HHS Public Access

Author manuscript

Metabolism. Author manuscript; available in PMC 2015 December 01.

Published in final edited form as:

Metabolism. 2014 December ; 63(12): 1463–1468. doi:10.1016/j.metabol.2014.08.009.

Stress- and PTSD-associated obesity and metabolic dysfunction: A growing problem requiring further research and novel treatments

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Abstract

Posttraumatic stress disorder (PTSD) is a growing public health concern. More recently, evidence has indicated that PTSD leads to obesity and associated metabolic dysfunction. Possible mechanisms of this link are through dysfunction of the hypothalamic-pituitary-adrenal axis and related moderation of appetite hormones and neural activity, leading to changes in consumptive behaviors. Although research has been examining associations between PTSD and obesity, diabetes, cardiovascular disease, and metabolic syndrome, future research should delineate potential mechanisms for these associations and develop targeted treatments to reduce these metabolic outcomes.

Obesity and its associated metabolic problems are increasing in prevalence and pose a tremendous threat to human health nationally and worldwide [1]. Approximately a third of the US population is obese, another third overweight, and a quarter of the population have metabolic syndrome [2]. Posttraumatic stress disorder (PTSD) has emerged as predictor of obesity and metabolic dysfunction in more recent years. Both obesity and PTSD are growing concerns within both the general and veteran populations. The lifetime prevalence rates of PTSD are high and the implications of the associations between PTSD and obesity have a wide reach. For instance, PTSD is estimated to have lifetime prevalence rates of up to 30% in US Vietnam War veterans, with current prevalence rates of around 15% [3]. Other studies find similar rates (11.2–17.1%) amongst more recent US veterans returning from Iraq and Afghanistan, making PTSD an ever-present concern for veterans [4]. Amongst the general population, prevalence rates of PTSD have been found to be about 7.8%, which represents a decent impact on the populace at large [5]. Slightly over a third (35%) of both the veteran

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Disclosure Statement: The authors have nothing to disclose.

and general populations are obese, regardless of PTSD status [6]. However, PTSD may be a key predictor of obesity. Indeed, PTSD has been associated with higher BMI/obesity and its complications, including high blood pressure and metabolic syndrome, not only when compared to the healthy state, but also when compared with other psychiatric disorders such as schizophrenia, mood disorders, and dementia [7, 8]. There is a large health cost associated with obesity that places a burden on the individual and health care system and an increased urgency to develop new and effective treatments to target this substantial problem [9, 10]. There is no current therapy for treating PTSD-associated obesity or metabolic syndrome. Taken together, it is imperative 1) to gain a better understanding of the mechanism underlying the relationship between PTSD and obesity and 2) to address the challenges of treating PTSD-associated obesity and metabolic dysfunction, with the goal of eventually developing effective treatment options.

PTSD is one manifestation of the link between stress and metabolic outcomes, perhaps regulated through sympathetic nervous system activation and the release of stress hormones by the hypothalamic-pituitary-adrenal axis affecting both metabolic and brain processes [11, 12]. Similar to PTSD, other forms of stress have been found to impact metabolic outcomes and lead to central obesity. For instance, childhood adversity, which may predispose individuals to and/or be the underlying cause of PTSD, predicts central obesity even when controlling for other risk factors such as gender, race, family history, smoking, diet, and exercise [13]. Similarly, early life stress has been linked with obesity, metabolic syndrome, cardiovascular disease and type 2 diabetes [14–16]. Inflammation appears to be higher in adults exposed to early life adversity, including increased levels of interleukin-6 (IL-6), c-reactive protein (CRP), and tumor necrosis factor (TNF), which may further contribute to risk of cardiovascular disease [17, 18]. Adipokines, including leptin and adiponectin, are also dysregulated in individuals with high levels of childhood adversity [19]. Indeed, poor diet along with higher levels of stress-related hormones, such as cortisol and catecholamines, appear to lead to worsened adipokine profiles and central obesity, insulin resistance, and metabolic syndrome- particularly when the stress occurs in childhood and adolescence [16, 20]. Other forms of psychosocial stress, including work-related, social, isolation, and socioeconomic stresses, have also been found to predispose individuals to obesity and related metabolic comorbidities, including type 2 diabetes and cardiovascular disease [21–33]. For instance, isolation stress caused increased consumption of high fat foods and altered adipokine levels [30]. Regardless of adversity, adolescent obesity has been associated with increased cortisol levels and disrupted circadian rhythms of these stress hormones, representing hypothalamic-pituitary-adrenal axis overactivity and reactivity and potentially indicating increased stress underlying the obesity [34]. Early life adversity, work-related stress, and/or stress resulting from a traumatic event either by themselves, or in the extreme case of PTSD, could lead to central obesity and metabolic dysfunction.

Thus, the first goal in understanding how PTSD may lead to obesity should be to study the mechanisms that may link the two (Figure 1). One possible mechanism underlying PTSD-associated obesity may be through neural changes known to occur in PTSD that may lead to altered cognitive/central control of feeding behaviors and thus, obesity. To date, no studies have examined how PTSD may alter metabolic neural outcomes, such as responses to food cues. However, studies examining functional brain changes in PTSD have implicated areas

that overlap with food-related brain areas. For instance, in an fMRI study of an affective cognitive control task, patients with PTSD showed altered inferior frontal, insular and parietal activations [35, 36], areas which have also been implicated in food image processing and the control of eating behaviors [37, 38]. These same areas have been implicated in other fMRI studies involving patients with PTSD while performing various other tasks, often involving emotional processing [39–43]. Furthermore, patients with PTSD have altered reward-processing circuitry, which is also well-known to be a key aspect of eating behaviors [44]. Altogether, these findings suggest that the processing of food images in these brain areas would also be affected in PTSD, although this remains to be confirmed.

Cognition is also altered in PTSD and this altered cognition may confer changes leading to altered consumptive behaviors. Previous studies of PTSD have consistently found structural brain differences in hippocampus and amygdala that correlate with severity of PTSD symptoms [45–54]. Furthermore, the reduction in hippocampal volume has been seen to correlate with duration of PTSD [50]. Thus, verbal memory impairments are the most consistent finding in PTSD, particularly autobiographical memory [55]. Other studies have seen other structural changes with PTSD in the corpus callosum [51, 56], premotor cortex [57], and areas of the prefrontal cortex [54, 58, 59]. Notably, these are areas often affecting brain responses to food cues and influencing feeding behaviors.

These altered neural and cognitive changes that occur in PTSD along with the clear association of PTSD with obesity may suggest altered consumptive behaviors, e.g., increased eating of foods with high calorie content, such as high fat foods or alcohol. However, past-year PTSD was associated with a 1.51 fold risk of obesity that was not modulated by binge eating suggesting mechanisms other than simple binge eating for this link [60]. Regardless, both US veterans and community members reported eating less nutritious foods as well as more guilt and episodes of overeating [61]. Indeed, PTSD symptom severity has been associated with emotional eating [62]. Chronic stress, a clear correlate of PTSD, has also been linked with overeating [63, 64]. Aside from the increased consumption of high fat foods, hypothalamic-pituitary-adrenal dysfunction with increased glucocorticoid secretion increases abdominal fat deposition specifically, which further leads to central obesity [63, 64]. Additionally, PTSD severity correlates with alcohol dependence, and the combination of PTSD and alcohol dependence leads to greater psychosocial and medical problems [65]. PTSD symptoms are highly correlated with drinking-to-cope motives in civilian and veteran populations with comorbid alcohol dependence and PTSD [66]. Greater PTSD symptoms have also been associated with increased alcohol craving in a combined civilian and veteran population [67]. Alcohol consumption may also mediate the effects of PTSD on neuroscientific outcomes, and thus, must be carefully controlled and considered in any studies with PTSD. For instance, hippocampal volume is reduced in PTSD, and these hippocampal deficits are exacerbated by alcohol abuse [68]. Further, in a PTSD model of rats, traumatic stress avoidance coping strategies increased alcohol consumption and altered prefrontal and amygdala activity [69]. Further research should attempt to parcel these linkages to determine how the brain changes associated with PTSD may influence consumptive behaviors that lead to the observed association between PTSD and obesity.

Another potential modulator of the interactions between PTSD and obesity may be through altered control of appetite hormones, such as adipokines and certain cytokines. Indeed, disruptions in the hypothalamic-pituitary-adrenal axis and increased sympathetic nervous system activity may lead to PTSD-associated metabolic and cardiovascular disorders [70]. Relatedly, adults with PTSD have been shown to exhibit exaggerated stress hormone release, representing dysfunction of the hypothalamic-adrenal-pituitary axis [11]. These effects need to be further defined and the linkages elucidated, as it is not clear whether they may influence the development of obesity or are outcomes of this particular category of PTSD-associated obesity. Thus, confounds such as BMI, diet, exercise, gender, and depressive symptoms, which can have significant impact on the associations between PTSD and these biomarkers, need to be carefully controlled. However, there do appear to be connections between PTSD and stress-related hormonal activity with adipokines, which regulate appetite. Leptin, a key adipokine regulating food intake, is increased in patients with PTSD [71]. Even subclinical PTSD has been associated with leptin levels, where greater PTSD symptoms, without full diagnostic criteria for PTSD, correlate with higher levels of leptin [72]. Neuropeptide Y (NPY), a hormone that regulates feeding behaviors in the hypothalamus and reduces stress more globally, has also been linked with PTSD. NPY is consistently lower in individuals with PTSD and appear to be higher in those who have a past history of but not current PTSD, suggesting a role in recovery from stress that may also regulate feeding behaviors [73–75]. Other appetitive hormones, including ghrelin and adiponectin, need further investigation to define their relationship with PTSD.

PTSD also appears to affect inflammatory markers either directly or indirectly. For instance, when depression and demographic variables were controlled, patients with PTSD had altered inflammatory biomarkers- more specifically, PTSD increased IL-6 and decreased CRP [71]. However, another study found that PTSD increased both CRP and intercellular adhesion molecule 1 (ICAM-1) [76]. Similarly, a twofold increase for CRP with PTSD has been observed after adjustment for potential confounders, including BMI and blood pressure [77]. Thus, the link between CRP and PTSD needs to be better defined as past results have shown conflicting increases or decreases. More significantly, fibrinogen, a clotting factor and marker for cardiovascular risk, appears to be elevated in PTSD [78]. Furthermore, fibrinogen correlated with PTSD severity and PTSD symptoms of hyperarousal in currently physically healthy patients [79]. In a study examining present stress influences on fibrinogen within the context of PTSD, patients with PTSD displayed higher fibrinogen levels with both baseline and induced stress than controls without PTSD [78]. Altogether, these data may indicate that PTSD leads to metabolic and inflammatory concerns that remain to be mapped.

It is clear that, regardless of the mechanism, PTSD leads to obesity, which eventually links to significant obesity-related complications, including metabolic syndrome, cardiovascular disorder, and type 2 diabetes mellitus. Indeed, research has consistently found that PTSD increases the risk of developing metabolic [80–84] and cardiovascular disorders [85–87]. PTSD alone has been associated with higher BMI/obesity and may be the psychiatric disorder most linked with obesity [8, 88]. Furthermore, PTSD status predicts the diagnosis of metabolic syndrome after adjustment for potential confounders such as depression, demographic factors, and antipsychotic drug usage [83]. PTSD severity also predicts

metabolic syndrome, controlling for antipsychotic use, with greater severity conferring greater risk [81, 89]. Other studies have found that when PTSD co-exists with depression, the risk of developing metabolic syndrome is further elevated [90]. PTSD also increases the risk of cardiovascular disease, often the endpoint of obesity and metabolic syndrome, in two meta-analyses [91, 92]. In a prospective study of World Trade Center survivors, those who developed PTSD and had been injured in the attacks had a three-fold risk of developing cardiovascular disease as compared to those without injuries or PTSD [93]. The risk of developing type 2 diabetes was also found to be significantly increased in individuals with PTSD in a well-controlled, prospective twin study [94]. In another prospective study of World Trade Center survivors, PTSD significantly predicted the development of type 2 diabetes [95]. Individuals with PTSD, who do not yet have diabetes, have also been found to have increased insulin resistance, suggesting future diagnoses of type 2 diabetes [96]. Increased PTSD symptom severity appears to confer worsened type 2 diabetes, as measured by increased HbA1c [97]. Evidence from a mouse model of PTSD suggested an adipokine-related mechanism for the decreased glucose tolerance, which was specific to PTSD [98]. Altogether, these studies show consistent findings of altered metabolic and obesity-related comorbidities with PTSD and may suggest adipokine and/or central nervous system mechanisms.

In summary, research has accumulated to suggest that PTSD leads to obesity and related metabolic complications. However, mechanisms of this association are not yet well-defined and future investigations should attempt to determine how PTSD may confer these significant metabolic risks. Evidence may suggest altered brain activity leading to altered consumption and food choices that cause PTSD-associated obesity, but this remains to be confirmed. Future research should determine the relationships between altered adipokines and inflammatory cytokines with PTSD and how they may lead to and/or be modulated by PTSD-associated obesity. Furthermore, associations between these changes and brain/cognitive responses remain to be seen. More importantly, as the prevalence of PTSD remains high, health care requires adequate treatments for this specific type of obesity. Given that there are currently no targeted, effective treatments for PTSD-associated obesity or metabolic syndrome, there is a clear need to develop and test treatments targeting this particular type of obesity.

Acknowledgments

Olivia M. Farr is supported by a training grant through the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) 5T32HD052961 (PI: Steven Grinspoon).

Abbreviations

PTSD	post-traumatic stress disorder
IL-6	interleukin-6
CRP	c-reactive protein
TNF	tumor necrosis factor

ICAM-1 Intercellular Adhesion Molecule 1

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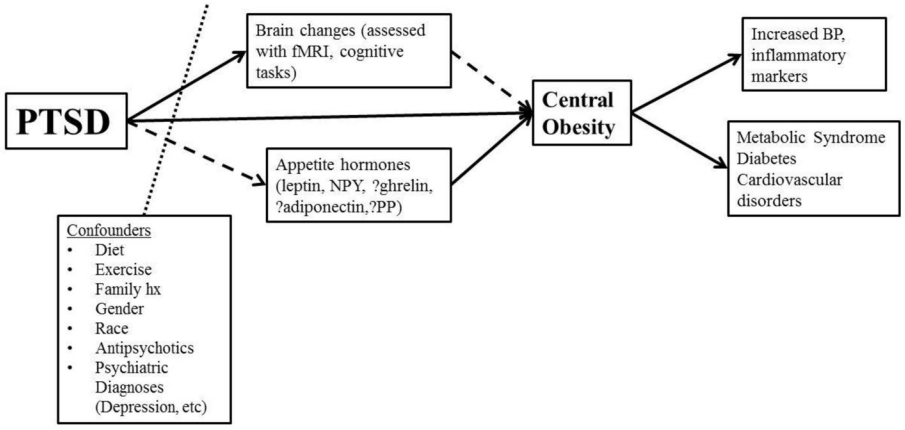

Figure 1. Potential mechanisms and linkages between PTSD and obesity

PTSD is known to lead to central obesity, brain changes, and likely changes in appetite hormones. The brain and appetite hormone changes may be moderating the connection between PTSD and central obesity. In turn, central obesity leads to known changes and comorbidities. Dashed lines represent presumed linkages.