Anxiety and Hypertension: Is There a Link? A Literature Review of the Comorbidity Relationship Between Anxiety and Hypertension

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Abstract

Purpose of Review To review the most recent literature on the association between comorbid anxiety disorders and hypertension.
Recent Findings Recent longitudinal and cross-sectional studies across geographic regions and age groups predominantly demonstrate a positive association between comorbid anxiety and prevalent or incident hypertension. Growing research on blood pressure variability and reduced baroreflex sensitivity in response to autonomic dysfunction provides a greater understanding of mechanistic relationships between anxiety and hypertension. Observational studies demonstrate that young adults are at a higher risk for developing incident hypertension after an anxiety diagnosis, supporting longer exposure to alterations in autonomic mechanisms. Confounding relationships of comorbid anxiety with depression likely contribute to prior conflicting results on the association between anxiety and hypertension.
Summary There is increasing evidence of a positive association between comorbid anxiety and hypertension. This contemporaneous review supports similar findings in historical studies and provides mechanistic hypotheses for larger, longitudinal studies.

Keywords Hypertension · Anxiety disorder · Health behavior · Autonomic nervous system · Comorbidity · Risk factors

Introduction

Hypertension is the leading preventable risk factor for premature death, cardiovascular disease, and stroke worldwide [1, 2]. Globally, over 40% of adults (≥ 20 years old) have hypertension [3]; 46% of adults in the USA [4]. In parallel to hypertension, psychiatric disorders also represent a significant public health burden [5]. Anxiety disorders (e.g., panic disorder and generalized anxiety disorder) are the most prevalent psychiatric disorders worldwide [6, 7], ranking as the 6th contributor to disability [6]. Globally, approximately one-third of the population is expected to be affected by an anxiety disorder during their lifetime [7, 8]. According to the National Institute of Mental Health, approximately 19% of US adults (≥ 18 years old) had an anxiety disorder in the past 12 months [6]; 31% of US adults will experience an anxiety disorder in their lifetime [9]. Comorbid hypertension and anxiety (with or without depression) have been associated with lower treatment adherence, lower levels of daily functioning, lower health-related quality of life, and higher healthcare-associated costs [10, 11••].

The causal relationship of anxiety in the development of incident hypertension has been a subject of controversy since the early twentieth century [12, 13]. Historically, there have been conflicting results across observational and prospective cohort studies [14–18]. Although most prior studies have suggested a positive correlation between comorbid hypertension and anxiety, a few small cross-sectional studies have demonstrated an inverse relationship between anxiety and hypertension [19–21]. Study limitations that may have contributed to prior mixed results include a small sample size, differing hypertension diagnosis thresholds (e.g., ≥ 160/95 mmHg, ≥ 140/90 mmHg), lack of gender or racial/ethnic diversity, use of self-reported diagnoses, differing psychological diagnostic tools, and/or evaluation of anxiety scores or individual anxiety-related traits (e.g., time urgency) [12, 14,18,19, 22–26].

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Therefore, the objective of this review is to summarize contemporaneous studies evaluating the relationship between prevalent anxiety and comorbid prevalent hypertension, or the development of incident (future) hypertension. For this review, anxiety disorders include the following diagnoses reflecting common genetic, cognitive behavior, and biological features [9]: generalized anxiety disorder (GAD), panic disorder, phobias, social anxiety disorder, obsessive-compulsive disorder (OCD), and post-traumatic stress disorder (PTSD) [8, 9]. This review does not include studies that focused solely on anxiety-related traits. Prevalent hypertension is defined as a systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg and/or currently taking antihypertensive medication, per the US National Health and Nutrition Examination Survey (NHANES) [27]. This blood pressure threshold, in contrast to $\geq 130/80$ mmHg, reflects the hypertension clinical practice guidelines during the years studied. Incident hypertension is defined as a new diagnosis of hypertension. The methodologies to define incident hypertension vary broadly across studies: self-report, with or without new antihypertensive medication, a new ICD-9 hypertension diagnosis code per established algorithms [28], and/or follow-up research visit blood pressures with a systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg [29].

Anxiety and Incident Hypertension

Over the past 5 years, there have been new studies evaluating the relationship between prevalent anxiety and the development of incident hypertension. A secondary analysis of the Mechanisms and Outcomes of Myocardial Silent Ischemia (MOMSI) Study evaluated longitudinal data of baseline non-hypertensive individuals ($n = 197$, ≥ 18 years old, English or French speaking; 33% women; 58 [10] years old) who were recruited at the Montreal Heart Institute [5]. Baseline anxiety was identified using the Primary Care Evaluation of Mental Disorders (PRIME-MD); incident hypertension was defined as self-report of a new diagnosis or started taking antihypertensive medication. Overall, baseline anxiety was associated with a higher rate (odds ratio OR 4.24; 95% CI 1.29–14.01) of developing incident hypertension over 1 year, compared to those without an anxiety disorder [5]. Mood disorders were not significantly associated with developing incident hypertension [5]. The relationship between anxiety and incident hypertension remained significant among middle-aged women after adjusting for (age, sex, body mass index [BMI], smoking status, and psychiatric medication use) [5].

Using the World Mental Health Surveys from household samples across 19 countries, survival analyses estimated the association between an incident mental health diagnosis and the subsequent development of self-reported incident hypertension [30]. The *Diagnostic and Statistical Manual of Mental Disorders*, *Fourth Edition* (DSM-IV) criteria were used to diagnose the following anxiety disorders: panic disorder, agoraphobia without panic, specific phobia, social phobia, post-traumatic stress disorder, generalized anxiety disorder, and obsessive compulsive disorder [30]. Panic disorder (OR 1.2; 95% CI 1.1–1.5), social phobia (OR 1.1; 95% CI 1.0–1.3), and specific phobia (OR 1.3; 95% CI 1.1–1.4) were the anxiety diagnoses associated with developing incident hypertension, after adjusting for age, gender, country of residence, and the presence of other mental health disorders. The time to developing incident hypertension ranged from 11.7 to 34.2 years [30]. Additionally, individuals with multiple mental health diagnoses and/or an initial mental health diagnosis at an earlier age (< 21 years old) were more likely to develop incident hypertension [30].

A larger, racial/ethnically diverse prospective cohort study evaluated the risk of developing incident hypertension and other cardiovascular risk factors over 10 years (2005 to 2015) among $n = 524,952$ patients (≥ 30 years old; 45.9 [13.0] years old; 17.0% Black, 27.6% South Asian, 41.9% White) across 140 primary care practices in London [22]. At baseline, patients were diagnosed with anxiety, schizophrenia, depression, bipolar, or personality disorder; models were adjusted for age, gender, race/ethnicity, antidepressants, antipsychotics, and social deprivation [22, 31]. Cox regression models demonstrated that a baseline diagnosis of anxiety (hazard ratio HR 1.09; 95% CI 1.05–1.14, $p < 0.001$), schizophrenia (HR 1.17; 95% CI 1.05–1.30, $p < 0.003$), or depression (HR 1.07; 95% CI 1.02–1.11, $p = 0.003$), independently demonstrated an increased risk of developing incident [22]. Interestingly, antidepressant use was independently associated with a higher risk of incident diabetes mellitus, hypertension, and hyperlipidemia over 10 years, despite lower rates of smoking, obesity, and physical inactivity among patients prescribed antidepressants [22]. However, this may be confounded by the use of antidepressants (serotonin reuptake inhibitors [SSRIs]) for pharmacologic treatment of anxiety [32].

Analysis of the national population-based Australian Longitudinal Study on Women's Health (ALSWH) evaluated the association of self-reported prevalent anxiety with self-reported incident hypertension among 9149 women (49.5 [1.4] years) [33]. Overall, 29.8% of women developed incident hypertension during the 15-year follow-up. However, in contrast to prior studies, the relationship of anxiety with incident hypertension was not significant after adjusting for covariates, which included comorbid depression [33]. Additionally, a retrospective analysis of the ESTHER study [34], an 8-year follow-up population-based cohort, evaluated the association of hypertension with *symptoms* of generalized anxiety [35]. The study was conducted in South West Germany ($n = 1659$, 57–84 years old); baseline hypertension was defined using a general practitioner-based diagnosis or self-report of a diagnosis or antihypertensive medication. The Generalized Anxiety Disorder (GAD-7) Scale assessed

generalized anxiety symptoms severity (sensitivity 0.63; specificity 0.9) [35]. Overall, $n = 434$ (13.9%) demonstrated a presence of "clinically relevant GAD symptoms." However, after covariate adjustment, including depressive symptoms, the presence of the GAD symptoms in this elderly population was not significantly associated with the development of hypertension (OR 1.1; 95% CI 0.85–1.44) [35]. The contrasting results of these studies may reflect prior observed relationships between depression and hypertension, confounding the relationship between anxiety and hypertension [36]. Additionally, other observational cohorts have demonstrated a higher number of "depressive episodes" with increasing age, also confounding the combined relationship of comorbid anxiety *and* depression with hypertension [15].

Overall, the majority of studies across age groups and geographic regions support an association between prevalent hypertension and the development of incident hypertension. Due to the observational design, studies to date have not found a direct causal pathway between prevalent anxiety and incident hypertension. The negative association studies likely highlight confounding between comorbid anxiety and depression diagnoses and development of incident hypertension.

Anxiety and Prevalent Hypertension

Historical cross-sectional studies have demonstrated a positive, bidirectional association between prevalent anxiety and prevalent hypertension [25, 26, 37]: adults with hypertension were more likely to have anxiety and those with anxiety were more likely to have hypertension [19], independent of other risk factors for hypertension [14]. The World Mental Health Survey Initiative conducted 18 cross-sectional surveys in 17 countries among adults within the general population ($n = 42,249$, including North and South America, Asia, South Pacific, Europe, Middle East, and African geographic regions). The diagnosis of anxiety and/or depression was defined using the World Mental Health version of the World Health Organization (WHO) Composite International Diagnostic Interview (WMH-CIDI). Overall, adults diagnosed with anxiety disorders were statistically more likely to have one or more of the following self-reported comorbid conditions: obesity, diabetes mellitus, asthma, hypertension, arthritis and other musculoskeletal disorders, gastrointestinal diseases, heart disease, chronic pain, and headaches [38]. The adjusted odds ratio for comorbid anxiety and hypertension, without depression, was (OR 1.7; 95% CI 1.5–1.9) with the range of odds ratios for the remaining conditions of ORs: 1.2–2.3 (all $p < 0.05$) [38]. A more recent cross-sectional ambulatory and inpatient medical record analysis evaluated prevalent comorbid hypertension and psychiatric disease, including anxiety, among residents in Stockholm County, Sweden ($n = 2,058,408$). Overall, men and women with hypertension were more likely to have a medical record diagnosis of

anxiety, with greater comorbid rates among men (adjusted OR 1.28; 95% CI 1.24–1.32] compared to women (adjusted OR 1.05; 95% CI 1.02–1.09) [39•].

Dose-Response Relationship

Some studies have identified positive relationships between the level (severity) of anxiety and comorbid prevalence of hypertension; higher anxiety scores had a greater association with prevalent hypertension [13, 14, 38, 40, 41]. This dose-response relationship has also been recognized between the severity of anxiety (and/or depression symptoms) and other prevalent conditions, for example, cardiovascular disease, autoimmune diseases, and neurodegenerative diseases [38, 40, 41]. A cross-sectional US study was conducted of $n = 989$ primary care patients with a baseline anxiety diagnosis (defined using the Mini-International Diagnostic Interview [MINI]). Patients reporting more severe symptoms of anxiety with comorbid depression had more medical chronic conditions, including asthma ($p = 0.039$), coronary heart disease (including heart attack, angina, heart failure; $p = 0.038$), back/disk/spine problems ($p = .001$), gastrointestinal ulcer ($p = 0.001$), migraine headaches ($p = 0.011$), and vision difficulties ($p < 0.001$) [40]. Overall, a one standard deviation increase in anxiety and depression symptom severity was associated with a 15% increase in chronic medical comorbidities, even after adjusting for patient demographics (age, gender, marital status, ethnicity, and education) and health behavior (BMI, smoking, exercise, and alcohol use) [40].

Physiologic Mechanisms Linking Hypertension and Anxiety

Anxiety, defined as a negative emotion, has both psychological (e.g., tension, worry) and somatic (e.g., palpitations, chest discomfort) characteristics [19], which have been attributed to autonomic arousal and an increase in blood pressure [19]. Additionally, stress is commonly experienced through anxiety, mediated by the hypothalamic-pituitary-adrenal (HPA) axis, altering and increasing production of circulating catecholamine levels [19, 42]. Changes in circulating catecholamines, with alterations in autonomic mechanisms has been attributed to insulin resistance, endothelial dysfunction, inflammation, and hypertension, all contributors to cardiovascular disease [9, 14, 19, 41].

O'Donovan et al. developed a theoretical model demonstrating that individuals with an anxiety disorder have an exaggerated neurobiological sensitivity to threat (i.e., threat-related vigilance and preparedness) resulting in recurrent, prolonged activation of stress and inflammatory systems [9]. As a brief summary, individuals with an anxiety disorder may detect threatening stimuli earlier, perceive a greater threat, and are less likely to resolve perceived threatening situations

compared to individuals without an anxiety disorder, resulting in a sustained threat perception. However, to process a perceived threat, the hypothalamic-pituitary-adrenal (HPA) axis and autonomic nervous system are activated, raising concerns for prolonged activation from chronic, sustained threat perception [9].

Blood Pressure Variability

Blood pressure variability (*BPV*; i.e., fluctuations in blood pressure) has been a growing focus in clinical, observational, and epidemiological studies. Multiple studies have demonstrated relationships between high BPV, incident stroke and cardiovascular events, independent of mean systolic blood pressure [43]. Higher blood pressure variability has also predicted the development, progression, and severity of target organ damage associated with hypertension, likely reflecting autonomic nervous system dysregulation [44]. Blood pressure variability is measured using different methodologies and over different time intervals: beat-to-beat (very short-term BPV), within a 24-h period (short-term BPV), day-to-day, visit-to-visit, or during seasonal changes (long-term BPV). Generalized anxiety disorder (GAD) and major depression have been associated with higher BPV in the short-term (hours) and long-term (days) [43, 44].

However, a prospective cohort study of 1454 elderly participants (78.5 [3.8] years; 59% women) conducted 3 consecutive days of home blood pressure monitoring and subsequent serial clinic blood pressure measurements over 8 years. Overall, generalized anxiety disorder was associated with significantly increased systolic, but not diastolic, BPV over 8 years [43]. In small cross-sectional studies, adults with higher anxiety scores have also demonstrated higher blood pressure variability and lower heart rate variability, with a sympathovagal imbalance towards sympathetic hyperactivity [43, 45]. Reduced baroreflex sensitivity reflects decreased parasympathetic outflow to the heart and may increase blood pressure variability through an increased sympathetic predominance [42, 43, 46]. In small studies, anxiety and hostility were related to reduced baroreflex sensitivity and increased low-frequency power of systolic arterial blood pressure variability [46].

Health Behaviors

Prevalent anxiety has also been associated with higher rates of unhealthy behavior patterns (e.g., tobacco use, unhealthy food choices and/or patterns, and physical inactivity) which increase the risk of developing hypertension [9, 22, 47]. Analysis of the 2006 Behavioral Risk Factor Surveillance System (BRFSS), a large population-based US survey ($n = 217,379$), demonstrated that individuals with a lifetime diagnosis of anxiety (i.e., ever been told of anxiety diagnosis) were significantly more likely to smoke, have a BMI in the obese range $\geq 30 \, \text{kg/m}^2$, have lower levels of physical activity, binge drink and/or have excess daily alcohol consumption, compared to those without a diagnosis [47].

In general, individuals' eating styles reflect a complex interaction of multiple factors, including physiological, psychological, and social that influence food choices and eating behavior [48, 49]. Three primary eating styles have been defined: (i) emotional eating (overeating in response to a specific emotional states), (ii) external eating (an increased consumption in response to external cues), and (iii) restraint eating (limiting intake to achieve weight loss) [50]. Emotional eating has been associated with weight gain, unhealthy food choices [49, 51, 52], and has been shown to mediate the relationship between anxiety, loss of eating control, and elevated body mass index [47, 53–55]. However, studies between anxiety disorders and prevalent hypertension have demonstrated comorbid associations independent of health behavior, supporting the need to study other mechanisms [9].

Clinical Implications

In contrast to many other psychiatric diagnoses, anxiety disorders are predominantly treated in the outpatient/ambulatory setting [7]. However, there remains a significant under-recognition and under-treatment of anxiety disorders and hypertension [7, 28]. Additionally, different anxiety disorders have demonstrated varying patterns in health care utilization. For example, Bandelow et al. reported that patients with panic disorder tend to be more concerned about medical conditions, compared to individuals with social phobias, resulting in more healthcare contacts and examinations [7]. A 4-year retrospective analysis of $n = 4362$ primary care patients within the USA (≥ 18 years old, 52 [14] years old) demonstrated that patients with anxiety (and/or depression) had more healthcare utilization, including primary and specialty care visits, than those without either psychiatric diagnosis [56].

Improved understanding of the determinants, consequences, and management of comorbid anxiety and hypertension remains a research priority. The comorbid presence of chronic mental and physical chronic conditions complicates medical treatment, may change the severity and/or progression of disease, contribute to greater disability, and may increase mortality [38, 57]. Effective, sustainable interventions are urgently needed to improve the diagnosis and care coordination among patients with comorbid hypertension and anxiety. Prior studies, primarily focused on depression, have demonstrated that multifaceted Collaborative Care Model interventions may improve the coordinated delivery of chronic comorbid conditions [58].

Limitations

This review highlights ongoing methodological limitations, including use of cross-sectional and/or retrospective analyses, making it difficult to infer causation and/or directionality [19, 40]. Additionally, self-reported medical diagnoses lacked clinical validation of hypertension and/or mental health diagnoses [30]. Other challenges included inconsistent definitions of psychiatric and hypertension diagnoses, including variation in the use of the psychiatric diagnostic criteria (e.g., different versions of the *DSM*) and differing blood pressure thresholds. Finally, there were varying methodologies of cardiovascular data acquisition, psychiatric interview and/or survey data collection, and/or type of interviewer [7, 42].

Future Directions

There remain numerous gaps in understanding the comorbid relationship between anxiety and prevalent hypertension and the development of incident hypertension. Additional research is needed across differing anxiety disorders and comorbid cardiovascular risk factors. Numerous mechanistic questions remain including stress reactions, threat perception, and neurobiological responses. Larger studies on blood pressure variability are needed and studies on reduced heart rate variability with hypertension and psychological disorders are emerging [59], which may impact treatment of both hypertension and anxiety. There is a growing body of research of potential chromosomal and genetic markers related to stress and adverse cardiovascular outcomes [19]. Additional prospective studies are needed on comorbid associations between anxiety and the severity of prevalent hypertension, including resistant hypertension [60]. Finally, possible mediating and moderating factors confounding the relationship between combined prevalent anxiety and depression with hypertension need to be understood to guide clinical management [15].

Conclusions

In summary, this review of contemporaneous studies demonstrates increasing evidence of a positive association between comorbid anxiety and prevalent or incident hypertension. This review supports prior cross-sectional, prospective, and meta-analyses [61, 62]. Additionally, this review highlights newer research on potentially contributing mechanisms between prevalent anxiety and development of hypertension, including increased blood pressure variability contributing to autonomic dysfunction and reduced baroreflex sensitivity. These mechanisms likely explain why some prior studies demonstrated conflicting (no association or negative associations) between anxiety and hypertension. Additionally, confounding relationships of comorbid anxiety *and* depression with hypertension are not understood and also appear to contribute to prior mixed results. At this time, healthcare systems and clinical care teams can focus interventions to improve screening, diagnosis, and timely treatment of anxiety disorders, understanding that this population should also be monitored for hypertension and other cardiovascular risk factors. Additional research on physiologic and genetic mechanisms across diverse populations (age groups, race/ethnicity, geography, type of hypertension, and/or type of anxiety disorder) will guide future clinical care in a population at higher risk for cardiovascular disease.

Compliance with Ethical Standards

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Papers of particular interest, published recently, have been highlighted as:
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•• Of major importance

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