ORIGINAL RESEARCH

Association between anxiety and hypertension: a systematic review and meta-analysis of epidemiological studies

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Background: Epidemiological studies have repeatedly investigated the association between anxiety and hypertension. However, the results have been inconsistent. This study aimed to summarize the current evidence from cross-sectional and prospective studies that evaluated this association.

Methods: Seven common databases were searched for articles published up to November 2014. Cross-sectional and prospective studies that reported an association between the two conditions in adults were included. Data on prevalence, incidence, unadjusted or adjusted odds ratios or hazard ratios, and 95% confidence intervals (CIs) were extracted or calculated by the authors. The pooled odds ratio was calculated separately for cross-sectional and prospective studies using random-effects models. The Q test and I^2 statistic was used to assess heterogeneity. A funnel plot and modified Egger linear regression test were used to estimate publication bias.

Results: The search yielded 13 cross-sectional studies (n=151,389), and the final pooled odds ratio was 1.18 (95% CI 1.02–1.37; $P_Q<0.001$; I^2=84.9%). Eight prospective studies with a total sample size of 80,146 and 2,394 hypertension case subjects, and the pooled adjusted hazard ratio was 1.55 (95% CI 1.24–1.94; $P_Q<0.001$; I^2=84.6%). The meta-regression showed that location, diagnostic criteria for anxiety, age, sex, sample size, year of publication, quality, and years of follow-up (for prospective study) were not sources of heterogeneity.

Conclusion: Our results suggest that there is an association between anxiety and increased risk of hypertension. These results support early detection and management of anxiety in hypertensive patients.

Keywords: human, epidemiological association, anxiety disorder, hypertension, meta-analysis

Introduction

Hypertension, one of the most common diseases worldwide, is estimated to affect one quarter of all adults, and has been identified as the leading cause of mortality and the third cause of disability-adjusted life years worldwide.[1] According to a report by Kearney et al the total number of adults with hypertension in 2025 was predicted to increase to 1.56 billion worldwide.[2] Identifying and characterizing modifiable risk factors of hypertension remain important for public health and clinical medicine.

Hypertension has a multifactorial etiology, where genetic as well as psychosocial and environmental factors appear to be of importance.[3,4] However, there are complex physiological processes involved and the linkage among psychosocial factors and hypertension is not fully understood.[5–7] Anxiety is one of the most common psychiatric illnesses in adults and is a major public health problem in many countries,[8,9] damaging the affected individual's health and quality of life.[10] Because both hypertension and

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anxiety confer significant public health challenges, the association between the two conditions has recently attracted attention.

A number of epidemiological studies have been conducted to investigate this association, with inconsistent results reported. Some investigations show that anxiety is associated with hypertension, individuals with anxiety having a higher risk of hypertension than those without anxiety.[11–14] Further, hypertension patients have a higher risk of anxiety than those without hypertension.[15,16] However, some researchers do not support the role of anxiety symptoms in the development of hypertension.[17,18] Some studies have even reported that anxiety is associated with a decrease in blood pressure.[19,20] To date, there has not been a meta-analysis to explore the association between anxiety and hypertension. Therefore, we summarized the available data from cross-sectional and prospective studies, and performed meta-analyses to investigate the cross-sectional correlation and longitudinal relationship between anxiety and hypertension.

Methods
Search strategy
A comprehensive search, restricted to human studies published in the English or Chinese language, was performed using the following databases: PubMed, ISI Web of Science, EMBASE, PsycInfo, China National Knowledge Infrastructure, China Biology Medical literature database, and Database of Chinese Scientific and Technical Periodicals. The search terms ("anxiety" or "worry" or "post-traumatic stress" or "panic" or "agoraphobia" or "phobia" or "obsessive-compulsive") and ("hyperten*" or "high blood pressure") were used in various combinations for relevant articles without time restriction (Figure 1 shows details of the search process and study selection). The last search was performed on November 6, 2014. In
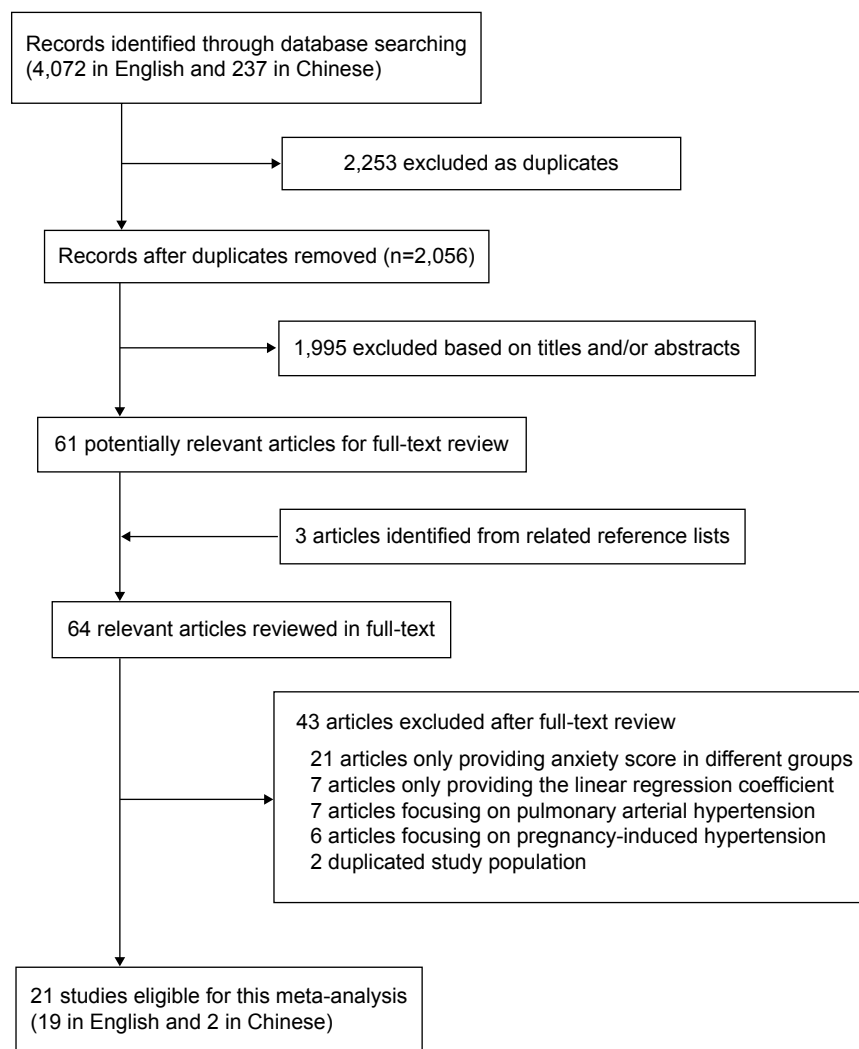

Figure 1 Flow diagram of studies selection in meta-analysis.

addition, we searched and identified studies not captured by our database by reviewing the reference lists in retrieved articles.

Inclusion criteria

Articles were considered for inclusion in the systematic review if: the authors reported data from an original, peer-reviewed study (ie, not case reports, comments, letters, meeting abstracts, or review articles); the study was a cross-sectional or prospective study with an adult population (age ≥ 18 years); the exposure of interest was one or more types of anxiety defined according to standard instruments: and odds ratio (OR), relative risk, or hazard ratio (HR) with 95% confidence interval (CI; or data to calculate it) were reported. If multiple articles were published from the same population, the most informative report was included.

Data extraction and quality assessment

The following data were extracted from each study: the first author's name, year of publication, study site, number of participants, and years of follow-up for prospective studies, participants' characteristics (age range or mean age and sex composition), anxiety measures, analysis strategy (statistical models and covariates adjusted in the models), and results (prevalence, incidence, unadjusted or adjusted OR, and 95% CI). For some studies providing ORs for different types of anxiety, we used meta-analysis to incorporate these values into one combined OR that presents the association of anxiety with hypertension. The nine-star Newcastle-Ottawa Scale[21] and eleven-score Agency for Healthcare Research and Quality[22] were used, respectively, to estimate the quality of prospective studies and cross-sectional studies. Study inclusion, data extraction, and quality assessment were performed by two independent investigators (YP and JY). Any disagreement was settled by discussion among all of the authors.

Statistical analysis

The research strategy has been described in previous studies.[23] The pooled measure was calculated as the inverse variance-weighted mean of the logarithm of the OR (HR) with 95% CI to assess the strength of association between anxiety disorders and risk of hypertension. Heterogeneity among studies was assessed using the Q test and the I^2 statistic, which describes the proportion of total variation attributable to between-study heterogeneity as opposed to random error or chance.[24] In the presence of substantial heterogeneity ($I^2 > 50\%$),[25] the DerSimonian and Laird random effect model (REM) was applied as the pooling method; otherwise, the fixed effect model

was adopted. Meta-regression with restricted maximum likelihood estimation was performed to assess the potentially important covariates exerting substantial impact on between-study heterogeneity. The "leave one out" sensitivity analysis[26] was conducted using $I^2 > 50\%$ as the criterion to assess the key studies with substantial impact on between-study heterogeneity. An analysis of influence was conducted,[27] which describes how robust the pooled estimator is to removal of individual studies. An individual study is suspected of excessive influence if the point estimate of its omitted analysis lies outside the 95% CIs of the combined analysis. Publication bias was estimated using Egger's regression asymmetry test.[28] All statistical analyses were performed using STATA/SE version 13.1 (Stata Corporation, College Station, TX, USA). All P-values were two-sided, and those less than 0.05 were considered to be statistically significant.

Results

Literature search and study selection

The study's identified and selected procedures are summarized in Figure 1. Twenty-one studies were finally included in our analysis. Among them, 13 cross-sectional studies[11,15,18,20,29–37] (two in the USA, five in Europe, three in the People's Republic of China, one in Brazil, one in South Africa, and one worldwide) and eight prospective studies[6,12–14,17,38–40] (six in the USA and two in Europe) of the association between anxiety and hypertension were included in the analysis. General characteristics in the published articles included in this meta-analysis are shown in Tables 1 and 2. The duration of follow-up ranged from 1 to 25 years for the prospective studies. Stars in Tables 1 and 2 indicate the quality of the study. Among the 13 studies in Table 1, three scored nine stars, five scored eight stars, and five scored seven stars. Among the eight studies in Table 2, one scored nine stars, five scored eight stars, and one scored six stars. The ORs were extracted or calculated from the original articles. Other characteristics, such as age of participants, sample size, and diagnostic criteria for anxiety were also presented in Tables 1 and 2.

Cross-sectional studies of the association between anxiety and hypertension

Thirteen cross-sectional studies including 151,389 subjects were included in the analysis of the association of anxiety with risk of hypertension. REM was used because substantially significant between-study heterogeneity was observed ($P_Q < 0.001$; $I^2 = 84.9\%$). Pooled results showed that anxiety had a significant positive association with hypertension (OR 1.40, 95% CI 1.20–1.62; Figure 2). Significant publication

Table 1 Characteristics of cross-sectional studies in the meta-analysis

Reference	Study name, country	Total sample size	Sample composition	Anxiety measures	Anxiety case/ total HP case (prevalence [%])	Anxiety case/ total non-HP case (prevalence [%])	OR (95% CI)	Quality (stars)	Notes
Paterniti et al[29]	Etude sur le Vieillissiment Arteriel Study, France	767	Age 59–71 years; 40.4% M	STAI >36			2.71 (1.55–4.76)	9	Only in adjusted OR meta
Wei et al[30]	Zhejiang, People's Republic of China	922	Age ≥45 years; 55% M	SAS >40	103/891 (11.6%)	10/163 (6.1%)	2.00 (1.02–3.92)	8	Only in crude OR
Cheung et al[31]	Hong Kong, People's Republic of China	226	Age 50.1±12.8 years; 50.2% M	HADS-A ≥8	31/113 (27.4%)	21/113 (18.6%)	1.71 (0.90–3.25)	7	Only in crude OR
Schmitz et al[32]	German National Health, Germany	4,149	Age 18–65 years; 52.3% M	DSM-IV	148/1,656 (8.9%)	224/2,500 (9.0%)	1.12 (0.89–1.39)	8	Only in crude OR meta
Hildrum et al[20]	Nord-Trøndelag Health Study, Norway	60,799	Age 20–89 years; 48.5% M	HADS-A ≥8			0.90 (0.82–0.99)	7	Only in adjusted OR
Han et al[33]	Nanjing, People's Republic of China	740	Age ≥35 years; 34.7% M	SAS >40	31/326 (9.5%)	18/414 (4.3%)	2.45 (1.23–4.89)	7	
Grimsrud et al[15]	South African Stress and Health, South African	4,351	Age ≥18 years; 46.3% M	DSM-IV	105/767 (13.7%)	270/3,584 (7.5%)	1.55 (1.10–2.18)	9	
Carroll et al[34]	Vietnam Experience Study, USA	4,180	Age 31–49 years; 100% M	DSM-III	171/1,381 (12.4%)	232/2,801 (8.3%)	1.48 (1.18–1.87)	8	
Hildingh and Baigi[35]	National Institute of Public Health, Sweden	12,166	Age 18–84 years; 45.4% M	Dichotomous variables			1.45 (1.28–1.64)	8	Only in adjusted OR meta
Saboya et al[36]	Hospital São Lucas, Brazil	302	Age ≥18 years; 20.2% M	STAI ≥40	84/152 (55.3%)	67/150 (44.7)	2.83 (1.55–5.18)	7	Only in adjusted OR meta
Fiedorowicz et al[37]	National Comorbidity Survey-Replication, USA	5,692	Age ≥18 years; 41.8% M	DSM-IV			1.48 (1.22–1.80)	9	Only in adjusted OR meta
Wiltink et al[18]	Gutenberg Heart Study, Germany	5,000	Age 35–74 years; 50.8% M	Mini-Spin; GAD; PHQ	354/2,058 (17.2%)	403/1,938 (20.8)	1.08 (0.91–1.29)	8	Only in adjusted OR meta
Stein et al[11]	World Mental Health Surveys, World	52,095	Age ≥18 years; M	DSM-IV			1.16 (1.08–1.25)	7	Only in adjusted OR meta

Abbreviations: M, male; STAI, Spielberger State-Trait Anxiety; SAS, Self-Rating Anxiety Scale; HADS-A, Hospital Anxiety and Depression Scale-Anxiety; DSM, Diagnostic and Statistical Manual of Mental Disorders; GAD, Generalized Anxiety Disorder; PHQ, Patient Health Questionnaire; Mini-Spin, Mini-Social Phobia Inventory; HP, hypertension; OR, odds ratio; CI, confidence interval; meta, meta-analysis.

Table 2 Characteristics of prospective studies included in the meta-analysis

Reference	Study name, country	Incident case subjects/total sample size	Follow-up (years)	Sample composition	Anxiety measures	OR/RR/HR (95% CI)	Quality	Adjustment factors
Markovitz et al[38]	Framingham Heart Study, USA	140/330	18–20	Age 45–59 years; 100% M	Tension scale ≥0.7	2.19 (1.22–3.94)	8	Age, initial systolic blood pressure, initial heart rate, relative weight, alcohol intake, glucose intolerance, smoking, and education
Jonas et al[39]	National Health and Nutrition Examination Survey, USA	493/2,992	7–16	Age 25–64 years; 43.3% M	GWB-A	1.42 (1.21–1.66)	8	Age, systolic blood pressure, education, smoking, BMI, alcohol, initial heart rate, and other disease
Raikkonen et al[40]	Healthy Women Study, USA	75/541	9.2	Age 42–50 years; 0% M	STAI, FTS, Social Anxiety Scale	1.18 (1.04–1.33)	7	Only in crude OR meta
Shinn et al[7]	Reno Diet Heart Study, USA	55/370	4	Age 20–75 years; 27.2% M	GWB-A <13	0.70 (0.30–1.64)	8	Age, BMI, systolic blood pressure, sex, parental history of hypertension, anxiolytic use
Yan et al[6]	Coronary Artery Risk Development in Young Adult, USA	430/3,156	10	Age 23–35 years; 44.4% M	STAI <30	1.32 (1.09–1.60)	9	Age, sex, BMI, systolic blood pressure, education, alcohol and other psychosocial factors
Johannessen et al[12]	Danish Psychiatric Register, Denmark	966/75,268	25	Age >18 years; 26.5% M	ICD-8 ICD-10	1.96 (1.73–2.22)	7	Gender
Ginty et al[13]	Dutch Famine Birth Cohort Study, The Netherlands	219/455	5.5	Mean age 58.22±0.91 years; 50.8% M	HADS-A ≥8	2.08 (1.17–3.72)	8	Age, sex, socioeconomic status, smoking, sports participation, alcohol consumption, SBP, antidepressant and anxiolytic medication
Bacon et al[14]	Mechanisms and Outcomes of Myocardial Silent Ischemia, Canada	16/190	1	Age ≥18 years; 60.5% M	DSM-IV	6.57 (1.82–23.76)	8	Age, sex, BMI, smoking status, and psychiatric medication

Abbreviations: BMI, body mass index; M, male; GWB-A, General Well-Being Schedule-Anxiety; STAI, Spielberger State-Trait Anxiety; FTS, Framingham Tension Scale; ICD, International Classification of Diseases; HADS-A, Hospital Anxiety and Depression Scale-Anxiety; DSM, Diagnostic and Statistical Manual of Mental Disorders; OR, odds ratio; RR, relative risk; HR, hazard ratio; CI, confidence interval; SBP, systolic blood pressure.
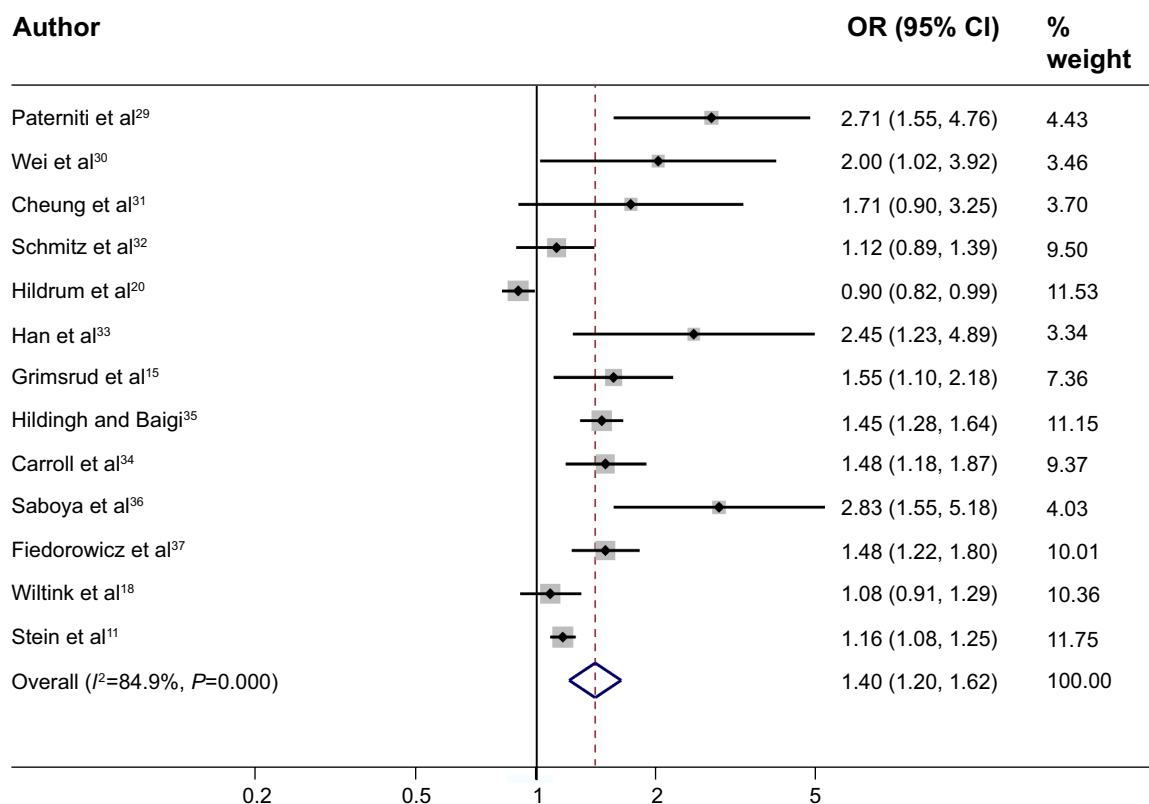
Figure 2 Random effects meta-analysis of cross-sectional studies of the association between anxiety and hypertension (13 studies included).
Note: Weights are from random effects analysis.
Abbreviations: OR, odds ratio; CI, confidence interval.

bias was detected (P=0.016). After trim and fill analysis, the final result was still significant (OR 1.18, 95% CI 1.02–1.37).

Prospective studies of anxiety predicting hypertension risk

Eight prospective studies investigated the association between the baseline anxiety status and incident hypertension with a total sample size of 80,146 and 2,394 hypertension case subjects. Characteristics of the studies are shown in Table 2. The pooled adjusted HR by REM was 1.55 (95% CI 1.24–1.94; Figure 3), with strong heterogeneity detected (P_Q<0.001; I^2=84.6%). No publication bias was detected (P=0.663).

Sources of heterogeneity and sensitivity analysis

The strong heterogeneities between studies were found in both cross-sectional studies and prospective studies. The univariate meta-regression, with the covariates of location (categorized as American, European, East Asian, and other), diagnostic criteria for anxiety (categorized as structured diagnostic interviews, ie, Diagnostic and Statistical Manual of Mental

Disorders or International Classification of Diseases, and self-report symptom scales), age (categorized only as middle-aged and other) and sex, sample size, year of publication, quality, and years of follow-up (≥7 and <7, only for prospective study), showed that none of the aforementioned covariates had a significant impact on between-study heterogeneity.

Subgroup analyses for location, diagnostic criteria for anxiety, age, sex, years of follow-up (only for prospective study) also did not find a source of heterogeneity and indicated that the effects of anxiety in nearly all subgroups were still significant (Table 3).

"Leave one out" sensitivity analysis was performed for the all groups with an I^2>50%, and the pooled results did not change substantially.

Discussion

To the best of our knowledge, this is the first meta-analysis examining the association between anxiety and hypertension using data from both cross-sectional and prospective studies. We found that anxiety and hypertension were significantly correlated in cross-sectional studies, and a direct association was also observed in prospective studies.
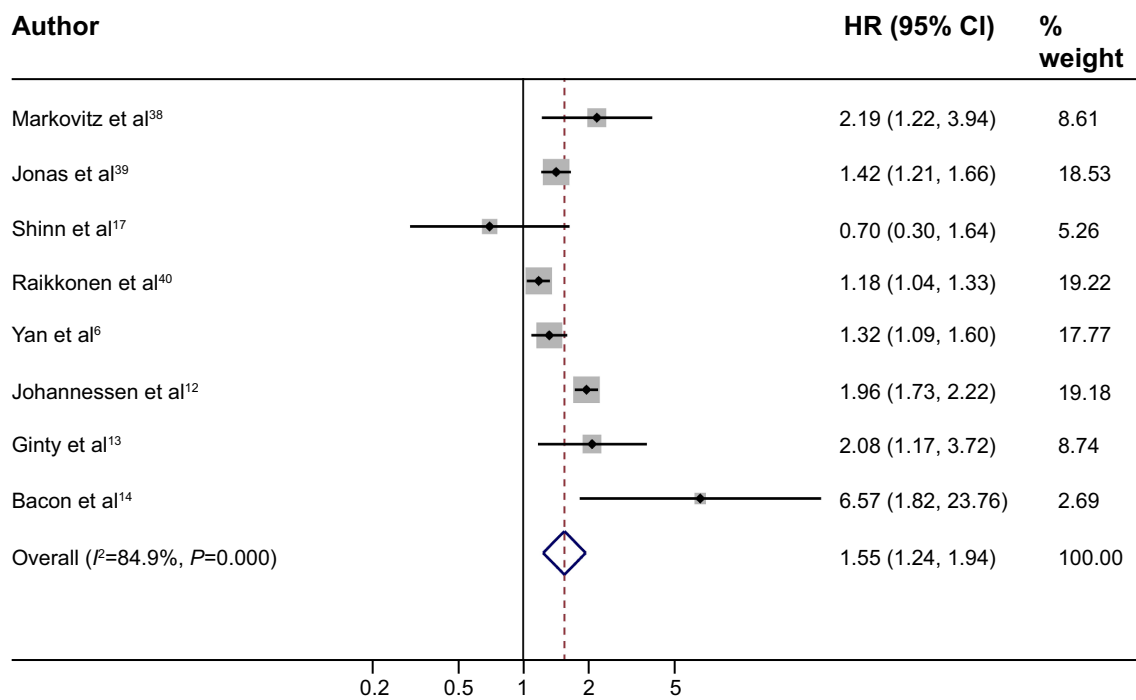
Author	HR (95% CI)	% weight
Markovitz et al[38]	2.19 (1.22, 3.94)	8.61
Jonas et al[39]	1.42 (1.21, 1.66)	18.53
Shinn et al[17]	0.70 (0.30, 1.64)	5.26
Raikkonen et al[40]	1.18 (1.04, 1.33)	19.22
Yan et al[6]	1.32 (1.09, 1.60)	17.77
Johannessen et al[12]	1.96 (1.73, 2.22)	19.18
Ginty et al[13]	2.08 (1.17, 3.72)	8.74
Bacon et al[14]	6.57 (1.82, 23.76)	2.69
Overall (I^2=84.9%, P=0.000)	1.55 (1.24, 1.94)	100.00

0.2   0.5   1   2   5

Figure 3 Random effects meta-analysis of prospective studies of the association between anxiety and risk of hypertension (eight studies included).
Note: Weights are from random effects analysis.
Abbreviations: HR, hazards ratio; CI, confidence interval.

Some cross-sectional studies reported a higher anxiety score in participants with hypertension than for those without hypertension. However, the methods used for assessment of anxiety varied significantly in the different studies. Therefore, we could not pool the anxiety scores; instead, we pooled the ORs, a measure of association that was more consistent across studies. Our final pooled OR was 1.18 (95% CI 1.02–1.37),

suggesting that anxiety and hypertension are significantly related. The pooled ORs remained significant in subgroups for location, diagnosis criteria for anxiety, age, and sex. Although strong heterogeneity was found, meta-regression showed that the location, diagnostic criteria for anxiety, age and sex, sample size, year of publication and quality were not the source of between-study heterogeneity.

Table 3 Subgroup analyses to explore source of heterogeneity

Subgroups	Cross-sectional studies			Prospective studies		
	n	I^2 (%)	OR (95% CI)	n	I^2 (%)	HR (95% CI)
Location						
American	2	0.0	1.480 (1.276–1.717)	6	66.2	1.366 (1.124–1.660)
European	5	91.4	1.237 (0.956–1.601)	2	0.0	1.965 (1.740–2.220)
East Asian	3	0.0	2.014 (1.370–2.961)			
Other	3	81.3	1.571 (1.032–2.390)			
Diagnosis of anxiety						
Structured diagnostic interviews	5	62.9	1.308 (1.138–1.504)	2	70.4	3.010 (0.968–9.355)
Self–report symptom scales	8	89.3	1.575 (1.195–2.075)	6	55.4	1.354 (1.153–1.590)
Age						
Middle–aged	8	78.6	1.611 (1.333–1.947)	5	83.5	1.543 (1.169–2.038)
Other	5	80.3	1.146 (0.933–1.408)	3	72.7	1.632 (1.017–2.620)
Sex						
Male	4	25.7	1.410 (1.208–1.645)	3	75.9	2.063 (1.395–3.052)
Female	3	70.9	1.533 (1.005– 2.339)	3	88.0	1.421 (1.031–1.957)
Follow–up, years						
<7				3	77.5	1.945 (0.677–5.590)
≥7				5	88.8	1.505 (1.192–1.900)

Note: I^2 indicates heterogeneity.
Abbreviations: OR, odds ratio; HR, hazard ratio; CI, confidence interval.

Cross-sectional studies do not provide the temporal relationship between anxiety and hypertension, so we conducted a further meta-analysis to investigate the association between anxiety and hypertension in prospective studies. The pooled adjusted HR by REM was 1.55 (95% CI 1.24–1.94), indicating that anxiety was an independent risk factor for incident hypertension. This prospective association between anxiety and hypertension was consistent with results from the cross-sectional studies and also in agreement with two recent meta-analyses showing a reciprocal association between anxiety and coronary heart disease[41] and between anxiety and heart rate variability.[42] Anxiety and depression are closely linked.[43] A previous review also shows an increased risk of hypertension in depressed patients and an increased risk of depression in hypertensive patients.[44] However, a recent meta-analysis in the elderly does not support that view that hypertension is a possible risk factor of depression.[45] Considering current contradictory results in original articles,[46] a systematic review should be undertaken to explore the relationship between depression and hypertension with the most up-to-date evidence.

The mechanism between anxiety and hypertension is complex. Generally, anxiety increases blood pressure, systemic vascular resistance, sympathetic activity, plasma renin activity, the homeostasis model, and blood lipids. First, anxiety increases blood pressure in the short term, and the white coat effect derived from anxiety is a typical example.[47,48] A recent ambulatory blood pressure monitoring study reported that anxiety disorder was associated with nocturnal and early morning hypertension in hypertensive outpatients.[49] Second, anxiety has a close relationship with the renin angiotensin system and increases the level of angiotensin II.[50,51] Long-term anxiety may decrease vascular variability, so that persistent vascular resistance leads to hypertension.[52] Third, some experiments show that patients with anxiety usually have physiological signs of sympathetic activation, and anxiety can strongly stimulate sympathetic nervous outflow and the vasovagal reflex.[53,54] Rozanski et al contend that anxiety can activate the sympathetic nervous system, increase cardiac output, constrict blood vessels, and raise arterial blood pressure.[55]

Moreover, a long-term anxiety state will improve the sympathetic response and more easily activate the sympathetic nervous system.[56] Activation of the sympathetic nervous system not only reduces renal blood flow, increases renal water and sodium retention, and elevates blood pressure,[57] but also damages endothelial cells, causes endothelial dysfunction and increasing the risk of atherosclerosis. Sympathetic activation can cause abnormal hemodynamic changes and abnormal lipid metabolism, such as decreasing high-density lipoprotein cholesterol and increasing low-density lipoprotein cholesterol, which affects endothelial function.[58] In addition, endothelial cells in animals with heightened sympathetic nervous activity present structural changes and greater immunoreactivity.[59] Fourth, the hypothalamo-pituitary-adrenal axis is the major physiological stress response system in the body.[60] When this axis is dysfunctional, increasing steroid hormone secretion causes water and sodium retention, leading to high blood pressure.[61] Further, the indirect association between anxiety and increased risk of hypertension might also derive from the characteristics of anxious subjects, who usually have a more unhealthy lifestyle in general. In other words, they usually have some adverse behaviors, such as increased eating, smoking, and alcohol use, and take less exercise, due to stress and anxiety, that impacts health.[62]

On the other hand, previous studies have also found that patients with hypertension awareness have an increased risk of anxiety disorders.[16,32] Thus, anxiety and hypertension may interact to affect human health. Moreover, anxiety is one of the barriers in treatment of hypertension.[63] Khatib et al identify stress, anxiety, and depression as the most common reported barriers hindering or delaying lifestyle modification.[64] Therefore, conventional antihypertensive therapy with psychological support and antianxiety treatment, such as diazepam,[65] and metacognitive detached mindfulness therapy and stress management training[66] could achieve better efficacy in hypertensive patients with anxiety.

This meta-analysis had several strengths. It is the first to explicitly examine the association between anxiety and hypertension on the basis of a comprehensive literature search. This meta-analysis also had a large sample size, which increased the accuracy of the effect estimate. However, the potential limitations of this meta-analysis should be considered. First, it only included English and Chinese language articles; eligible articles published in other languages were not included in this analysis, which may influence the pooled estimated value. Second, because of the inability to obtain raw data, we could perform only a study-level but not a patient-level meta-analysis, which enabled us to adjust for multiple factors. Third, the measurements of anxiety varied among the 21 included studies with regard to different diagnostic instruments, so this might affect the pooled results. We suggest that the DSM-IV should be a preferred instrument to diagnose anxiety disorder in the future because it is the newest standard developed by many experts. Fourth, the outcomes of anxiety and hypertension in our study focused on

OR, relative risk, and HR, so some studies with other indices, such as a linear regression coefficient, were excluded. Finally, the heterogeneity between studies included in our study should be paid attention to, although some common factors have been considered to detect the source of heterogeneity.

The results of this meta-analysis indicate an association between anxiety and increased risk of hypertension.

Conclusion

It is important to explore the short-term and long-term effect of anxiety on hypertension. In addition, importance should be attached to the bidirectional association between anxiety and hypertension, especially in the treatment of hypertension. Moreover, the association between anxiety and increased risk of hypertension in this meta-analysis might be confounded by various factors. Therefore, large-scale, randomized controlled trials are recommended to assess the impact of anxiety on incidence rates of hypertension.

Acknowledgment

Disclosure

All authors declare that they have no competing interests in this work.

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