# Type 2 Diabetes Among People With Posttraumatic Stress Disorder: Systematic Review and Meta-Analysis

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## ABSTRACT

**Objective:** To clarify the prevalence and predictors of Type 2 diabetes mellitus (T2DM) in people with posttraumatic stress disorder (PTSD) and where possible compare this to healthy controls.

**Methods:** We searched major electronic databases until May 2015 for studies reporting T2DM prevalence in people with PTSD. Two independent authors extracted data and completed methodological quality appraisal. A random-effects meta-analysis was used.

**Results:** From 1171 candidate publications after exclusions, nine publications were included ($n$ = 23,396; 28.6% male; mean age = 35–60 years). The overall prevalence of T2DM was 10.0% (95% confidence interval [CI] = 8.1%–12.0%). Subgroup analysis demonstrated that war veterans experience higher prevalence of T2DM (16.3%; 95% CI = 5.2%–31.8%; $n$ studies = 3, $n$ = 473) compared with mixed samples (11.8%; 95% CI = 6.34–18.7, $p < .001$; $n$ studies = 4, $n$ = 2753). Increasing age ($\beta$ = 0.0593, 95% CI = 0.010–0.109, $z$ = 2.34, $p$ = .019), median year of publication ($\beta$ = −0.08, 95% CI = −0.14 to −0.03, $z$ = −3.09, $p$ = .002), and a lower percentage of white participants ($\beta$ = −3.21, 95% CI = −5.12 to −1.29, $z$ = −2.28, $p$ = .001) predicted prevalence of T2DM. A relative risk meta-analysis comparing controls ($n$ = 125,723) against those with PTSD ($n$ = 23,203) demonstrated a significantly increased risk of T2DM ($n$ studies = 5, relative risk = 1.49, 95% CI = 1.17–1.89, $p$ = .001).

**Conclusions:** People with PTSD are at a high risk for developing T2DM. The current findings should, however, be interpreted with caution because most studies were based on self-report data.

**Key words:** diabetes mellitus, glucose, PTSD.

## INTRODUCTION

Posttraumatic stress disorder (PTSD) typically occurs after exposure to potentially traumatic events including war, torture, physical or sexual assault, or natural disasters, with an estimated lifetime prevalence of 6.8% (1). PTSD is particularly prevalent and of increasing concern among certain populations including first responders (police officers, paramedics, fire fighters) and veterans. For example, the estimated point prevalence of PTSD among combat veterans is reported to be in excess of 30% (2). Associated adverse consequences of PTSD include severe impairments in psychosocial functioning (3), significantly increased risk of suicide and suicidal ideations (4), and substance abuse and dependence (5). People with PTSD are also known to experience an excess mortality rate two to three times higher than the general population (6–8). This increased risk is mainly due to cardiovascular diseases (CVDs), which predict mortality independent of age, sex, and conventional risk factors (9).

Type 2 diabetes mellitus (T2DM) is an established risk factor for CVD. It confers approximately a two-fold excess

**CVD** = cardiovascular disease, **NOS** = Newcastle-Ottawa Scale, **PTSD** = posttraumatic stress disorder, **RR** = relative risk, **T2DM** = Type 2 diabetes mellitus

SDC Supplemental Content

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risk for coronary heart disease, major stroke subtypes, and deaths attributable to other vascular causes (10). Because of the increasing prevalence of T2DM in the general population (11), it now rivals several more commonly known risk factors such as physical inactivity, cigarette smoking, hypertension, and cholesterol disorders (12) as one of the most important independent risk factors for CVD. In addition to these cardiovascular complications of T2DM, it is an important comorbidity in people confronted with mental health problems (13,14) and its prevention and treatment demand more attention in vulnerable populations. A previous systematic review of earlier onset of senescence-related medical conditions in PTSD (15) suggested an association between PTSD and T2DM. To the best of our knowledge, no systematic review and meta-analysis has attempted to pool and compare T2DM prevalence in people with PTSD in comparison to healthy controls. A meta-analysis pooling T2DM prevalence and predictors in this population will provide rigorous risk profile evidence to researchers, health care professionals, and decision makers. This, in turn, might help elucidate important clinical information such as whether the T2DM risk profile is the same depending on sex, age, setting (inpatient, outpatient, community), subpopulation (e.g., veterans), ethnicity, duration since first traumatic exposure, personality factors (e.g., hostile personality), psychotropic medication use and type, T2DM assessment method used, and geographical region.

This systematic review and meta-analysis has three aims: a) to obtain a weighted pooled prevalence rate for T2DM among individuals with PTSD, b) to examine predictors of T2DM among people with PTSD, and c) to examine the relative risk (RR) of T2DM in people with PTSD compared with people without PTSD.

## METHODS

This systematic review was conducted in accordance with the meta-analysis of observational studies in epidemiology guidelines (16) and reported in accordance with the preferred reporting items for systematic reviews and meta-analyses statement (17) following a predetermined, but unpublished, protocol (Supplemental Digital Content 1, http://links.lww.com/PSYMED/A267).

### Inclusion and Exclusion Criteria

Observational studies including retrospective, cross-sectional, and prospective designs were eligible if they focused on people with PTSD, irrespective of age and psychiatric setting (inpatient, outpatient, community, or mixed). Specific inclusion criteria were as follows: a) a diagnosis of PTSD according to the *Diagnostic and Statistical Manual* (18) or *International Classification of Disease* (19) criteria, or validated instruments, and b) at a minimum age or sex distribution of the included participants was available. When we encountered studies lacking data on age and sex, we contacted the authors up to two times over a 1-month period to ascertain the variables of interest in the group of people with PTSD. If these data were not available, the study was excluded. We did not place any restriction on the method of diabetes assessment. There was also no language restriction upon our searches. If we came across studies that reported data from the same sample at different points in time, we selected the data with the most rigorous diabetes assessment method. If the assessment method was the same, we used the most recent article or the article with the largest sample. For estimation of the diabetes prevalence, we excluded studies reporting only a) Type 1 diabetes and b) incidence rates. Studies limited to people with known or without cardiovascular risk factors were only included in the comparison analyses if control data were available.

### Search Strategy

Two reviewers (D.V. and S.R.) independently conducted searches on PubMed, EMBASE (major focus strategy), PsycARTICLES, and CINAHL from inception until May 2015 using the search terms "diabetes" OR "glucose" AND "posttraumatic stress disorder" OR "PTSD" within keywords, titles, and abstracts. In addition, the reference lists of all eligible articles and reviews of the literature were screened to assess eligibility of additional studies. Also, abstracts of international diabetes meetings were handsearched to identify unpublished relevant trials. Registered trial lists were searched for unpublished data: The European Union Clinical Trials Register (https://www.clinicaltrialsregister.eu/ctr-search/search), Current Controlled Trials (ww.controlled-trials.com), the US National Institutes of Health (https://clinicaltrials.gov/).

### Study Selection

After removal of duplicates, two independent reviewers screened the titles and abstracts of all potentially eligible articles. Two 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 a final list of included articles was reached through consensus.

### Data Extraction

Two authors independently conducted data extraction using a predetermined format. The data collected from each article included the following: study design, geographical location, PTSD sample and control sample characteristics if available (number, % male, mean age, % white), PTSD diagnosis method, method of diabetes assessment, and the prevalence of T2DM in people with PTSD and in healthy controls if available.

### Methodological Quality Assessment

Two independent authors completed methodological quality assessment of included articles using the Newcastle-Ottawa Scale (NOS) (20) Studies were considered as case-control studies for the purposes of methodological assessment in accordance with previous reviews (21,22). The NOS (19) is used to assess the methodological quality of nonrandomized trials and has acceptable validity and reliability. The assessment tool focuses on three main methodological features a) the selection of the groups, b) the comparability of the groups, and c) the ascertainment of the outcome of interest. The NOS can be modified, and we adapted the NOS (19) to take into account age and sex as comparability measure and considered T2DM assessment in the exposure category. A diagnosis based on international criteria, for example, the American Diabetes Association criteria (23), was considered as the most objective. Studies are given a score from 0 to 9, with a score of 5 or greater being indicative of satisfactory methodological quality. Because 4 of the 9 points on the NOS are allocated to how well the PTSD and control group are matched, we anticipated studies without a control group would score below this and present their results with due consideration.

### Statistical Analyses

We pooled individual study data using the DerSimonian-Laird proportion method (24). Heterogeneity was assessed with the Cochran $Q$ statistic. A random-effects meta-analysis was used using StatsDirect. A random-effects meta-analysis model assumes that the observed estimates of an effect size can vary across studies because of a) real differences in the effect size in each study and b) sampling variability (chance) (25). Under the random-effects model, studies are weighted to account for this variation

(heterogeneity). We calculated the RR to investigate the differences in T2DM prevalence between people with PTSD and members of the general population. To investigate sources of heterogeneity, we conducted unrestricted maximum likelihood random-effects meta-regressions analyses (26) when data were available in at least three studies to investigate if study design, median year of data collection, age (mean years), sex (percentage males), ethnicity (% white), prevalence of those receiving antipsychotic treatment, prevalence of hostile personality, and the method of diabetes assessment (following international standards, self-report or clinician report, medical records, or based on antidiabetic medication use), depression status, and geographical region influence the prevalence of T2DM. Following the *Cochrane Handbook* (27), we assessed publication bias with a visual inspection of funnel plots and the Begg-Mazumdar Kendall $\tau$ (28) when a minimum of 10 studies were available.

## RESULTS

### Search Results and Included Participants

The initial electronic database search resulted in 1171 valid hits. From candidate publications after exclusions, our search generated nine publications (29–37) fulfilling the inclusion criteria (see Fig. 1 for search results including reasons for exclusion). The data set of the pooled analysis comprised 23,396 unique persons (28.6% male; mean age = 35–60 years) with a diagnosis of PTSD. Published studies involved sample sizes that ranged from 33 to 10,581 participants. Details on the included studies are presented in Table 1. Of the nine publications included in the pooled analysis, one was conducted among inpatients and one in an outpatient setting, whereas seven studies included community-based participants. Two studies assessed T2DM with a blood test, one relied on the use of antidiabetic medication, and six studies relied on self-report. While two studies were executed in Germany, the others were all from the United States. Five studies presented data on ethnicity and indicated that 89.3% were of non-Hispanic white ethnicity. Three studies were executed in war veterans and four in people with mixed trauma exposure and two in studies not including war veterans. There was no difference in weighted mean age between war veterans studies and mixed samples (weighted mean age = 50.3 versus 46.1 years, $t = 0.58$, $p = .59$). In contrast, veterans studies included significantly more male participants (96.0% versus 32.7%, $t = 7.5$, $p = .001$). There were five longitudinal studies comparing T2DM prevalence in patients with PTSD with healthy controls. Of the 12 contacted research groups, five groups provided the data requested for the meta-analysis (see acknowledgments).

Because less than 10 studies were available, we did not perform publication bias analyses. No unpublished trials were, however, detected,

### Methodological Quality

Overall, the methodological quality of the included articles was low to moderate and the mean NOS was 3.6 (range, 2–5). The NOS summary scores are presented in Table 1.

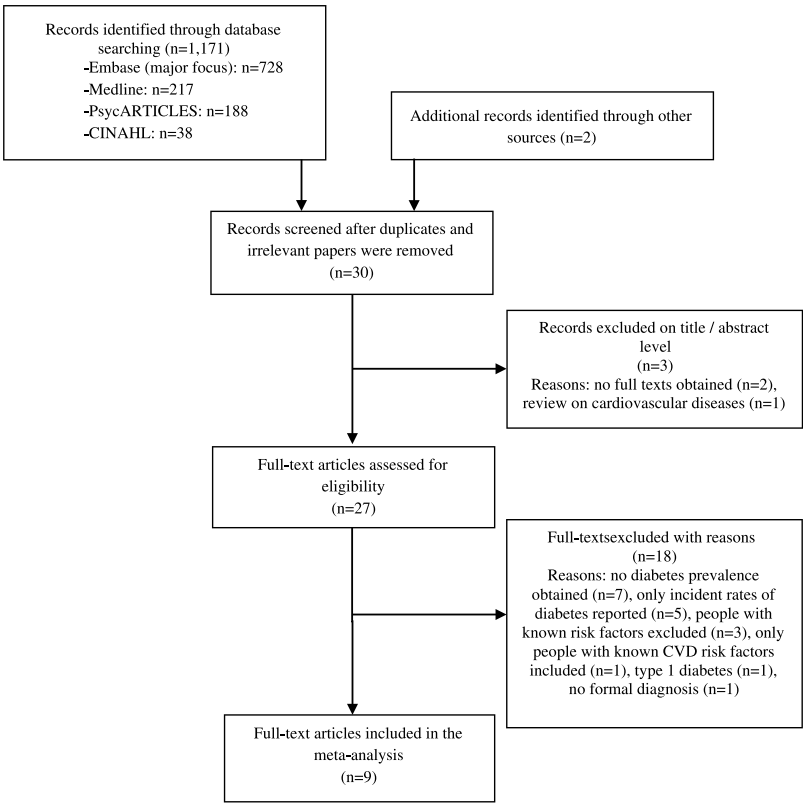


**FIGURE 1.** Flow diagram for the search strategy. CVD = cardiovascular disease.

**TABLE 1.** Characteristics of the Included Studies ($n$ = 9)

| Reference No. | First Author and Study Year | Design | NOS | Country | Participants' Characteristics | Diabetes Assessment | Diabetes Prevalence |
|---|---|---|---|---|---|---|---|
| 37a | Weisberg 2002 | Longitudinal | 4 | USA | 185 (148♀) with primary care anxiety patients with DSM-IV PTSD; 38.3 (10.8)y; 81% white versus 84 (68♀) controls; 39.7 (11.9)y; 86% white | Self-report | 15% versus 6% |
| 31 | David 2004 | Cross-sectional | 3 | USA | 55 male veterans with DSM-IV PTSD; 49.7 (5.7)y; 62% white | Fasting glucose | 24% |
| 32 | Jin 2009 | Longitudinal | 2 | USA | 33 (4♀) veterans with DSM-IV PTSD and with psychotic symptoms; 59.7 (10.5) y | Antidiabetic medication use | 21% |
| 34[a] | Spitzer 2010 | Cross-sectional | 2 | Germany | 55 (39♀) with DSM-IV PTSD; 55.0 (16.4) y | Self-report | 18.2% |
| 33 | Petrzak 2011 | Longitudinal | 4 | USA | 2463 (1707♀) with DSM-IV PTSD; 69.6% white versus 26,716 (13,144♀); 72.4% white | Self-report | 10.9% versus 8.0% |
| 35[a] | Lukaschek 2013 | Cross-sectional | 5 | Germany | 50 (31♀) with ICD-10 PTSD; 54.3 (11.9) y | OGTT | 20% |
| 36[a] | Miller-Archie 2014 | longitudinal | 4 | USA | 10,581 (5215♀) with PTSD diagnosed using a validated 9/11-specific PTSD Checklist; 44.9 (11.0) y versus 54,422 (20,259♀); 43.9 (12.0) y | Self-report | 8% versus 4.8% |
| 38[a] | Vaccarino 2014 | Cross-sectional | 4 | USA | 375 male veterans with DSM-III PTSD; 41.4 y versus 3965 male controls; 41.9 y | Self-report | 2.6% versus 1% |
| 37[a] | Roberts 2015 | Longitudinal | 4 | USA | 9589 women with DSM-IV PTSD; 35.3 y versus 40,497 female controls; 34.6 y | Self-report | 7.5% versus 6.7% |

NOS = Newcastle-Ottawa Scale; DSM = Diagnostic and Statistical Manual; PTSD = posttraumatic stress disorder; ICD= International Classification of Disease; OGTT = oral glucose tolerance test.

[a] Diabetes prevalence and demographical data obtained from the authors.

### Prevalence of T2DM in PTSD

Based on a meta-analysis involving 23,396 unique persons with a PTSD diagnosis, the estimated weighted mean prevalence of T2DM in a random-effects model was 10.0% (95% confidence interval [CI] = 8.1%–12.0%, Cochran $Q = 86.6$, $p < .001$). Figure 2 shows the estimated T2DM prevalence of each individual study together with the weighted mean T2DM prevalence. As expected, the adjusted pooled prevalence according to Duvall and Tweedie's (29) trim and fill remained the same after adjustment for potential outliers (10.0%; 95% CI = 8.1%–12.0%).

### RR for T2DM in PTSD Compared With Healthy Controls

Compared with healthy controls ($n = 125,723$), those with PTSD ($n = 23,203$) had a significantly increased risk of T2DM ($n$ studies = 5, RR = 1.49, 95% CI = 1.17–1.89, $p = .0011$; see Fig. 3).

### Subgroup Analyses Investigating Prevalence of T2DM Among People With PTSD

There was no significant difference in T2DM according to study design ($z = 0.10$, $p = .46$). In contrast, in studies with a T2DM diagnosis based on a blood assessment (fasting glucose or oral glucose tolerance test; $n$ studies = 2, $n = 105$), the prevalence was higher than in studies relying on self-report data ($n$ studies = 6, $n = 23,258$; 22.4% [95% CI = 15.0%–30.8%] versus 8.5% [95% CI = 6.9%–10.3%], $z = 5.17$ $p < .001$). The prevalence of T2DM was significantly ($z = 4.03$, $p < .001$) higher in studies in Europe (Germany; 19.60% [95% CI = 12.6%–27.7%]; $n$ studies = 2, $n = 105$) compared with North America (United States; 10.2% [95% CI = 8.4%–12.1%]; $n$ studies = 6, $n = 22,906$). The prevalence of T2DM was also significantly higher ($z = 4.84$, $p < .001$) for samples drawn from war veterans (16.3% [95% CI = 5.2%–31.8%]; $n$ studies = 3, $n = 9677$) compared with mixed samples (11.8% [95% CI = 6.3%–18.7%]; $n$ studies = 5, $n = 3128$).

### Predictors of the Prevalence of T2DM Among People With PTSD

The meta-regression analysis demonstrated that increasing age (in years; $n$ studies = 8, $n = 20,933$; $\beta = 0.0593$; 95% CI = 0.010-0.109; $z = 2.34$, $p = .019$) predicted a higher prevalence of T2DM. Median year of data collection ($n$ studies = 9, $n = 23,396$; $\beta = -0.08$; 95% CI = −0.14 to −0.03; $z = -3.09$, $p = .002$) and a higher percentage of non-Hispanic whites ($n$ studies = 5, $n = 12,325$; $\beta = -3.21$; 95% CI = −5.12 to −1.29; $z = -2.28$, $p = .001$) predicted lower prevalence of T2DM. Sex was not a predictor of T2DM (% male; $n$ studies = 9, $n = 23,396$; $\beta = -0.06$; 95% CI = −1.38 to 1.25; $z = -0.09$, $p = .45$). Also, the NOS score did not predict the prevalence of T2DM ($n$ studies = 9, $n = 23,396$; $\beta = -0.31$; 95% CI = −0.77 to 0.14; $z = -1.34$, $p = .18$). Data were too limited for a meta-regression including age, median year of data collection, and ethnicity in one model to be conducted. There were also insufficient data to explore the effects of the variance in duration since first traumatic exposure, personality factors, depression status, or psychotropic medication use on the variance in T2DM in PTSD.

## DISCUSSION

### General Findings

To the best of the authors' knowledge, this is the first systematic review and meta-analysis to investigate the prevalence of T2DM in people with PTSD. We were able to

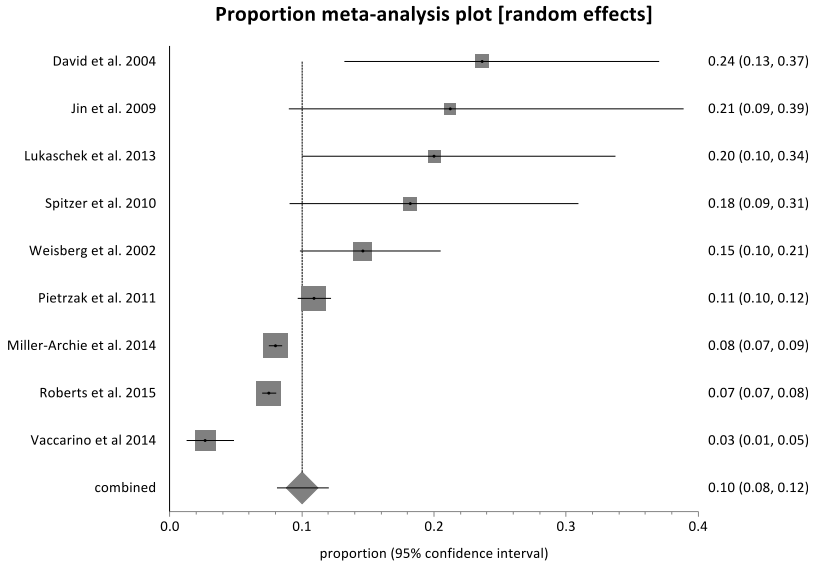


**FIGURE 2.** Forest plot (random effects) of the included studies ($n = 9$).

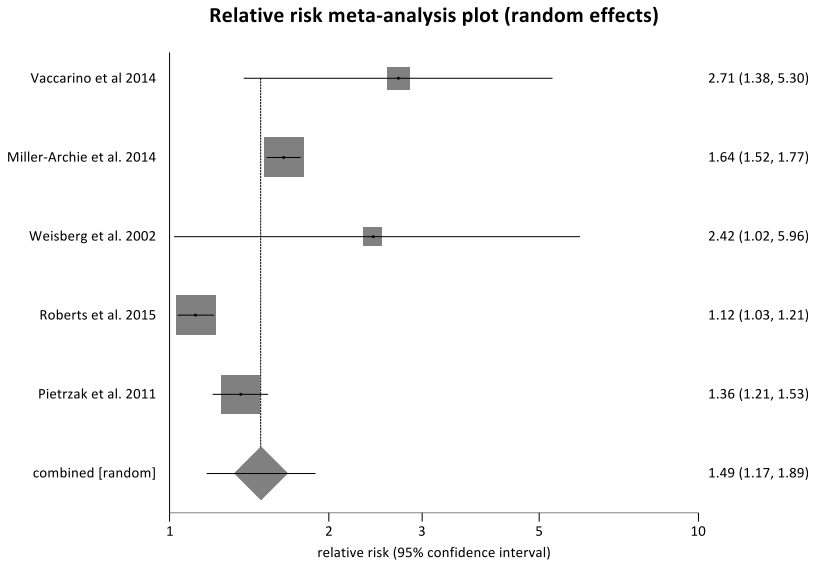


**FIGURE 3.** Relative risk plot (random effects) ($n$ = 5).

include nine publications in the pooled analysis involving 23,396 individuals with PTSD, all published within the last 15 years and found that 10.0% had T2DM. Our comparative meta-analysis demonstrated that people with PTSD are at approximately 50% increased risk of experiencing T2DM compared with healthy controls (RR = 1.49, 95% CI = 1.17–1.89). Our meta-analytic data also indicate that war veterans seem more likely to have T2DM compared with those from mixed samples. In addition, increasing age and an increasing percentage of nonwhite participants also predicted T2DM. In line with a recent meta-analysis in people with schizophrenia (14), we found that studies relying on self-report/medical history for a diagnosis of T2DM seem to greatly underestimate the actual prevalence of T2DM compared with the gold standard blood glucose. Our results highlight the importance of identifying those with PTSD who currently have or are at high-risk for T2DM. Our study suggests that there is a need to develop proactive screening programs to identify those with PTSD who are at risk.

The influences of age and ethnicity on the prevalence of T2DM are in agreement with findings in the general population (38). Previous research in the general population (39) has demonstrated that people with nonwhite ethnicities may engage in less physical activity and that the inverse association of a healthy diet with diabetes is stronger for ethnic minorities than for white people (40). PTSD may further compound these existing demographic gradients in the prevalence of T2DM. Therefore, people from nonwhite ancestries may require additional support to establish healthy life-style changes. It was, however, not possible to investigate the influence of life-style directly on people diagnosed as having PTSD due to limitations in the data.

Consistent with findings in the general population (41), no significant differences between men and women were found, indicating that equivalent amounts of clinical attention are warranted for both sexes. However, the current findings should be interpreted with caution because data directly comparing men and women with PTSD were not available for the current review and men were significantly underrepresented in the overall sample.

The reason for a higher prevalence of T2DM in war veterans, on its turn, is unclear. Although studies in war veterans relied on a higher percentage of male participants, sex was, as indicated, not a significant predictor in the current meta-analysis. Further research should therefore clarify whether the relationship between PTSD and T2DM risk differs according to the trauma that was associated with the PTSD onset. For example, any traumatic experience that is associated with physical injury compromising function of the endocrine organs could have adverse metabolic effects. In addition, traumatic experience co-occurring with central nervous system damage responsible for impulse control and daily life functioning, such as what might occur in traumatic brain injury, may have adverse effects on the development of T2DM via its effects on life-style choices. It might be hypothesized that these physical injuries are more likely to occur in war veterans than in other PTSD patients. Physical and psychiatric comorbidities were not well reported in the studies examined. Therefore, we were also not able to investigate whether comorbid major depressive disorder accounted for the variability in T2DM prevalence. Previous research has demonstrated that people with major depressive disorder are at an increased risk for T2DM (42).

## Limitations

We wish to acknowledge several limitations. First, there was, as anticipated, methodological heterogeneity across studies. This heterogeneity may be attributable to the

differences in study design, sample size, participants' characteristics, and different assessment methods of T2DM. We attempted to circumvent this by conducting subgroup analyses and data stratification. Second, given that less than 10 studies were included, we were not able to investigate the role of publication bias into detail. Although no unpublished trials were detected, publication bias cannot be excluded. Third, predictor variables were not always reported, reducing the power for these analyses. In particular, trauma exposure, personality factors (e.g., level of hostility), depression status, psychotropic medication use, and life-style habits were recorded insufficiently, precluding the meta-analytic assessment of these factors as moderating or mediating variables.

### Future Research

Notwithstanding the limitations of this article, this is the largest study of T2DM proportions and predictors in PTSD, and the first formal meta-analysis of this important topic. The results demonstrate that people with PTSD seem to be at greater risk for having T2DM. However, the results of this review have also identified several areas where further investigation is warranted. First, the pathophysiology underlying the association between PTSD and T2DM is complex and not well understood, requiring further investigation (43). Emerging evidence suggests that both share pathophysiological features, including hypothalamic-pituitary-adrenal and sympathoadrenomedullary dysfunction (44,45), inflammation (46), common genetic links, and epigenetic interactions (47,48). Examining whether T2DM is moderated not only by genetic factors but also by clinical characteristics or mediated by individual treatments should therefore be clinical research priorities. For example, prospective studies are needed to investigate the direct relationship between the risk for T2DM and the use of individual medications including antidepressants, mood stabilizers, and antipsychotic medication. Previous studies have found that some antidepressants may reduce hyperglycemia and normalize glucose homeostasis (49,50), whereas other antidepressants including tricyclic antidepressants may exacerbate glycemic dyscontrol or have little effect on glucose homeostasis (51,52). Because antipsychotics differ in their metabolic risk profile (53,54), it is advisable for future studies to report T2DM proportions in people with PTSD by individual medication classes and groups. Second, interventions that target diabetes in PTSD should be evaluated. Given the fact that exercise is the cornerstone for the prevention and management of T2DM in the general population (54) and that exercise also helps improve the mental and physical health of people with PTSD (55,56), research is required to investigate the effectiveness of exercise interventions on T2DM risk in this group. Third, that more data collected more recently were associated with a lower T2DM prevalence warrants further investigation. Fourth, few of the included studies provided sufficient detailed information on characteristics of PTSD patients with T2DM versus PTSD patients without T2DM to conduct separate comparative analyses of predictor variables. It is evident that future research will be enhanced by improved consistency in reporting of differences between PTSD patients with and those without T2DM. Future large-scale systematic reviews and meta-analyses at the patient level might also assist in the identification of factors associated with T2DM. Some of the variation in the prevalence of T2DM may be attributed to differences in culture, life-style factors (nutrition, physical activity), and medical care. There were, however, inadequate data to investigate this in the current meta-analysis, and future research should seek to better understand these factors. Last, long-term follow-up studies are required to accurately document the emergence of more distal T2DM outcomes, such as CVD and/or premature mortality.

## CONCLUSIONS

The current meta-analysis demonstrates that 10% of people with PTSD are currently affected by T2DM. Mental health professionals, general practitioners, and medical specialists involved in providing services to patients with PTSD have a duty of care to ensure the promotion of life-style advice and implementation of the necessary screening assessments following national and international standards.

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