This narrative review was aimed to analyze the scientific data about the association of post-traumatic stress disorder, insomnia, obstructive sleep apnea syndrome, dyssomnias, heart rate variability, metabolic syndrome, type 2 diabetes mellitus, and cardiovascular autonomic neuropathy, along with potential pathophysiological mechanisms underlying these associations.

The results of experimental, cohort, prospective, and randomized clinical studies provide evidence of common pathogenetic pathways contributing to their development.

Searches were conducted in Scopus, Science Direct (from Elsevier), EBSCO, and PubMed databases, including the Medline databases. Additionally, a manual search of publication bibliographies was undertaken to uncover research outcomes not accessible through online searches.

**Keywords**: Post-traumatic stress disorder, insomnia, obstructive sleep apnea, heart rate variability, metabolic syndrome, type 2 diabetes mellitus, cardiovascular autonomic neuropathy.
Introduction

Dysfunction of the autonomic nervous system (ANS) is associated with numerous pathophysiological states and diseases, including obesity, hypertension (HTN), impaired glucose tolerance (IGT), metabolic syndrome (MetS), and type 2 diabetes mellitus (T2D) [1, 2]. However, the topographical location of the ANS prevents direct physiological testing, necessitating indirect measurements. Analyzing heart rate variability (HRV) is an effective method to determine how effectively the ANS is functioning [3]. A 32–45% increased risk of the first cardiovascular (CV) event and an increased risk of all-cause death is linked to HRV suppression [4, 5]. The correlation between changes in glycated hemoglobin A1c (HbA1c) and abnormalities in the HRV in patients with T2D with diabetic cardiac autonomic neuropathy (CAN) has been reported [6,7]. HRV assessment is important in diagnosing the severity of MetS and comorbid CAN [8]. It has been demonstrated that CAN precedes hyperglycemia and is linked to components of the MetS, specifically obesity and hypertension [2, 9].

Violation of the functional state of the ANS is associated with post-traumatic stress disorder (PTSD) [10, 11]. MetS and PTSD frequently coexist and share similar clinical and neurobiological symptoms [12]. Meta-analyses reveal that individuals with PTSD have a greater frequency of MetS than the general population [13, 14]. MetS risk factors include PTSD as well. This coincidence can be partially explained by the involvement of common pathogenetic mechanisms characteristic of both conditions [15].

A common clinical symptom of PTSD is insomnia or dyssomnia. Nowadays, it has been suggested that post-traumatic circadian sleep rhythm disturbances, which mediate the neurobiological correlates of disease caused by homeostatic imbalance, are the primary hallmark of PTSD rather than a secondary one [16]. In addition, the pathophysiology of obesity, MetS and insulin resistance (IR) includes chronodestruction, depressive disorders, and dyssomnia/insomnia. This suggests that dyssomnias may be a common neurobiological bridge between PTSD and several diseases [15].

It has been demonstrated that algorithms of HRV disturbances at night correlate with the severity of obstructive sleep apnoea (OSA) [17]. The sympathetic nervous system (SNS) can become more excitable due to sleep fragmentation and intermittent hypoxia, leading to metabolic disorders [18]. Particularly, reports suggest that OSA may be accompanied by IGT [19]. OSA, possibly “due to” MetS and the influence of independent mechanisms, is also associated with CAN [20]. Autonomic dysfunction is likely to mediate the mechanisms underlying such pathophysiological changes. However, research in this area has shown conflicting results, and the cause-and-effect relationships remain unclear.

The objective of this narrative review was to examine and summarize the existing literature on the significance and characteristics of the relationships between PTSD, insomnia/dyssomnia, HRV, CAN, and MetS, as well as possible pathophysiological mechanisms that cause these changes.

PTSD, ANS, and HRV

Time, frequency, and non-linear methods can quantify HRV parameters [21]. The most common indicators of the time domain of the HRV spectrum are the standard (root mean square) deviation of the difference of consecutive N-N intervals, a measure of the short cycle duration HRV (RMSSD), and the standard deviation of all normal to normal R-R (NN) intervals, which reflects the total HRV (SDNN). Frequently studied parameters of the frequency domain are the high-frequency component (HF, 0.15-0.40 Hz), the low-frequency component (LF, 0.04-0.15 Hz), and the LF/HF ratio [22]. RMSSD and the HF component are strongly interrelated and associated with n. vagus activity [23].

The physiological condition of the ANS and parasympathetic nervous system (PSNS) affect the SDNN, which reflects the overall flexibility of the ANS [24]. Simultaneously, the findings from studies examining the influence of the ANS and the PSNS on the state of the LF component are quite controversial. The LF component may be associated with baroreceptor activity and, therefore, may primarily reflect the state of parasympathetic activity [24].

High functional activity of the HRV is a sign of sufficient adaptive capacity of the cardiovascular system, which allows the body to adapt to internal and external stimuli [25, 11]. At the same time, excessive activation of the SNS and a decrease in the PSNS can lead to HRV depression [3, 26]. Low HRV can cause patients with PTSD to develop comorbid cardiovascular disease (CVD) [27]. In particular, the analysis of the results of 15 clinical trials demonstrated a significant association of PTSD with a decrease and/or a tendency to decrease HRV in most cases [28]. It has been reported that patients with PTSD usually have dysregulation of the ANS, usually with a hyperactive sympathetic tone [29]. Analysis of HRV parameters using time, frequency, and non-linear approaches reveals that PTSD impacts both the SNS and PSNS. Patients with PTSD demonstrate decreased HRV values, indicating altered sympathetic and parasympathetic functioning [30]. Nevertheless, the outcomes are subject to debate, potentially because of the varying
characteristics of the traumatic stimulus and the exclusion of potential subtypes of PTSD, or, most likely, publication bias [31]. The study of different periods of PTSD progression could potentially explain the apparent discrepancy between the data on the increase or decrease in HRV in PTSD. The current study has examined a varied cohort of patients with PTSD, encompassing a broad spectrum of traumatic events and demographic characteristics, and, as a result, it is impossible to determine the standardized value of the impact of PTSD on the state of HRV [29, 32].

The results of the analysis of several publications indicate that most of them report increased SNS activity and decreased PSNS (and hence autonomic imbalance) in patients with PTSD. Furthermore, there is plenty of information indicating impaired baroreflex function in individuals with PTSD, resulting in the dysregulation of BP. The authors suggest that the persistent and intense nature of PTSD symptoms can independently increase the risk of CVD, potentially due to disruptions in autonomic function [33].

In their study, Campbell et al. (2019) performed a meta-analysis of the findings of various research involving individuals diagnosed with PTSD that addressed HRV parameters reflecting parasympathetic activity. Several vagally-mediated HRV parameters were pooled, resulting in one mean effect size per trial. The results of a meta-analysis demonstrated suppression of vagally mediated HRV in individuals with PTSD (Hedges’ g = -0.26) [31]. The findings of a meta-analysis of 4,145 trials showed that persons with PTSD had lower HRV both at rest and under stress. The small size of the negative effects for RMSSD, HF-, and LF-components indicates a decrease in parasympathetic (i.e., vagal) activity, and the moderate negative effect for SDNN emphasizes a decrease in overall HRV power. The presence of a positive LF/HF effect likely suggests alterations in the balance between SNS and PSNS activity in individuals with PTSD. Additionally, the rise in heart rate (HR) both at rest and during periods of stress may reflect heightened ANS functioning. The findings indicate that there is a connection between PTSD and disruption in the ANS. The results indicate that the changes in the ANS in persons with PTSD are not restricted to specific parameters related to HRV that are influenced by the vagus nerve but may instead represent a more general dysregulation of the ANS [10].

In addition, it has been demonstrated that HRV parameters as biomarkers of cardiac dysautonomia are significantly associated with the severity of PTSD symptoms in women who have suffered child loss during pregnancy. In particular, the scores of the scale for assessing PTSD according to the PTSD Checklist (PCL-5) of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) had a significant relationship with HRV parameters (SDNN, RMSSD, and the number of pairs of adjacent NN intervals differing by more than 50 ms). Patients diagnosed with PTSD exhibited comparable average HR values to those without PTSD. However, they demonstrated significantly elevated SDNN and RMSSD [29].

PTSD, insomnia/dyssomnia and HRV

The ANS regulates a range of internal bodily activities, including breathing and neuroendocrine secretion, to maintain homeostasis. Given the proximity of cell populations and efferent signals responsible for autonomic regulation to those engaged in regulating the sleep-wake cycle, there is a reciprocal relationship between sleep architecture and autonomic coordination. This means that they mutually influence each other [34].

Sleep is a complex phenomenon that is largely controlled by the ANS. Complaints about sleep disturbances are an important component of the constellation of symptoms that make up PTSD. Recurrent, disturbing dreams and difficulty falling asleep are among the main features of PTSD. Thus, attempts to explain the physiology of PTSD should take these symptoms into account [35].

Short and long sleep durations and dyssomnias, primarily OSA, contribute to CV and metabolic disorders [5]. Too little sleep decreases insulin sensitivity in adipocytes and affects the phosphorylation of serine/threonine kinase (Akt/protein kinase B), which is involved in the insulin signaling pathway [36]. Finally, sleep is linked to other risk factors that contribute to the occurrence of MetS, including depression and lack of physical activity [37].

There is accumulating evidence that autonomic dysfunction is a pathophysiological link between dyssomnias and their pathophysiological consequences [38]. PTSD is characterized by a significant number of symptoms and comorbidities that are also associated with sleep deprivation and circadian disorders [15]. Currently, two main hypotheses have been put forward regarding the relationship between autonomic function and insomnia [34]. The first source states that sleep fragmentation can lead to autonomic changes. Studies have demonstrated that autonomic arousal, which is not controlled by the cerebral cortex, is a secondary effect of sleep fragmentation and interruption of its continuity [39].
Furthermore, autonomic sleep fragmentation is linked to a daily rise in sympathetic activity and elevated blood pressure in healthy older adults [40]. Based on the second source, autonomic alterations can be a manifestation of a state of hyperarousal [41]. Elevated HR, the lack of a normal decline in autonomic function during sleep, and alterations in the secretion of stress hormones might be seen as markers of an aroused state that makes one more susceptible to dyssomnia [42]. Therefore, examining the condition of the ANS can offer a fresh perspective on the connection between dyssomnia/insomnia and CVD [38]. Although the hypothesis of ANS disturbance in insomnia is widely acknowledged, there is currently little actual data to support it [43].

OSA is a highly prevalent sleep disease, with an estimated impact on 1 billion individuals globally [44]. Disorders caused by OSA exert a detrimental influence on the cardiovascular system; in particular, autonomic dysfunction plays a key role in mediating the risk of CVD in OSA [45]. Numerous large cohort studies, such as the WISCONSIN Sleep Cohort Study, have demonstrated a clear link between OSA and the occurrence of CVD [46]. OSA decompensation is a risk factor that increases the poor prognosis of CV events in patients with HTN by 93% [47]. Meta-analyses have found that there is a correlation between OSA and persistent fatigue [15], HTN, T2D [48, 49], chronic coronary syndrome, stroke [50], atrial fibrillation, congestive heart failure, and an increased risk of death [51,52]. PTSD and OSA are often comorbidities which affect the severity of the course and the results of the treatment. Individuals with PTSD have a higher occurrence of OSA compared to the general population. This indicates a probable reciprocal influence between these two conditions. There is strong evidence that dyssomnia or insomnia may contribute to the pathophysiology of PTSD. The presence of hyperarousal and hypervigilance symptoms in individuals with PTSD can decrease the threshold for arousal, leading to an increased occurrence of sleep fragmentation linked to obstructive episodes. On the other hand, sleep disruptions caused by OSA can disrupt the normal functioning of rapid eye movement and exacerbate night terrors [53].

Patients with OSA exhibit a cyclic pattern of HR and BP spikes associated with SNS and PSNS activation due to recurrent episodes of apnea. In OSA, changes in the baroreceptor and chemoreceptor reflexes, which are linked to heightened SNS activity, may have a role in elevating the risk of CV complications [54]. It has been demonstrated that OSA is associated with altered autonomic function, particularly increased SNS activity [45]. The altered autonomic function may be crucial in connecting OSA and CVD, and treating OSA to mitigate these autonomic changes may reduce CV risk [55].

Various sleep-related parameters, including arousal and sleep quality, and respiratory factors, including respiratory rhythm and intrathoracic pressure, control HRV in patients with OSA [56]. Simultaneously, individuals with OSA frequently experience multiple disruptions in their glucose and lipid metabolism. These disruptions play a crucial role in the progression of dyslipidemia, obesity, MetS, T2D, and CVD [57, 58].

Ischemic CV events in OSA are caused by several things, including oxidative stress, high sympathetic activity, and endothelial dysfunction, with the main factor being SNS hyperactivity [59]. The activity of the SNS is synchronized with repetitive episodes of apnea that occur continuously during sleep in patients with OSA [5]. According to reports, the use of HRV analysis in OSA has been reported to provide insight into the autonomic control of the myocardium at different stages of sleep [59]. Another systematic review found that adults with OSA had increased sympathetic activity and decreased parasympathetic tone [56]. However, prior investigations have shown no significant decrease in parasympathetic tone, as measured by RMSSD, in individuals with OSA [56, 5].

A reduction in HRV may suggest adverse alterations in autonomic control and the development of CAN [60]. A statistical analysis of the study results among 4,152 patients who were thought to have OSA, using a combination of non-linear analysis and segmented linear models, revealed that the risk of CAN increases in a non-linear relationship with the severity of OSA, particularly from slow changes in the early stages to fast changes in the later stages. Using a segmented multivariate linear regression (SMLR) model showed that the total value of changes in carbohydrate (pre-prandial glucose, insulin, and IR) and lipid metabolism was more significant for predicting HRV disorders than OSA parameters in the early stages of CAN. At the same time, OSA parameters proved to be effective predictors in the more severe stages of CAN. The results indicate stage-specific involvement of carbohydrate and lipid metabolism parameters underlying non-linear changes in CAN in patients with OSA. Therefore, controlling carbohydrate and lipid metabolism may help to control the onset of CAN in patients with OSA [57].

**MetS, insomnia, PTSD, and HRV**

Proinflammatory signal transduction, IR, obesity and MetS can form a vicious circle of disturbed metabolism with detrimental health consequences [61]. PTSD is often accompanied by many medical and psychiatric illnesses, such as
metabolic or cardiovascular diseases, cognitive dysfunction, mood disorders, drug abuse, and sleep disturbances [62, 15]. Therefore, there are comparable processes at play in the deterioration of PTSD symptoms and the occurrence of negative cardiovascular events linked to MetS. However, it is believed that external factors, such as environmental exposure, can modulate the influence of biological factors on the severity of PTSD and MetS and thereby contribute to the heterogeneous clinical picture [63, 15].

The identification and characterization of the relationship between metabolic disorders and mental disorders, including PTSD, has received considerable attention in recent years [64]. It has been reported that patients with PTSD are more likely to have MetS and its components; in particular, they diagnose MetS almost twice as frequently [14]. At the same time, combat veterans are more likely to develop obesity, MetS, and PTSD [65]. The medical concept of “two hearts” is becoming more important as the death rate rises for persons with both conditions, PTSD and MetS, which means that the high frequency of comorbidity requires more attention [66].

Thus, MetS may result from individual neuroendocrine adaptations to chronic stress. At the same time, clinical and translational data support the idea that PTSD is likely to be a metabolic disorder in itself [13].

After analyzing data from 7,880 people in the sixth Tromsø Health Study (Tromsø 6), researchers discovered a significant negative correlation between the number of metabolic syndrome (MetS) components and heart rate variability (HRV). HRV was measured using short-term pulse wave signals (PRV). The decline in PRV was not consistently gradual but plateaued after the third component, with no notable disparity in PRV observed between individuals with MetS and T2D. There was a significant negative relationship between HbA1c and PRV, indicating a decrease in short-term PRV signals already within the physiological range of HbA1c. Thus, patients with MetS and T2D differ from healthy individuals in terms of PRV, which indicates a violation of the ANS in both conditions [8].

The results of a systematic review and meta-analysis indicate that patients with MetS have changes in the time domain of HRV in the form of a significant decrease in SDNN and RMSSD and in the frequency domain (decrease in HF and LF) [67].

The Midlife in the United States II (MIDUS II) study aimed to examine how sleep disorders and the reduction of HRV affect the chance of developing MetS. It was reported that deterioration in sleep quality in 966 subjects was associated with MetS in cases where the global score of the Pittsburgh Sleep Quality Index (PSQI) questionnaire was estimated as continuous (odds ratio, OR) 1.07, 95% (confidence interval, CI) 1.03-1.11) or non-significant. There was also an association between reduced HRV and MetS [natural logarithms (ln) LF (OR 0.82, 95% CI 0.72 to 0.92); In HF (OR 0.89, 95% CI 0.80 to 0.99); In RMSSD (OR 0.75, 95% CI 0.60 to 0.94); ln SDNN (OR 0.59, 95% CI 0.43 to 0.79). The combined effect of poor sleep quality and low HRV, compared with physiologic sleep and HRV status, further increased the likelihood of developing MetS [68].

The trial results among 74 patients with MetS show a notable reduction in HRV, specifically in the SDNN index (by 26%), which represents the overall strength of neurohumoral regulation of HR, and particularly in RMSSD (by 44%) and HF (by 69%), which are indicators of short-term, vagal influences. In addition, the baroreflex center in the medulla oblongata, as measured by the spectral strength of the LF component, was reduced by 55%. Simultaneously, there were no notable disparities in the mean duration of the R-R interval, a highly LF component, LF/HF, InLF, InHF, and thus, no substantial alteration in the autonomic balance favoring sympathetic dominance. The analysis of variance verified that the MetS component has a substantial impact on the state of HRV. Therefore, the acquired results suggest the occurrence of CAN in patients with MetS [69].

Concluding remarks
Various chronic mental disorders, including PTSD, exhibit changes in the functioning of the ANS [15]. At the same time, the prevalence of MetS is higher in PTSD, with patients having an increased risk of premature death. Data suggests that there is a bidirectional longitudinal relationship between PTSD and MetS and that the intensity and duration of symptoms have a proportional effect on this relationship. The coexistence of MetS and PTSD is affected by a shared genetic predisposition and physiological processes, namely those that result in increased activation of both the immune-metabolic and endocrine systems in both the central and peripheral levels [70]. Researchers have reported changes in HRV due to chronic autonomic dysfunction to correlate with insomnia and OSA [71]. HRV is a reliable indicator of autonomic modulation of the cardiovascular system, which combines sympathetic and parasympathetic effects on the myocardium. PTSD is associated with an intricate disturbance of several neurobiological regulatory mechanisms and an imbalance in the parasympathetic-sympathetic balance, which can be
quantified using HRV. It is still uncertain if a low HRV is a risk factor for PTSD, indicating vulnerability, or if the suppression of HRV contributes to the development of PTSD. Research has shown that a low HRV can affect the frequency and recovery of intrusive recollections, indicating an increased susceptibility [72]. Longitudinal studies are necessary to explore the impact of HRV by analyzing the variations in HRV both before the traumatic incident and throughout the progression of PTSD. Until now, cross-sectional research has mostly examined the correlation between HRV and PTSD. Hence, it is not feasible to establish a cause-and-effect relationship relying on the computed effect sizes. Without a doubt, further investigation is necessary to elucidate the role of HRV in the progression of PTSD [10].

Epidemiological studies have established a clear connection between the occurrence of PTSD and an elevated risk of illness, cardiovascular death, and overall mortality associated with the chronic collapse of the CAN. However, CAN in IGT and MetS is increasingly reported, with a prevalence of up to 11% and 24%, respectively [2]. The HRV is a key component for assessing the relationship between PTSD, insomnia/dyssomnia, MetS, and CAN. However, only a few studies have attempted to examine the relationship between cardiac autonomic function and metabolism, OSA [73, 57]. Although a certain degree of interaction between risk factors and the state of the ANS was observed, these studies were not comprehensive.

Another significant element could be that in the case of certain chronic disorders, such as MetS and T2D, the connection between a risk factor and its result is seldom linear. In particular, the dose-response relationship between OSA severity and dyslipoproteinemia is ambiguous and consists of several stages with plateaus [74]. Thus, the relationship between CAN and OSA may be non-linear due to the powerful influence of carbohydrate and lipid metabolism disorders on disease outcomes [57]. Autonomic dysfunction in PTSD may be linked to a higher susceptibility to CVD. Nevertheless, it is still necessary to determine whether autonomic dysfunction can work as a biomarker for the initiation and advancement of PTSD [75]. It is also necessary to determine the specifics of the impact/no impact of autonomic imbalance on the risk of developing PTSD. Biomarkers of sympathetic activation in the blood may enable a better understanding of anatomical function and its role in the risk of CVD and CAN, as well as approaches to their prevention and treatment. Additional research is needed to develop standardized methods for non-invasive evaluation of autonomic function in individuals with PTSD, OSA, insomnia, and MetS.

References


