAL AND EXPERIMENTAL

The prevalence and risk of metabolic syndrome and its components among people with posttraumatic stress disorder: A systematic review and meta-analysis

Simon Rosenbaum[1], Brendon Stubbs[2], Philip B. Ward[1], Zachary Steel[1], Oscar Lederman[1], Davy Vancampfort[3,4,*]

[1]School of Psychiatry, University of New South Wales, Sydney, NSW, Australia

[2]School of Health and Social Care, University of Greenwich, Southwood Site Avery Hill Road, Eltham, London, UK

[3]UPC KU Leuven, campus Kortenberg, KU Leuven – University of Leuven, Department of Neurosciences, Kortenberg, Belgium

[4]KU Leuven – University of Leuven, Department of Rehabilitation Sciences, Leuven, Belgium

Running title: metabolic syndrome in PTSD

Word count: 3098

*Corresponding author: Davy Vancampfort. UPC KU Leuven, campus Kortenberg, KU Leuven – University of Leuven, Department of Neurosciences, Leuvensesteenweg 517, 3070 Kortenberg, Belgium; Tel.: +32 2 758 05 11; Fax: +32 2 759 9879. E-mail address: davy.vancampfort@uc-kortenberg.be

ABSTRACT

Objective: People with posttraumatic stress disorder (PTSD) have a higher mortality than the general population, mainly due to cardiovascular diseases (CVD). Metabolic syndrome (MetS) and its components are highly predictive of CVD. The aim of this meta-analysis was to describe pooled frequencies of MetS and its components in people with PTSD and to compare MetS prevalences in PTSD versus the general population.

Method: Medline, PsycARTICLES, Embase and CINAHL were searched until 02/2015 for cross-sectional and baseline data of longitudinal studies in adults with PTSD. Two independent reviewers conducted the searches and extracted data. Random effects meta-analysis with a relative risk, subgroups and meta-regression analyses were employed.

Results: Overall, 9 studies met the inclusion criteria including 9,254 individuals in midlife with PTSD and 6,852 general population controls. The pooled MetS prevalence was 38.7% (95%CI=32.1%-45.6%; Q=52.1, p<0.001; N=9; n=9,673; age range=44-61years). Abdominal obesity was observed in 49.3% (95%CI=29.7%-69.0%), hyperglycaemia in 36.1% (95%CI=18.8%-55.6%), hypertriglyceridemia in 45.9% (95%CI=12.2%-81.9%), low high density-lipoprotein-cholesterol in 46.4% (95%CI=26.4%-67.0%) and hypertension in 76.9% (95%CI=67.9%-84.8). The MetS prevalence was consistently high across geographical regions, settings or populations (war veterans or not). Compared with matched general population controls, people with PTSD had an almost double increased risk for MetS (RR=1.82; 95%CI=1.72-1.92; p<0.001). Most analyses were not statistically heterogeneous.

Conclusions: MetS is highly prevalent in people with PTSD. Routine screening and multidisciplinary management of medical and behavioral conditions is needed. Future

research should focus on how cardio-metabolic outcomes are moderated by clinical and treatment characteristics and genetic factors.

Key words: PTSD, metabolic syndrome, glucose, MetS, cardiovascular disease, lipids.

1. INTRODUCTION

People with posttraumatic stress disorder (PTSD), experience an excess mortality rate two to three times higher than the general population [1-3]. Previous research has demonstrated that PTSD is associated with poor physical health [4], including the presence and severity of cardiovascular diseases (CVD), which predicts mortality independent of age, gender, and conventional risk factors [5]. To assist clinicians in identifying and treating patients at an increased risk of CVD, the concept of the metabolic syndrome (MetS) has been introduced. MetS is defined by a constellation of risk factors including central obesity, high blood pressure, low high-density lipoprotein (HDL) cholesterol, elevated triglycerides and hyperglycemia. In the general population, these clustered risk factors have been associated with the development of CVD and excess mortality [6-8]. Although several definitions have been proposed for MetS, the most commonly used are the Adult Treatment Panel III (ATP-III) and adapted ATP-III criteria (ATP-III-A) [9, 10] by the National Cholesterol Education Program (NCEP) and the International Diabetes Federation criteria (IDF) [11] by the World Health Organization (WHO) [12]. Current definitions for MetS are aimed at being easy to use in clinical settings and share similar diagnostic thresholds. However, the role of abdominal obesity is central to the IDF definition [11], with provision of ethnic specific thresholds for waist circumference, while central obesity is not a mandatory NCEP/ATP [9, 10] MetS criterion. As a prevalent condition and predictor of CVD across racial, gender, and age groups, MetS provides the opportunity to identify high-risk populations and prevent the progression of some major causes of morbidity and mortality [13].

Despite the established link between the MetS and mental disorders such as schizophrenia [14-16], depression [17] and bipolar disorder [18], little research

appears to have considered the prevalence of MetS and its components among people with PTSD. Specifically, one previous meta-analysis [19] attempted to quantify the risk of MetS among people with PTSD and they found that people with PTSD have an increased risk for developing MetS compared with the general population (odds ratio (OR) 1.37 (95%CI=1.03–1.82) (n=528). Whilst helpful, a range of important questions remains. Importantly little information is currently available documenting the prevalence of MetS and constituent components including the frequency of central obesity, high blood pressure, low high-density lipoprotein (HDL) cholesterol, elevated triglycerides and hyperglycemia. Such information is important to establish an overview of the full metabolic risk profile of people with PTSD. It is also important to understand whether the risk profile of those with PTSD is the same depending on gender, age and the severity of depression in order to detect high-risk groups in need of priority screening and treatment. The role of such potential moderators on the association between PTSD and MetS can be determined through the use of meta-regression analysis. Similarly, it remains to be explored whether the MetS prevalence in people with PTSD differs between settings (inpatient, outpatient, community settings) and populations (e.g. veterans) and between those who are taking antipsychotics, mood stabilizers or antidepressants and those who are not. If risk stratification were observed, it would help guide clinicians in monitoring and treatment decisions.

Given the uncertainties outlined above and the pressing issue of premature mortality among people with PTSD attributable to CVD, we conducted a systematic review and meta-regression analysis to describe pooled prevalences of MetS and its components in people with PTSD taking into account variations in demographic and clinical variables and psychotropic medication use. Our secondary aim was to

compare the MetS prevalence in studies directly comparing persons with PTSD with age- and gender matched general population samples.

2. METHODS

2.1 Inclusion and Exclusion Criteria

This systematic review was conducted in accordance with the MOOSE guidelines[20] and in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standard [21] following a predetermined protocol prepared by the authors (Supplement 1). We included observational studies (cross-sectional, retrospective and prospective studies) in adults that fulfilled the following criteria: (a) a diagnosis of PTSD as diagnosed by the Diagnostic and Statistical Manual [22], the International Classification of Disease [23] or a validated instrument irrespective of clinical setting (inpatient, outpatient, community setting or mixed); and (b) a MetS diagnosis according to ATP-III [9], ATP-III-A [10], IDF [11] or WHO [12] standards, only allowing modification for body mass index cut-off of ≥30 instead of waist circumference. If we encountered a randomised control trial, we extracted the variables of interest at baseline. No language restrictions or time restrictions were placed upon the eligibility criteria of included articles. For estimation of the prevalence of MetS, we excluded studies with: (a) non-standardized diagnoses, (b) insufficient data for extraction of MetS frequencies, and (c) restriction to children and/or adolescents. In the case of multiple publications from the same study, only the most relevant paper or article was included. When required, we contacted the primary/corresponding authors of potential studies to (a) confirm eligibility, and (b) acquire the variables of interest if they were not available in the publication. Authors of articles were contacted up to two times over a 3-week period.

2.2 Search Criteria, Study Selection and Critical Appraisal

Two independent authors (SR, DV) searched Medline, PsycARTICLES, Embase and CINAHL from database inception to February 1st, 2015. Key words used were "metabolic syndrome" AND "posttraumatic stress disorder" in the title, abstract or index term fields. Manual searches were also conducted using the reference lists from recovered articles and the meta-analysis of Bartoli et al. [19]. After the removal of duplicates, both reviewers screened the titles and abstracts of all potentially eligible articles. Both authors applied the eligibility criteria, and a list of full text articles was developed through consensus. The two reviewers then considered the full texts of these articles and the final list of included articles was reached through consensus. A third reviewer (BS) was available for mediation throughout this process. Methodological appraisal was performed according to PRISMA standards [21], including evaluation of bias (confounding, overlapping data, publication bias). Publication bias was tested using the Egger's regression method [24] and Begg-Mazumdar test [25], with a p-value <0.05 suggesting the presence of bias. In addition, a funnel plot was created, in which the study-specific effect estimates are displayed in relation to the standard error in order to assess the potential presence of publication bias.

2.3 Statistical Analyses

We pooled individual study data using DerSimonian-Laird proportion method [26] with StatsDirect. Due to anticipated heterogeneity, a random effects meta-analysis was employed. We calculated the relative risk (RR) of MetS and its components between people with PTSD and matched general population control groups, also only

using data from studies in which they were directly compared. We conducted several meta-regression analyses (if N≥3) to investigate potential moderators (age, percentage males, major depression disorder comorbidity prevalence, prevalence of those receiving antipsychotic treatment, smoking prevalence, hostile personality or not) with Comprehensive Meta Analysis (version 3).

3. RESULTS

3.1 Search Results and Included Participants

Our search yielded 752 publications of which nine [27-35] met inclusion criteria (Figure 1). The list of excluded studies (with reasons) is presented in Supplement 2. The final sample comprised 9,673 unique persons in midlife with PTSD (of which 8,617 (89%) were men). Sample sizes of included studies ranged from 33 to 8,999 participants. Mean age was 53 years (range=44-61 years), 33.9% (SD 17.9, N=3) of the participants were currently employed and 39.3% (SD 25, N=3) also had major depressive disorder. Only two studies (n=161) reported smoking frequencies with 40.5% of participants identified as smokers (95% confidence interval (CI)=5.9%-82.1%; Cochran Q (Q)=31.1, p<0.001).

[Insert Figure 1 about here]

3.2 Prevalence of Metabolic Syndrome among people with PTSD

It was possible to pool data from 9 unique studies which established the estimated weighted mean prevalence of MetS for PTSD of 38.7% (95%CI=32.1%-45.6%; Q=52.1, p<0.001; N=9; n=9,673). The funnel plot was broadly symmetrical (Supplement 3) and both the Begg-Mazumdar (Kendall's tau b=0.44, p=0.12) and Egger test (bias=0.80 (95%CI=-1.84 to 3.44; p=0.50) indicated no evidence publication bias.

3.3 Individual Metabolic Abnormalities among people with PTSD

Three studies [28, 32, 35] reported on obesity frequency defined as waist circumference (>102cm in males and >88cm in females (ATP-III or ATP-III-A), while none of the studies reported the obesity frequency following the ethnicity-specific IDF-criteria. Overall, the proportion of people with PTSD with abdominal obesity by the ATP definitions was 49.3% (n=194; 95%CI=29.7%-69.0%; Q=14.8, p<0.001). It was possible to pool data from 3 studies studies [28, 32, 35] to establish that the prevalence of hyperglycemia was 36.1% (N=3, n=194; 95%CI=18.8%-55.6%; Q=14.0, p<0.001). Hypertriglyceridemia was present in 45.9% (N=3, n=194; 95%CI=12.2%-81.9%; Q=55.1, p<0.001) [28, 32, 35]; low high-density-lipoprotein (HDL)-cholesterol was present in 46.4% (N=3, n=194; 95%CI=26.4%-67.0%; Q=16.2, p<0.001) [28, 32, 35] [27, 31, 34] and hypertension was present in 76.9% (N=2; n=93; 95%CI=67.9%-84.8%; Q=0.49, P=0.48) [28, 32].

3.4 Subgroup analyses and Predictors of Metabolic Syndrome

The pooled MetS prevalence in Europe (Bosnia-Herzegovina) was 39.6% (N=3; n=265; 95%CI=32.7%-46.7%; Q=2.81, P=0.24) [28, 33, 34] which was similar to rates reported in North-America (USA) (38.6%; N=6; n=9,408; 95%CI=29.0%-48.6%; Q=47.1, P<0.001) [27, 29-32, 35]; z=1.47, p=0.14) with data on other geographical regions or countries not available. Similar rates of MetS prevalence in inpatients (N=2) [33, 34] or mixed settings (N=1)[27] combined was 34.8% (n=; 95%CI=32.7%-46.7%; Q=2.81, P=0.24), while in outpatients or community patients it was 38.6% (N=6; n=9,408; 95%CI=29.0%-48.6%; Q=47.1, P<0.001) [28-32, 35] (z=1.37, p=0.16). In the same way, we did not find significant differences between the prevalence of MetS in those studies only including veterans (44.0%; N=6;

n=9,493; 95%CI=13.1%-77.9%; Q=41.9, P<0.001) [27-29, 31, 33, 34] compared with studies in non-veterans or mixed samples (38.6%; N=3; n=180; 95%CI=29.0%-48.6%; Q=47.1, P<0.001)[30, 32, 35] (z=-0.15, p=0.087). The exploratory meta-regression analyses demonstrated that age variability between studies (N=7, n=9,467; coefficient=-0.006, 95%CI=-0.06 to 0.04, z=-0.24, p=0.81), differences in depression status (% with MDD) (N=3; n=285; coefficient=-0.417, 95%CI=-1.48to 0.57, z=-0.81, p=0.41) and gender (% male) (N=9; n=9,673; coefficient=0.56, 95%CI= -0.50 to 1.73 z=0.96, p=0.34) did not moderate the variability in MetS prevalence at study level. There was insufficient data to explore other potentially relevant moderators (e.g., psychotropic medication use, personality factors, lifestyle habits).

3.5 Relative Risk (RR) of MetS and Metabolic Abnormalities in Persons with PTSD Compared with Age- And Gender Matched General Population Controls

Four studies [27, 28, 30, 34] provided data on MetS prevalences in age and gender-matched healthy control subjects. In a pooled relative risk meta-analysis, compared with general population controls (n=6,852; 21,51%, 95% CI = 17.7 to 25.57, Q= 5.1, p=0.1) persons with PTSD (n=9,254; 36.39%, 95% CI = 31.32 to 41.62, Q=5.9, ==0.1) had significantly increased risk of MetS (RR=1.82; 95%CI=1.72-1.92; p<0.001; Q=2.43, p=0.48) (Figure 2).

[Insert Figure 2 about here]

4. DISCUSSION

In total, 38.7% (95% CI=32.1%-45.6%) of the included PTSD population had MetS and the relative risk for MetS was almost two times higher than in age- and gender matched general population controls (RR=1.82; 95%CI=1.72-1.92; p<0.001).

Moreover, the MetS prevalence was consistently high across geographical regions, clinical settings or population groups (war veterans or not). For the first time we found particularly high rates of abdominal obesity (49.3%, 95%CI=29.7%-69.0%;), hypertension (76.9%, 95%CI=67.9%-84.8%;) hypertriglyceridemia (45.9%, 95%CI=12.2%-81.9%), hyperglycaemia (36.1%, 95%CI=18.8%-55.6%;) and low high density-lipoprotein (HDL)-cholesterol levels (46.4%, 95%CI=26.4%-67.0%). The high prevalence of MetS and its constituent risk factors established within the current meta-analysis are of considerable concern.

Knowledge of factors associated with the highest MetS risk can help to identify individuals with PTSD at greatest need for intensive monitoring and intervention. Consistent with population studies [36, 37], we encountered no significant differences as a function of the number of women included within the studies possibly suggesting that men and women with PTSD require the same care. However, our findings should be interpreted with some caution due to the fact women were underrepresented across the 9 included studies (11%) and the studies reviewed did not report disaggregated MetS data by gender precluding direct comparison. In our exploratory meta-regression, we were not able to elucidate any significant moderators. This is almost certainly due to the paucity of data and the current meta-regression analyses should be viewed as exploratory. The fact that age differences between studies was not associated with MetS prevalence may be due to the limited mean age variation across the included studies (range=44-61 years). We did not find a difference between different populations (e.g., veterans or not) however this should be interpreted with caution as the majority of the included studies recruited participants from a veteran background (N=6). Previous research [17] demonstrated that people with MDD are at an increased risk for MetS. At study level the variability in

percentage of people with PTSD with co-morbid MDD did not appear to explain the variability in MetS prevalence. Findings of individual studies were also inconsistent. While Jakovljević et al. [33] showed that PTSD among war veterans with MDD have a higher MetS risk than those without MDD, Weiss et al. [29] and Heppner et al. [31] indicated that MetS risk was not different for participants with comorbid PTSD and depression than for those with PTSD alone. The strongest evidence to date that the association of PTSD to incident cardio-metabolic diseases is independent of general distress is a recent study by Vaccarino et al. [38] in which it was found that adjustment for depression and other psychiatric diagnoses did not diminish the PTSD - cardiometabolic disease association. Future studies that focus on the unique association of PTSD with cardiometabolic disease risk mechanisms are however needed before any firm conclusions can be made.

5. Future Research

The current meta-analysis provides some indications for future research. First, since antipsychotic medications are increasingly used as off-label treatments for PTSD [39] and as an adjunctive treatment for co-morbid MDD [40], research on the underlying mechanisms for the development of metabolic abnormalities after pharmacotherapy initiation is needed. Future studies should examine as well more in detail whether antidepressants or mood stabilizers significantly modulate MetS risk. For example, previous studies [41, 42] found that some antidepressants may, in some circumstances, reduce hyperglycemia, normalize glucose homeostasis and also increase insulin sensitivity, whereas others, including tricyclic antidepressants, may exacerbate glycemic dysfunction or have little effect on glucose homeostasis [43, 44]. Second, the pathophysiology underlying the association between PTSD and MetS is

complex and not well understood, requiring further investigation [45]. Emerging evidence suggests that both share pathophysiological features, including hypothalamic–pituitary–adrenal (HPA) and sympathoadrenomedullary dysfunction [46, 47], inflammation [48], common genetic links and epigenetic interactions [49, 50]. Third the extent to which traumatic experiences associated with physical injury may moderate associations between PTSD and MetS need to be examined, particularly in relation to compromised function of the endocrine organs. Additionally, traumatic experience co-incident with central nervous system damage responsible for impulse control and daily life functioning, such as might occur in traumatic brain injury, may have adverse effects on the development of MetS through poor lifestyle. However, psychiatric comorbidity may also have a pivotal role and requires careful consideration. Fourth, it might be that a cumulative long-term effect of poor health behaviors places people with PTSD at the greatest risk for cardio-metabolic disorders, more so than the psychiatric diagnosis per se. People with PTSD are more likely than the general population to have unhealthy lifestyle behaviors, such as being sedentary [51], smoking [52], alcohol and substance abuse [53], and having diets that are high in saturated fats and refined sugars [54], while low in fruit [55], placing them at higher risk for MetS and CVD than the general population. Future research should comprehensively assess MetS risk factors and evaluate lifestyle interventions. Previous research [56] demonstrated that a 12-week exercise programme in addition to usual care reduces PTSD and depressive symptoms, while decreasing waist circumference, improving sleep quality, and reducing sedentary time. Finally, long-term follow-up is required to accurately document the emergence of more distal outcomes, such as diabetes, ischemic heart disease, medical costs, and premature mortality.

6. Limitations

Whilst the current meta-analysis is a first to investigate the prevalence of MetS and its constituents in people with PTSD conducted to date, we should acknowledge that variables such as psychotropic medication use, trauma exposure, time since exposure and diagnosis, personality factors (e.g. level of hostility) and lifestyle habits were not reported or were insufficiently reported or controlled for in most available studies. In addition, the low number of studies that have documented MetS within PTSD samples to date resulted in limited numbers of participants and studies available for review. Nevertheless allowing for these caveats, the results of the current study provide a unique insight in the MetS risk among people with PTSD. Given the predictive accuracy of MetS for mortality and that CVD appears to contribute to a significant amount of the excess premature mortality among people with PTSD, the results of the present study are of clinical relevance and concern.

7. Conclusions

The current meta-analysis demonstrates that Metabolic Syndrome and its constituent components are highly prevalent amongst individuals identified with PTSD, who are almost twice as likely to have MetS compared to age and sex matched controls. The findings underscore the need for a multidisciplinary approach to assessment for patients presenting with PTSD that includes a focus on physical health as well as psychiatric symptoms. Treatment facilities should provide lifestyle interventions. Future research should focus on how cardio-metabolic outcomes are moderated by clinical and treatment characteristics and genetic factors.

Acknowledgements

Dr. Vancampfort has received grant support from the Research Foundation – Flanders (FWO- Vlaanderen). The other authors have no disclosures to report. The current work was not funded.

Disclosure statement

The authors have nothing to disclose.

References

[1] Boscarino JA. Posttraumatic stress disorder and mortality among U.S. Army veterans 30 years after military service. Annals of Epidemiology 2006;16:248-56.

[2] Boscarino JA. Psychobiologic predictors of disease mortality after psychological trauma: implications for research and clinical surveillance. Journal of Nervous & Mental Disease 2008;196:100-7.

[3] Xue Y, Taub PR, Iqbal N, Fard A, Wentworth B, Redwine L, et al. Cardiac biomarkers, mortality, and post-traumatic stress disorder in military veterans. The American journal of cardiology 2012;109:1215-1218.

[4] Pacella ML, Hruska B and Delahanty DL. The physical health consequences of PTSD and PTSD symptoms: A meta-analytic review. Journal of Anxiety Disorders 2013;27:33-46.

[5] Ahmadi N, Hajsadeghi F, Mirshkarlo HB, Budoff M, Yehuda R and Ebrahimi R. Post-traumatic Stress Disorder, Coronary Atherosclerosis, and Mortality. American Journal of Cardiology 2011;108:29-33.

[6] Galassi A, Reynolds K and He J. Metabolic syndrome and risk of cardiovascular disease: a meta-analysis. The American journal of medicine 2006;119:812-819.

[7] Gami AS, Witt BJ, Howard DE, Erwin PJ, Gami LA, Somers VK, et al. Metabolic syndrome and risk of incident cardiovascular events and death: a systematic review and meta-analysis of longitudinal studies. Journal of the American College of Cardiology 2007;49:403-414.

[8] Mottillo S, Filion KB, Genest J, Joseph L, Pilote L, Poirier P, et al. The metabolic syndrome and cardiovascular risk: a systematic review and meta-analysis. Journal of the American College of Cardiology 2010;56:1113-1132.

[9] Expert Panel on Detection E. Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on Detection, Evaluation, and Treatment of high blood cholesterol in adults (Adult Treatment Panel III). Jama 2001;285:2486.

[10] Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, et al. Diagnosis and management of the metabolic syndrome an American Heart Association/National Heart, Lung, and Blood Institute scientific statement. Circulation 2005;112:2735-2752.

[11] Alberti K, Zimmet P and Shaw J. Metabolic syndrome—a new world- wide definition. A consensus statement from the international diabetes federation. Diabetic medicine 2006;23:469-480.

[12] WHO. Definition, diagnosis and classification of diabetes mellitus and its complications. Geneva: World Health Organization, 1999.

[13] Alberti K, Eckel R, Grundy S, Zimmet P, Cleeman J, Donato K, et al. A joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation 2009;120:1640-5.

[14] Mitchell AJ, Vancampfort D, De Herdt A, Yu W and De Hert M. Is the prevalence of metabolic syndrome and metabolic abnormalities increased in early schizophrenia? A comparative meta-analysis of first episode, untreated and treated patients. Schizophrenia bulletin 2013;39:295-305.

[15] Mitchell AJ, Vancampfort D, Sweers K, van Winkel R, Yu W and De Hert M. Prevalence of metabolic syndrome and metabolic abnormalities in schizophrenia and related disorders—a systematic review and meta-analysis. Schizophrenia bulletin 2013;39:306-318.

[16] Vancampfort D, Wampers M, Mitchell AJ, Correll CU, Herdt A, Probst M, et al. A meta- analysis of cardio- metabolic abnormalities in drug naïve, first- episode and

multi- episode patients with schizophrenia versus general population controls. World Psychiatry 2013;12:240-250.

[17] Vancampfort D, Correll CU, Wampers M, Sienaert P, Mitchell A, De Herdt A, et al. Metabolic syndrome and metabolic abnormalities in patients with major depressive disorder: a meta-analysis of prevalences and moderating variables. Psychological medicine 2014;44:2017-2028.

[18] Vancampfort D, Vansteelandt K, Correll CU, Mitchell AJ, De Herdt A, Sienaert P, et al. Metabolic syndrome and metabolic abnormalities in bipolar disorder: a meta-analysis of prevalence rates and moderators. Perspectives 2013;170.

[19] Bartoli F, Carra G, Crocamo C, Carretta D and Clerici M. Metabolic syndrome in people suffering from posttraumatic stress disorder: a systematic review and meta-analysis. Metabolic Syndrome & Related Disorders 2013;11:301-8.

[20] Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Jama 2000;283:2008-2012.

[21] Moher D, Liberati A, Tetzlaff J and Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Annals of internal medicine 2009;151:264-269.

[22] Association AP. Diagnostic and statistical manual of mental disorders, text revision (DSM-IV-TR). American Psychiatric Association, 2000.

[23] Organization WH. The ICD-10 Classification of Mental and Behavioural Disorders-Diagnostic Criteria for Research (Geneva, World Health Organization). J Gambl Stud 1993.

[24] Egger M, Smith GD, Schneider M and Minder C. Bias in meta-analysis detected by a simple, graphical test. Bmj 1997;315:629-634.

[25] Begg CB and Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994:1088-1101.

[26] DerSimonian R and Laird N. Meta-analysis in clinical trials. Controlled clinical trials 1986;7:177-188.

[27] Ahmadi N, Yehuda R, Ebrahimi R and Vaidya N. Post-Traumatic Stress Disorder, Metabolic Syndrome and Mortality: the Role of Selective Serotonin Reuptake Inhibitor and Tricyclic Antidepressants. Journal of Neuropsychiatry and Clinical Neurosciences 2014;26:6-7.

[28] Babic R, Maslov B, Babic D and Vasilj I. The prevalence of metabolic syndrome in patient with posttraumatic stress disorder. Psychiatria Danubina 2013;25 Suppl 1:45-50.

[29] Weiss T, Skelton K, Phifer J, Jovanovic T, Gillespie CF, Smith A, et al. Posttraumatic stress disorder is a risk factor for metabolic syndrome in an impoverished urban population. General Hospital Psychiatry 2011;33:135-42.

[30] Linnville S, Hoyt RE, Moore JL, Segovia F and Hain RE. Posttraumatic stress disorder and metabolic syndrome: retrospective study of repatriated prisoners of war. Military Medicine 2011;176:369-74.

[31] Heppner PS, Crawford EF, Haji UA, Afari N, Hauger RL, Dashevsky BA, et al. The association of posttraumatic stress disorder and metabolic syndrome: a study of increased health risk in veterans. BMC Medicine 2009;7:1.

[32] Jin H, Lanouette NM, Mudaliar S, Henry R, Folsom DP, Khandrika S, et al. Association of posttraumatic stress disorder with increased prevalence of metabolic syndrome. Journal of Clinical Psychopharmacology 2009;29:210-5.

[33] Jakovljevic M, Babic D, Crncevic Z, Martinac M, Maslov B and Topic R. Metabolic syndrome and depression in war veterans with post-traumatic stress disorder. Psychiatria Danubina 2008;20:406-10.

[34] Maslov B, Jakovljevic M, Crncevic Z, Ostojic L, Marcinko D, Babic D, et al. Metabolic syndrome and schizophrenia from integrative medicine perspective. Psychiatria Danubina 2008;20:384-9.

[35] Violanti JM, Hartley TA, Charles LE, Fekedulegn D, Andrew ME, Mnatsakanova A, et al. Police trauma and cardiovascular disease: Association between PTSD symptoms and metabolic syndrome. International Journal of Emergency Mental Health 2006;8:227-238.

[36] Ford ES, Giles WH and Dietz WH. Prevalence of the metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey. Jama 2002;287:356-359.

[37] Park Y-W, Zhu S, Palaniappan L, Heshka S, Carnethon MR and Heymsfield SB. The metabolic syndrome: prevalence and associated risk factor findings in the US population from the Third National Health and Nutrition Examination Survey, 1988-1994. Archives of internal medicine 2003;163:427-436.

[38] Vaccarino V, Goldberg J, Rooks C, Shah AJ, Veledar E, Faber TL, et al. Post-traumatic stress disorder and incidence of coronary heart disease: a twin study. Journal of the American College of Cardiology (JACC) 2013;62:970-978.

[39] Leslie DL, Mohamed S and Rosenheck RA. Off-label use of antipsychotic medications in the department of Veterans Affairs health care system. Psychiatric services 2009;60:1175-1181.

[40] Davidson JR. Major depressive disorder treatment guidelines in America and Europe. The Journal of clinical psychiatry 2010:e04.

[41] McIntyre RS, Soczynska JK, Konarski JZ and Kennedy SH. The effect of antidepressants on glucose homeostasis and insulin sensitivity: synthesis and mechanisms. 2006.

[42] M Hennings J, Schaaf L and Fulda S. Glucose metabolism and antidepressant medication. Current pharmaceutical design 2012;18:5900-5919.

[43] Knol M, Derijks H, Geerlings M, Heerdink E, Souverein P, Gorter K, et al. Influence of antidepressants on glycaemic control in patients with diabetes mellitus. Pharmacoepidemiology and drug safety 2008;17:577-586.

[44] Mojtabai R. Antidepressant use and glycemic control. Psychopharmacology 2013;227:467-477.

[45] Farr OM, Sloan DM, Keane TM and Mantzoros CS. Stress-and PTSD-associated obesity and metabolic dysfunction: A growing problem requiring further research and novel treatments. Metabolism: clinical and experimental 2014;63:1463-1468.

[46] Boscarino JA. Posttraumatic stress disorder and physical illness: results from clinical and epidemiologic studies. Annals of the New York Academy of Sciences 2004;1032:141-153.

[47] Dedert EA, Calhoun PS, Watkins LL, Sherwood A and Beckham JC. Posttraumatic stress disorder, cardiovascular, and metabolic disease: a review of the evidence. Annals of Behavioral Medicine 2010;39:61-78.

[48] Eraly SA, Nievergelt CM, Maihofer AX, Barkauskas DA, Biswas N, Agorastos A, et al. Assessment of plasma C-reactive protein as a biomarker of posttraumatic stress disorder risk. JAMA psychiatry 2014;71:423-431.

[49] Li H, Li X, Smerin SE, Zhang L, Jia M, Xing G, et al. Mitochondrial gene expression profiles and metabolic pathways in the amygdala associated with exaggerated fear in an animal model of PTSD. Frontiers in neurology 2014;5.

[50] Nevell L, Zhang K, Aiello AE, Koenen K, Galea S, Soliven R, et al. Elevated systemic expression of ER stress related genes is associated with stress-related mental disorders in the Detroit Neighborhood Health Study. Psychoneuroendocrinology 2014;43:62-70.

[51] Zen AL, Whooley MA, Zhao S and Cohen BE. Post-traumatic stress disorder is associated with poor health behaviors: findings from the heart and soul study. Health Psychology 2012;31:194.

[52] Fu SS, McFall M, Saxon AJ, Beckham JC, Carmody TP, Baker DG, et al. Post-traumatic stress disorder and smoking: a systematic review. Nicotine & Tobacco Research 2007;9:1071-1084.

[53] Blanco C, Xu Y, Brady K, Pérez-Fuentes G, Okuda M and Wang S. Comorbidity of posttraumatic stress disorder with alcohol dependence among US adults: results from National Epidemiological Survey on Alcohol and Related Conditions. Drug and alcohol dependence 2013;132:630-638.

[54] Carmassi C, Bertelloni CA, Massimetti G, Miniati M, Stratta P, Rossi A, et al. Impact of DSM-5 PTSD and gender on impaired eating behaviors in 512 Italian earthquake survivors. Psychiatry research 2015;225:64-69.

[55] Godfrey KM, Lindamer LA, Mostoufi S and Afari N. Posttraumatic stress disorder and health: a preliminary study of group differences in health and health behaviors. Annals of general psychiatry 2013;12:30.

[56] Rosenbaum S, Sherrington C and Tiedemann A. Exercise augmentation compared with usual care for post-traumatic stress disorder: a randomized controlled trial. Acta Psychiatrica Scandinavica 2014.

Figure 1. Flow diagram for the search strategy

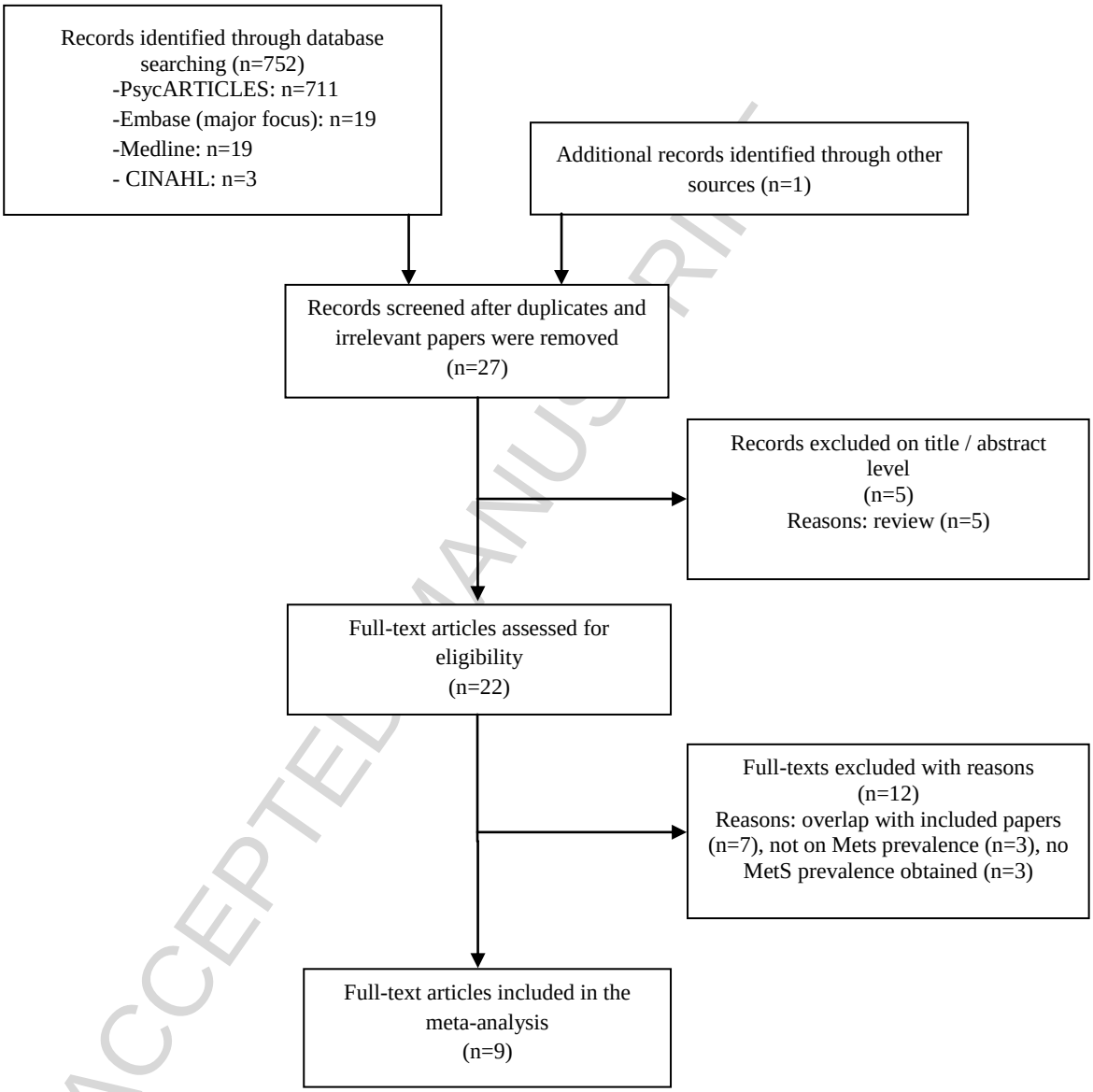

Figure 2. Relative risk meta-analysis plot (random effects) (n=4)

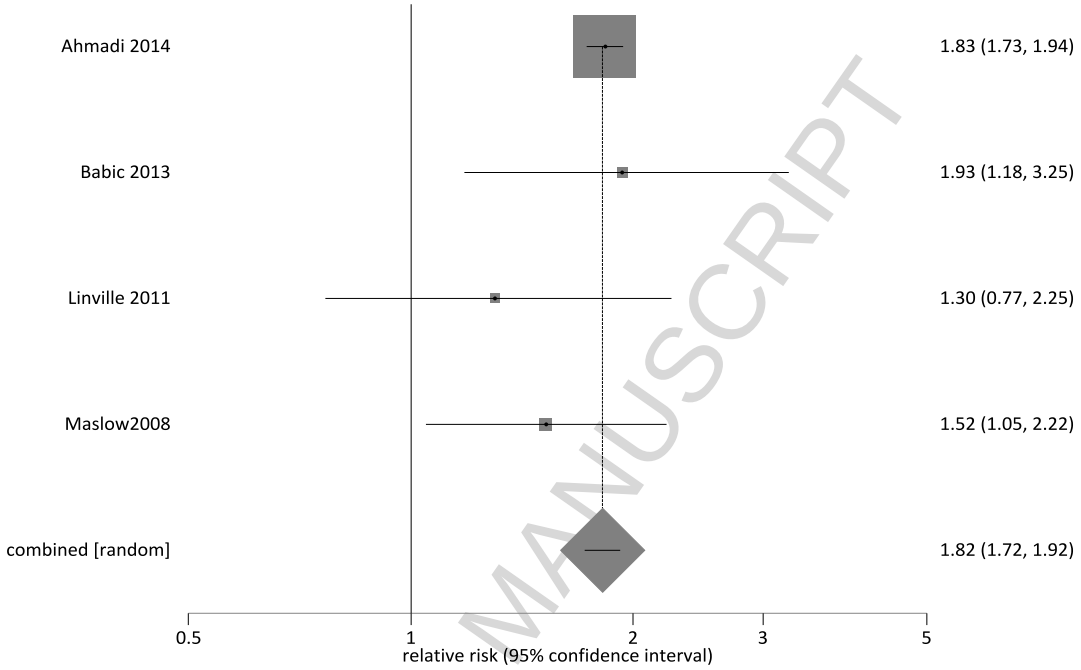

Table 1. Details of the included studies

Ref Nr.	First Author (year)	Country	Participants	MetS criterium	Mets prevalence	Prevalence MetS Criteria	MetS prevalence Controls*
27.	Ahmadi 2014	USA	8,999 Veterans versus 6,587 controls; 90% male; 58±15 years	ATP III	34.8%	/	19%
28.	Babic 2013	Bosnia Herzegovina	60 male Veterans versus 60 male controls; 49.6±10.8 years	ATP III	48.3%	WC=58.3%;BP=75%;HDL=31.7%; TG=40.0%;FG=33.3%	25%
29.	Weiss 2011	USA	46 with current PTSD; 30.4% male; 43.7±11.0 years	ATP-III-A	47.8%	/	/
30.	Linville 2011	USA	90 repatriated male prisoners of war (Vietnam-era) with PTSD versus 60 combat experienced male aviators without PTSD; mean age entire sample: 61 years	ATP-III-A (modified)	30.0%	/	23%
31.	Heppner 2009	USA	139 Veterans (Gulf-War) with at least moderate severity PTSD; entire	WHO ATP-III-A	43%	/	/

			sample: 92% male (76% White, 19% Black); 51.5±9.0 years				
32.	Jin 2009	USA	33 PTSD persons with psychotic symptoms; 88% male; 59.7±10.5 years	ATP-III-A	72%	WC=61%;BP=81%;HDL=72%; TG=61%;FG=58	/
33.	Jakovljevic 2008	Bosnia Herzegovina	100 male Combat Veterans; 47.4±10.8 years	ATP III	35%	/	/
34.	Maslov 2009	Bosnia Herzegovina	105 inpatients (war veterans) with PTSD; 54% male (75% White, 25% Black)	ATP III	38.1%	/	
35.	Violanti 2006	USA	101 police officers	ATP-III-A	16%	WC=32% (m=38%, f=23%); HDL=38% (m=39%, f=35%); TG=15% (m=23%, f=3%); FG=22% (m=33%, f=5%)	/

WWC= waist circumference, BP=blood pressure, HDL=high-density lipoproteins cholesterol,

TG=triglycerides, FG=fasting glucose