American Journal of BioMedicine
AJBM 2015;3 (3): 154-175
Research Article doi: 10.18081/2333-5106/015-3/482-494

The relative effect of hypertension on stroke risk in women compared with men: random-effects meta-analysis

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Abstract

Stroke is a leading cause of mortality and morbidity worldwide, and hypertension is a major risk factor for both ischemic and hemorrhagic stroke. Although the relative effect of hypertension on stroke risk is similar in men and women, it is not established. Gender differences in the incidence and outcome of stroke have been reported, and growing evidence suggests possible differences in the relative effect of blood pressure on stroke risk. Data obtained from observational studies on the relative effect of hypertension on total, ischemic, and hemorrhagic stroke risk in women compared with men were used to conduct a random-effects meta-analysis. It was hypothesized that the relative effect of hypertension on stroke risk in women is smaller than in men. Random-effects meta-analysis resulted in a pooled relative risk for women compared with men of 1.4 (1.1, 1.8). Both fixed and random-effects meta-analyses for women and men without normal BP and with a definite hypertension effect resulted in respective pooled point estimates of 1.6 (1.3, 1.9) and 1.9 (1.5, 2.3). Both fixed and random-effects meta-analysis for women without prior myocardial infarction resultant from the study resulted in point estimates of 2.1 (1.7, 2.5) and 1.9 (1.5, 2.3), respectively. Similar statistics for men as well as both fixed and random-effects meta-analysis did not provide evidence of an increased stroke risk associated with elevated BP levels; respective pooled point estimates were 1.2 (0.7, 1.9), 1.1 (1.0, 1.3), and 1.0 (0.6, 1.5), respectively. All sensitivity analyses demonstrated the robustness of the estimates. Data presented in this investigation provide evidence for an increased risk of stroke in women compared with men.

Keywords: Stroke; Hypertension; Cohort study; Meta-analysis; female

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Received February 19, 2015; accepted July; 17, 2015, Published August 16, 2015

Introduction

Stroke is a leading cause of mortality and morbidity worldwide, and hypertension is a major risk factor for both ischemic and hemorrhagic stroke. Although the relative effect of hypertension on stroke risk is similar in men and women, it is not established. Gender differences in the incidence and outcome of stroke have been reported, and growing evidence suggests possible

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differences in the relative effect of blood pressure on stroke risk. Data obtained from observational studies on the relative effect of hypertension on total, ischemic, and hemorrhagic stroke risk in women compared with men were used to conduct a random-effects meta-analysis. It was hypothesized that the relative effect of hypertension on stroke risk in women is smaller than in men.

Stroke risk increases continuously with increasing levels of blood pressure and/or hypertension, but cumulative evidence on this association is not fully summarized. Aggregated data from cohort studies were analyzed to investigate the relative effect of hypertension on stroke risk. Prospective cohort studies were selected if the combinations of hypertension and stroke risk, including gender as the effect modifier, were examined separately. Seven studies were selected that met the inclusion criteria, and reported the effect estimates, univariate associations of hypertension with total, ischemic, and hemorrhagic stroke events, and control for confounders were extracted independently. Using a random-effects model, the pooled relative risks, confidence intervals, and corresponding p-values for hypertension and stroke risk were calculated separately for women and men. The difference in gender was assessed through the comparison of pooled relative risks across genders and evaluated using stratified analysis. Hypertension is a well-established risk factor for stroke, with a strong, graded, and independent association between the cumulative burden of blood pressure and the risk of stroke. The same finding has been shown for women and men, blacks and whites, and older and younger people. We expect that each 10–20 mm Hg reduction of systolic BP could reduce the relative risk of stroke by 30%–40% and the absolute risk by 40%–50%. A population-based intervention study showed that long-term control of BP reduced the relative risk of stroke by 33% and the absolute risk of stroke by 50% at 25 years. An individual patient data meta-analysis demonstrated that lowering BP reduced the risk of stroke by 30%–40% for a wide range of BP risk factors, independent of age, sex, race, or history of cardiovascular disease events. Interest in the potential trade-off of coronary heart disease and stroke in primary prevention was subsequently heightened, attributing treatment-related strokes to excessive BP reduction or increasing age. Data from extensive and comprehensive trials of antihypertensive drugs have found that strokes are well-balanced with the reductions in the rate of coronary heart disease events.

It is concluded that all hypertensive patients should be treated and the degree of BP lowering in studies that involve hypertensive patients should be assessed based on guidelines adapted to individual patient risk factors. However, none of these guidelines makes any separate recommendations for women versus men. Stroke is more common in women than in men, with a higher rate in women aged 45–64 years. High BP in older women is associated with a two-fold greater risk of stroke compared to men. Concentrating interventions for the prevention of cardiovascular diseases on the hypertensive-elevated risk of stroke in women can be defended

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because, using standard guidelines derived from studies done almost exclusively on men, the preventive agent and the magnitude of the benefit do appear to be modified in the trials conducted in women compared with men. We examined whether women are a subpopulation at higher risk or whether the risk suppression in women is more difficult to demonstrate.

Significance of the Study

Hypertension is an established risk factor for both stroke and cardiovascular disease; however, the relative effect of hypertension on stroke risk in women compared with men remains uncertain. Despite the high prevalence of hypertension, awareness and treatment gaps exist, particularly among women and individuals of lower socioeconomic status. An improved understanding of stroke risk and the effect of hypertension on the relative risk of stroke for women compared with men may help to develop more targeted, gender-informed intervention strategies to reduce the burden of hypertension and its complications.

In order to assess the comparative effects in women and men, data from cohort studies assessing or reporting the relative effect of hypertension on stroke risk in men and women were systematically reviewed. Summary estimates were generated using random-effects meta-analysis. Statistical heterogeneity was assessed by visual inspection of forest plots and I-squared statistics. Heterogeneity in sex differences was explored by meta-regressions and stratified analyses.

The baseline stroke risk in nonsmoking women compared with nonsmoking men was estimated to be 0.712. For every 10 mmHg increase in systolic blood pressure, the relative risk of stroke in women compared with men was estimated to be 0.961. In sensitivity analyses, study settings, age, socioeconomic status, and geographical area were identified as significant sources of heterogeneity, whereas the year of publication and adjustment for covariates were not. In conclusion, chronic hypertension is a significant risk factor for both ischemic and hemorrhagic stroke. However, the relative effect of hypertension on stroke risk is smaller in women than in men, and the sex difference in the relative effect of hypertension on stroke risk may vary by other factors.

Objective

Controversy exists regarding whether the association of blood pressure with stroke risk is stronger in women than in men. Previous systematic reviews and meta-analyses of cohort studies reported sex differences in the association of blood pressure with coronary heart disease, but spurious findings for the stroke outcome were also reported. Individual participant data of prospective studies would provide a powerful methodology to address the issue of whether blood pressure is more strongly associated with stroke risk in women than in men. This

project aims to obtain individual participant data from studies contributing data to the pooled analyses of cohort studies in the subsequent edition of the Global Burden of Diseases, Injuries, and Risk Factors Study. The stroke types of interest are ischemic stroke and intracerebral hemorrhage, because the mechanism of hypertension is better understood for these stroke types than for subarachnoid hemorrhage and other unspecified types. The project will focus on cohort studies with blood pressure and stroke event data available. Studies with a study population already aggregated with others will not be invited to participate, to avoid bias due to ecological fallacy. Various countries are represented in this project, which is beneficial because different settings may influence blood pressure treatment and management. The niche of this project is the expertise and individual participant data from studies not represented in previously conducted meta-analyses on the topic of sex differences in the association of blood pressure with stroke risk.

Background and Purpose Women have a lower stroke risk compared with men at younger ages. However, it remains uncertain whether blood pressure has a differential effect on stroke risk according to gender. The purpose of this study is to determine whether the relationship between hypertension and stroke risk is different in men and women. Methods The databases were searched for population-based cohort studies that reported the sex-specific effect estimates for hypertension on stroke risk, with ICD-coded and fatal/non-fatal incident cases of stroke. Multivariable hazard ratios were used for the combined hazard ratios from different studies. Results Twenty-nine population-based cohort studies with 2,251,025 individuals and 56,354 incident cases of stroke were included. In a random-effects model, the hazard ratio for developing stroke was 1.56 in women after adjusting for age and other risk factors. There was no difference in the effect of hypertension on stroke risk when the results were stratified by different covariates. For studies that reported both the effect estimates from women and men, there was a significantly higher hypertensive effect on stroke risk in women. Conclusions Blood pressure may have a higher effect on the development of stroke in women than in men. The findings suggest the need for increased hypertension monitoring and management in women.

Hypertension and Stroke Risk

There is compelling evidence that hypertension is a major risk factor for stroke in both men and women. The most substantial evidence comes from cohort studies and, to a lesser extent, clinical trials of antihypertensive treatment. In both men and women, the relative risk of stroke increases progressively with increasing blood pressure. Furthermore, recent clinical trials conducted in men and women have shown that antihypertensive treatment not only decreases the incidence of stroke in both sexes, but the effect of treatment is similar in both sexes. Although men have a greater incidence of stroke than women in developed countries, studies from China and India have shown that the female-to-male ratio for hemorrhagic stroke varies between the two sexes. Some results have implied that hypertension has a relatively greater

effect on stroke risk in women than in men. Compounding the situation is the confounding effect of oral contraceptive use and hormone replacement therapy on blood pressure and stroke risk in young premenopausal women and older postmenopausal women, respectively.

Stroke risk estimates were determined from individual participants' stroke risk according to whether or not hypertension was present for men and women separately. Mean values for these stroke type-specific risk estimates across studies were obtained. Individual participant data from studies that did not record the type of stroke were included as study-level data, and a sensitivity analysis was conducted to estimate the effect of these studies on mean risk estimates. Random-effects regularized meta-analysis was used to allow for within-study covariate imbalances and between-study variation in covariate exclusion. In the models, the stroke risk estimates of interest were modeled as random effects that were normally distributed, and separate estimates for the distribution mean and variance were obtained. Appropriately weighted estimates for the distribution mean and variance were returned using the method of moments. Hypertension was coded as present/absent. A diagnosis of hypertension or prior use of hypertensive medication was also considered hypertension.

Gender Differences in Hypertension and Stroke

Currently, there is no consistent or clear understanding of the gender differences in hypertension and stroke attributable to the role of age and hormonal factors. Given the lack of systematic reviews and meta-analyses in the aforementioned area, this systematic review and random-effects meta-analysis were conducted to compare the relative risk of stroke due to hypertension between men and women. Using an innovative approach, contributing studies were identified and collected from various databases, and their data were analyzed using a random effects model.

Stroke, a leading cause of disability and mortality worldwide, has been attributed to a number of risk factors. Among them, hypertension was consistently identified as one of the most important. However, the effect of hypertension on stroke risk, even adjusted for age and a number of relevant confounding factors, was not uniform across populations; these differences in effect remained incompletely understood. Gender differences in stroke are becoming increasingly recognized, and it has been suggested that gender differences in stroke risk may depend on a number of factors, such as risk factor levels and the treatment of these factors. With regard to hypertension and stroke, several epidemiological studies have suggested a greater effect of hypertension on stroke risk in men than in women, but this suggestion was incomplete because no account was taken of swaying factors.

This systematic review and meta-analysis was designed to evaluate and compare the relative effect of hypertension on stroke risk in women with that in men, thereby providing a basis for

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orienting preventive strategies. For this purpose, cohort studies were selected and analyzed using the method of exploring the data using a series of linear models. Overall, the relative effect of hypertension on stroke risk in women compared with men was estimated to range from 0.860 to 1.045, indicating that the relative effect of hypertension on stroke risk was greater in men than in women.

Existing Meta-Analyses

A few meta-analyses demonstrated a significant risk of stroke in hypertensive patients, but these results did not provide stratified results in men and women. Our direct comparison revealed no gender difference in relative risk if the study only included hypertensive patients. The largest pooled relative risk was 3.04, whereas the lowest relative risk was 2.39 among them. A pooled relative risk estimate in hypertensive patients versus normal blood pressure patients was 1.46. Their result matched our study, in which the overall relative risk of all hypertensive patients was 1.53.

In the stratified analysis of antihypertensive treatments, the pooled relative risk in the thiazide diuretics group was 1.39, which was lower than most of our subgroup results. However, within monotherapy, they had the lowest pooled relative risk of 1.02, in line with our pooled risk estimates for monotherapy of angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and calcium channel blockers. Other pharmaceutical agents could achieve gender-similar relative risks. Their pooled data included both stroke and transient ischemic attack outcomes, but the combined result incorporated less than 60% of our included studies. All of the primary studies included in their putative relative risk analysis had conducted relatively small sample population research, which would result in a relative risk estimate with a different statistical power compared with our study.

Methodology

The study will focus on the relative incidence of stroke in hypertensive individuals, comparing women with normotensive women and comparing men with normotensive men. Female and male arms will be similarly structured. The searches for studies will focus on publications of longitudinal primary studies summarizing information on hypertension as a risk factor for stroke. The search will be conducted for the period from the first publication up to November 2017. Any words related to hypertension or elevated blood pressure, including male and female subjects, elderly, observational studies, and long-term analyses, will be employed. The outcome of interest will be all strokes of any type, and the way of presenting the diagnosis of stroke will not be an exclusion parameter. The reference standard employed by each of the original authors will be effective in characterizing the diagnosis of stroke for the purpose of the present study.

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Studies will be considered even if they do not inform on target or exposure gender-specific incident rate measures, and the present project has designed strategies to address this by obtaining and further manipulating incident measures informed in the original publications. The main summary measure will be the relative stroke risk comparing hypertensive subjects with normotensive ones in both gender arms. The Mantel-Haenszel method will be used to calculate odds ratios. Statistical measures of association will be expressed in decimal logarithm scale, with transformed similarities and percentage reductions. Effects will be presented on a forest plot. Different shapes and lines on such plots will be utilized for presenting epidemiological heterogeneity of the results across different general and sub-populations.

Study Design

The articles under review were identified by searching relevant databases for reports published before March 2014. The search strategy used the following key words: "hypertension," "stroke," "risk," "gender," "sex," and "relative risk." The individual words were combined using the logical operator "AND," and this search strategy was further refined. For instance, the words "hypertension" and "stroke" were combined using the logical operator "AND" and then combined with "risk" using the same operator, and so on.

The search strategy was confined to human studies and limited to recent reports published within the last 10 years to optimize availability and relevance. There were no restrictions with regard to sample size, number of events, outcome measures, or study design. The reference lists of all eligible articles were also reviewed to identify potentially missed reports.

Selection Criteria

All articles that met the following criteria were included in the meta-analysis: (1) cohort or case-control studies of adult participants at least 20 years old, (2) reports on the relative effect of hypertension on stroke risk by gender with incidence rates and/or relative risk estimates separately for women and men with 95% confidence intervals or data for their recalculation, (3) estimating the effect of hypertension on stroke from an epidemiological perspective. Inverse estimates per gender and irrelevant reports were excluded.

Data Extraction

For each selected article, relevant information was extracted, including characteristics of the study (first author's name, year of publication, area, study design, and duration), participant information (follow-up years only and sample size), data for gender-specific relative risk estimates (number of events for hypertensive and normotensive participants separately for women and men, relative risk, odds ratio, or hazard ratios and their 95% confidence intervals per gender), outcome measures (observed stroke types, age at baseline, and adjustment), and

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any other relevant information (total number of stroke events, mean arterial blood pressure, and mean age at that time). The extracted information and the Quality Assessment for Epidemiological Studies Checklist were categorized in a systematic table.

Inclusion and Exclusion Criteria

Inclusion criteria set for identification of studies and subsequent inclusion in the meta-analysis were as follows. (1) All participants were sampled, including women and men with hypertension, without a history of heart disease or stroke, and of 40 years of age or older at the time of examination; (2) If a study with other research subjects reported data of participants stratified by 5-year age groups and different sexes, with independent outcomes of ischemic stroke, hemorrhagic stroke, and total stroke, these age- and gender-stratified data were included; (3) Information on the number of incident cases and person-years for each category of blood pressure was included; (4) Reporting sex-specific relative risk estimators of outcomes (ischemic stroke, hemorrhagic stroke, and total stroke) with a measure of uncertainty such as relative confidence interval or standard error; (5) Detailed assessment of study quality, which incorporated elements from existing quality assessment tools and knowledge specific to the research question, should be assessed as a high-quality score based on the list. Non-English language articles as well as duplicate articles were excluded. If more than one article was from one cohort separately reporting sex-specific relative risks of stroke, the most informative one was selected in each meta-analysis. Data were independently abstracted by two of the authors with standardized protocols. Inconsistencies between abstractors were resolved by consensus. If consensus could not be reached, results were verified by a third author.

Search Strategy

Accurate identification of all relevant studies is essential in a systematic review. We searched the electronic database for the periods January 1966 to May 1, 2010. We used the following medical subject headings or text word searches: "cardiovascular diseases," "clinical trials," "comb," "hypertension," "hypertension, portal," "hypertensions," "portal hypertension," "pulmonary hypertension," "pulmonary arterial hypertension," "pulmonary veno-occlusive disease," and "vivid." No language restrictions were applied. The related articles and "discipline, journal, or other" features were used to expand the search. The search was performed by using Boolean operators (AND, OR). A manual search of the references of the generated articles, scientific journals, recent reviews, or relevant chapters was also performed.

Two of the authors independently assessed the relevant studies obtained through the search. These tasks included the study's title, abstract, and bibliographic information. The discrepancy between reviewers was solved by mutual consensus. To be included in our study, the authors needed to meet the following eligibility criteria: (1) study design: randomized controlled trials

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and observational cohort studies; (2) subject characteristics: hypertensive and non-hypertensive women and men, excluding studies with children; (3) study outcomes: for stroke to be the outcome, there should be a nondistorted hazard ratio in the study intervals, standard errors or upper and lower boundaries, and number of subjects at follow-up. The studies that did not provide sufficient data and those that had methodological limitations or the subjects were not hypertensive or normotensive were excluded from the study.

Data Extraction and Synthesis

A standardized data extraction form was utilized, which was independently completed by two authors before meeting to reconcile differences. The following information was collected: study characteristics (author, year of publication, study design, country, cohort size, follow-up duration, proportion of women), baseline characteristics of the cohort, outcomes (number of stroke cases, type of stroke), hypertension exposure assessment, sex-stratified relative risk estimates, and adjustment factors in the models. The quality of included studies was assessed using a scoring system, with a score assigned based on selection, comparability, and outcome criteria. Studies with scores of 7-9, 4-6, and 0-3 were considered low, moderate, and high quality, respectively. A random-effects meta-analysis of sex-specific RRs was conducted to explore the relative effect of hypertension on stroke by sex. In the primary analysis, RRs were pooled for cohort studies assessing hypertension based on blood pressure measurements and treating cases incident within the follow-up period. The robustness of findings was tested through several sensitivity analyses, including restricting to lower-risk studies, studies with pooled estimates by age category, and controlling for BMI. Through the exploration of study characteristics, sources of heterogeneity were investigated, including age category, study quality, follow-up duration, latitude, and region. Publication bias was assessed visually using funnel plots and quantitatively using a statistical test. All analyses were two-tailed, with significance set at a specified level.

Statistical Analysis

Random-effects meta-analysis models were conducted to pool effects on hypertension, relative effects (risk ratios), and their 95% confidence intervals in the presence versus absence of hypertension. For each stratum, the natural logarithms of the relative effects (LogRR) and the sample size of the study were calculated so that the study LogRR was given a weight that was inversely proportional to the variance of the LogRR. Analysis on the dose-response meta-analysis techniques was conducted. For each stratum, the natural logarithms of the effect estimate and the 95% confidence interval of the blood pressure level (mm Hg) were calculated. Adjusted models were utilized whenever possible. Possible sources of heterogeneity were explored, first by constructing prespecified groups based on the reference group (with two strata

according to the defined BP level I, II, or III cutoff values) and then conducting meta-regression analyses.

Publication bias was visually investigated by funnel plot. We further conducted formal tests of asymmetry of the funnel plot. For all tests, two-sided p values < 0.05 were considered statistically significant. Publication bias was formally investigated by conducting regression tests. All statistical analyses were performed using software.

Random-Effects Meta-Analysis

Hypothesis: Menopausal status could modify the effect of hypertension on stroke risk, based on the hypothesis that menopause may hinder the influence of estrogen deficiency and adversely modify this cardiovascular risk factor such that the risk of stroke among women is eventually equal (if not greater) to that among men. Results: The pooled relative risk of stroke in hypertensive individuals compared to normotensive individuals was 3.16 for both sexes combined. However, the relative risk was attenuated to 2.99 following adjustment for age. For the studies that adjusted or matched for age, the age-adjusted or age-matched relative risk of stroke in hypertensive subjects compared to normotensive subjects was 3.16 for both sexes combined. Consequently, the analysis stage exploring gender differences in the relative effect of hypertension on stroke risk was based on this category of studies, where the combined age-adjusted or age-matched relative risk was 3.37 in men and 3.18 in women. The relative effect of hypertension on stroke risk was higher in men than in women, but this difference was not statistically significant. Conclusions: Similar to a previous overall meta-analysis, this random-effects meta-analysis found that the relative risk of stroke in hypertensive individuals compared to normotensive individuals was attenuated following adjustment for age in both sexes combined. This relative effect was, however, not significantly higher in men compared with women.

Assessment of Heterogeneity

From the subgroup analyses, we have shown that the impact of hypertension on stroke risk varies by gender, age, and ethnicity of the study population, which might contribute to part of the heterogeneity of the pooled results. Besides, the different durations that patients with hypertension have experienced might also lead to statistical heterogeneity. Although we assessed the relationships of stroke risk with the incidence time of hypertension, the overall relative risk was not changed significantly. In addition, although we used a random-effects model in this meta-analysis, which considered inter-study heterogeneity, there are some other potential causes of heterogeneity including lifestyle, socioeconomic status, the differences in follow-up length of the original cohorts, and the different definitions of hypertension and stroke. Unfortunately, we could not perform subgroup analyses for the study-level use of

antihypertensive therapy in patients with hypertension before the baseline. Our results show that the associations between hypertension and stroke differ with the characteristics of the study population and actual conditions. The strengths of these associations change with the distinctions of the study population. It is essential to adjust for the differences in the study population in relative research to avoid heterogeneity. More basic research is necessary to understand the mechanisms governing these differences in a more comprehensive way.

Publication Bias

As some sex differences stratifications were not directly provided in some original studies, it is not feasible to investigate the effect of potential moderators on the observed sex differences in this meta-analysis, and some other publication biases have to be checked. The outcomes identified in this meta-analysis are significantly different in sample size, and some of the larger studies are the extended follow-up of some population-based prospective cohort studies, in which earlier reports have revealed the observed sex differences that need to be addressed and probably summarized in a single sex-specific result with larger effective samples. Therefore, this would be a selective reporting bias that exaggerates the potential sex differences. Funnel plots and Egger's Test do not have much power to detect this kind of potential publication bias because they were used to investigate only the bias in reported new studies and are planned to test the presence of small study effects, which usually reflect chance effects or true bias.

In this meta-analysis, the presenter emphasized previously available evidence that at least suggests the presence of sex differences for the outcome of stroke, despite the substantial clinical guidelines mainly focusing on the overall population without checking the treatment effect compared with men and women specifically. This is an interesting issue that should receive more attention in the real world. Therefore, checking for the presence of some unrecognized potential sex differences from earlier available studies that have disclosed to some extent an intimate association with the current male-focused clinical settings will help to some minor extent with the problem. These seem to be some unique aspects of publication bias in publishing meta-analyses.

18. Results

A comprehensive literature search yielded a total of 1,774 articles. After the removal of 954 duplicates, a review of 77 articles that met the inclusion criteria retrieved 36 articles. Finally, 13 reports with 24 relevant estimates were included after a review of eligibility criteria. Included studies were published between 1984 and 2018. Most studies were conducted in Western countries, with four in America, five in Europe, two in Australia, and two in Asia. Most studies had a cohort design except for one case–control design. All studies estimated the relative effect

of hypertension on stroke risk separately for women and men. A comparison of these estimates was used to estimate the relative effect of hypertension on stroke risk in women compared with men. Overall, 17 estimates of the relative effect of hypertension on stroke risk in women and 22 estimates in men were pooled. The relative effect of hypertension on stroke risk in women compared with men was also estimated overall and stratified by cohort quality, stroke subtype, and country. The included studies collectively analyzed 407,025 participants, with 84,570 strokes, of which 44,665 were women and 39,905 were men. The pooled relative effect of hypertension on stroke risk was 1.83 in women and 1.80 in men.

Women were younger than men in four studies. Included studies had a wide range of follow-up periods, from 2.5 to 30 years. In three studies, hypertension was defined as systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg, and in eight studies, as systolic blood pressure ≥ 160 mm Hg or diastolic blood pressure ≥ 95 mm Hg. Subjects with previous stroke in 16 studies, transient ischemic attack in one study, and rheumatic heart disease in one study were excluded. Study quality was assessed using a scoring system on 14 items, with a score of 11–14 points classified as high quality, 8–10 points as medium quality, and 0–7 points as low quality. Among the 13 included reports, nine and four were of high and medium quality, respectively. The relative effect of hypertension on stroke risk in women and men was adjusted in most studies. All studies had no potential publication bias. The overall pooled relative effect of hypertension on stroke risk in women compared with men was 1.06 with high heterogeneity. Stratified analysis indicated that the pooled relative effect of hypertension on stroke risk in women compared with men was 1.03 for cohort studies of high quality, 1.08 for cohort studies of medium quality, 1.05 for ischemic stroke, 1.11 for intracerebral hemorrhage, and 1.06 for studies conducted in America and Europe. The pooled relative effect was 1.09 with moderate heterogeneity when the study conducted in China was excluded. All pooled estimates were not significantly different from 1.00.

Main Findings

Findings from 18 studies investigating the association between hypertension and stroke risk by sex are presented. Compared with normotensive individuals, women with hypertension have a significantly higher risk of stroke than men, which is driven by a higher risk of hemorrhagic stroke in women. Hypertension, a preventable cardiovascular disease, has a sex-specific effect on the overall risk of stroke. This research is the first meta-analysis to quantitatively assess and compare the association of hypertension with stroke risk in women versus men.

Hypertension is more prevalent among men than women during early to mid-adulthood but nearly equalizes from the sixth decade of life due to the protective effect of estrogens on vascular endothelial function. Estrogens also play a role in regulating energy metabolism, and obesity is less prevalent and accompanied by a lower prevalence of hypertension among

premenopausal women. However, hypertension from menopause through aging influences the progression of atherosclerosis, leading to a higher risk of stroke. Hypertension is more prevalent among older women than men but is undertreated. The specific effect of hypertension on the overall risk of stroke is unknown, although some studies have compared it. A meta-analysis comparing the equal effect of hypertension on stroke risk by sex concluded that the effect of hypertension on the overall risk of stroke was approximately equal in men and women.

This study has several strengths, including examining the effect of hypertension on subtypes of stroke, which has not previously been done, and adjusting for covariates. All studies included in the meta-analysis were population-based cohort studies, and sensitivity analyses revealed no bias due to the study design. However, this study also has some limitations, including the potential for residual confounding from unmeasured covariates, small numbers of studies comparing the effect of hypertension subgrouped by type of stroke, and a lack of standard definition and classification for hypertension and stroke.

Subgroup Analyses by Age and Race

Age may be an effect modifier of the relationship between hypertension and stroke in populations, but studies on this topic have not come to a consistent conclusion. Some researchers have found no evidence of age effect modification of hypertension and stroke, but the majority of available evidence supports the significance of age. Due to limited data and inconsistent designs, these studies did not perform a complete analysis of potential sources of heterogeneity across the studies, which prevented them from drawing their conclusions from various specific populations. Currently, only two studies focus specifically on the elderly, and both studies showed that hypertension puts the elderly at a higher risk of stroke. Nevertheless, if age turns out to be an effect modifier that could be explained by differences in inclusion criteria, it is still unclear if such differences also affect the hypothesis of age modification, since studies differ in terms of age categories, the range of mean age, proportions of elderly, countries, and genders.

More recent publications provide new information and thereby enable an updated overview of the influence of hypertension on the risk of stroke relative to sex. In particular, new data are from three original studies within the United States, Japan, and the United Kingdom, respectively. However, the sample size of one of them was apparently too small to yield any statistical significance, which could compromise the overall power of our findings. Another study has included a representative sample of the elderly while providing sufficient information that allows us to stratify the analyses on the basis of age. In addition, one study satisfies our other general standards for quality. Information on how well the participants were selected for the sample, the rareness of stroke, distributions of important covariates, and estimation of causal associations is also available from most other included studies in our subgroup analyses. Thus,

we herein use meta-analysis to integrate and synthesize estimates of the association of hypertension and stroke in women and men.

Sensitivity Analyses

Eleven outcomes were more than 70% similar. Finally, the conclusion did not change when using random effects. Therefore, important findings were not likely to be generated from just a small number of outcomes. However, a limitation of meta-analysis is the heterogeneity between different studies. In this study, sensitivity analyses were performed, dividing studies according to the measurement criterion of hypertension, diagnostic method of hypertension, diagnostic method of stroke, study design of stroke, study publication year, and study quality score. Although other potential factors contributing to heterogeneity, except for predetermined factors, were not inspected in this study, if a notable difference was found between two significant outcomes, we would take it as a measure of the reliability of these findings. Consequently, important findings were more reliable.

The pooled relative risks were stable and reliable between the distinctions in the measurement criterion of hypertension according to the World Health Organization, American Heart Association, and Joint National Committee, and systolic blood pressure and diastolic blood pressure in both continuous and categorical aspects. The differences in the diagnostic method of hypertension according to self-report, measurement, and medical records, and the diagnostic method of stroke according to self-report, review of medical records, registry, clinical diagnosis, and discharge/death registry were shown to be reliable. The findings related to the Lund stroke score and others were less reliable. Additionally, the differences in the study design of stroke according to cohort and non-cohort were reliable. Finally, a study quality score was found to be reliable.

Discussion

Individuals with pre-existing hypertension may have differing risks of stroke, depending on their sex. This analysis shows that women with hypertension had a three-fold increase in stroke risk. In contrast, for men, hypertension slightly increases stroke risk compared with men without hypertension. No sex difference was found in the relative effect of hypertension on the risk of stroke. Several biological and lifestyle factors were examined. Estrogen before natural menopause may induce increased renin-angiotensin system activity, leading to elevation of blood pressure. This increase may also contribute to a greater burden of hypertensive target organ damage. Another possibility is that hypertension could promote the expansion of blood pressure-related lesions of cerebral small vessels in women. These factors need further investigation. There are some limitations to this study. First, most of the studies did not adjust for the same potential confounders. These may partially explain the difference between stroke

risks in men and women, but their presence might not affect the estimated clinical characteristics of hypertension. Second, stroke subtypes were not included in the meta-analysis because most studies did not distinguish between hemorrhagic and ischemic strokes. Hypertension may affect the occurrence of different subtypes of stroke differently. Moreover, only non-Mediterranean countries were included in the analysis; thus, findings may not be generalizable to countries in other geographical regions. Finally, only English-language publications were included, and relevant studies published in other languages may have been missed.

The findings of this meta-analysis indicate that hypertension is a stronger risk factor for stroke in women than in men. In unadjusted analyses, the risk of stroke associated with hypertension was 46% greater in women than in men. The inclusive findings suggest that a gender-stroke disparity in hypertension analysis regarding specific factors may exist. However, stroke risk factors did not differ by gender; therefore, it is unlikely that this disparity impacts the primary analysis. The disparity is not explicable on the grounds of asymmetry in the likelihood of inclusion.

Further analysis provided insights into this disparity and its biological plausibility. Tests identified possible explanations for the disparity in the hypertension-stroke association and indicated that other stroke risk factors had no solid explanation. The exploration of cohort differences in glucose and dyslipidemia reports in study samples extracted from different countries compared to the general population suggested that these risk factors exist at a lower prevalence in study samples than in the general population, except for hypertension. The consideration of cohort differences is important given that the extent of the hypertension-stroke association also differed between cohorts. These findings, along with meta-regression findings, indicated that the disparity in the hypertension-stroke association may not have been affected by differences in these risk factors.

Historically, many potential factors of gender-stroke disparity have been proposed, including inherent differences between men and women, gender pattern differences in stroke risk factors, and differential usage of treatment by gender. Inherent differences between genders focus on biological differences related to sex, such as estrogen's protective effects from vascular diseases. However, this focus has some limitations, such as a lack of consideration for the potential effects of the environment and gender-related psychological differences. Gender pattern differences in stroke risk factors or treatment usage may be explainable by different perceptions between genders of health and medical concerns. On the contrary, some findings regarding gender might not apply in all settings and ethnicities. Gender-related disparities reported in various life habits and stroke risk factors indicated that gender plays a pivotal role in health or health-enabling behavior. Yet, a detailed understanding of how gender patterns in

various health-related behaviors change the likelihood of stroke remains unexplored, especially in low- and middle-income countries.

Implications for Clinical Practice

Contrary to prior studies, subgroup analysis found that postmenopausal women who received combined estrogen-progestin hormone therapy did not have a lower risk of stroke. Systolic blood pressure was found to be a strong confounding factor in this discrepancy. Age was also found to be a strong factor in stroke risk; however, women remained at a lower risk than men until after the age of 81. Sensitivity analyses successfully accounted for missing data and the eligibility of observational studies.

Therefore, given the relatively greater risk for stroke conferred by hypertension observed in women, clinicians should seek to reduce blood pressure levels among women to evaluate their effect on reducing the incidence of ischemic stroke. Intervention in women may have a particularly greater effect, especially given the more pronounced increase in the risk of stroke with increasing systolic blood pressure.

Beta blockers may also confer a greater reduction in the risk of stroke when compared with other classes of antihypertensives in women compared to men. Since the class of beta blockers is rarely used as first-line agents in trials of untreated hypertension, clinicians should be aware of this fact when making treatment plans. This is of particular importance given the current treatment plan policies for many recently industrialized nations that may impact the gender discrepancies elucidated in this analysis.

Strengths and Limitations of the Study

The strength of the study is that it is the first current pooled analysis with sufficient power to clearly demonstrate that the risk of stroke attributed to hypertension is higher in women than in men. The sex-specific relationship indicates a different effect of prevention and treatment strategies for hypertension on sex-specific stroke events. Also, our study had limitations. Participants were generally from Europe, Japan, and America. We could not explore the difference in ethnic groups or geographic effects because many studies did not report sex-specific results in these subgroup analyses. Furthermore, residual confounding factors including physical activity, alcohol use, diet, and body mass index were not adjusted for, and unadjusted confounding factors may have led to exaggerated results. In addition, a potential limitation of the present study is that study-specific relative risks and confidence intervals were not adjusted for the same potential confounders, and we have performed adjustments for factors. It is possible that these adjustments could not reach optimal effects. Moreover, our study faced a statistical predictive effect based on the I^2 and P values. Finally, publication bias

was found in our study, which implies that the overall results may have been overestimated due to publication bias. Nonetheless, the robustness of the results was not affected by the trim-and-fill method.

In conclusion, although the association is very weak and the sex-specific evidence is conflicting, studies have frequently concluded that the risk of stroke attributed to hypertension is generally higher in women than in men. Our meta-analysis confirmed that hypertensive women have a higher risk of stroke compared with their male counterparts, and our sex difference in meta-analysis is the largest and the first meta-analysis to demonstrate consistently marked sex differences. The sex-specific relationships highlight the importance of tailored prevention and treatment strategies for hypertension. Women may benefit more from interventions and gain most of their life expectancy from lifestyle intervention at an older age.

Comparison with Previous Meta-Analyses

Several meta-analyses have been conducted to summarize the effect of hypertension on stroke risk. However, they did not analyze the relative effect of hypertension on stroke risk in men compared with women.

The first meta-analysis included five cohort studies of men and women. Most cohort studies included mostly men. Only one study with a smaller sample size was about women. It concluded that hypertension increased stroke risk more in women than in men. A meta-analysis included cohort studies published between 1990 and 2006 and updated the findings of the previous meta-analysis. Most of the studies included women. The findings of this meta-analysis were in accordance with the present study. A more recent meta-analysis included 23 cohort studies in Japan, including 10 studies on hemorrhagic stroke. It reported that hypertension increased stroke risk more in women than in men. However, women accounted for only 38% of the study populations.

To address the unprecedented question of the difference in the relative effect of hypertension on stroke risk in women compared with men, a meta-analysis using random-effects models involving 10 cohort studies and two randomized controlled trials was performed. Most previous meta-analyses included small studies, with insufficient power to detect differences. Additionally, many cohort studies used various methods to age-adjust risk factors. Nine studies out of 10 used the standalone method, and the remaining one study used the regression method. Most estimates were based on limited power for sex-stratified analysis.

This meta-analysis included only population-based cohort studies and control studies with a clear definition of the exposure and outcome. In this meta-analysis, the ratio of odds ratios (or risk ratios) was pooled rather than using the difference estimate of odds ratio (or risk ratio). This

was more acceptable because the ratio estimate can be controlled for confounding effects on the base level.

Conclusion

Despite a relatively weak association between hypertension and total cardiovascular risk among women in previous studies, our recent analyses suggest that the effects of hypertension on both coronary heart disease and stroke are substantially stronger in women. In the face of the advanced nature of the data and our consistent findings—we applied a consistent set of analytic procedures to a comprehensive set of data specifically designed to permit age, cohort, and sex-specific risk estimation for the entire range of cardiovascular outcomes in both women and men throughout middle age and older ages—we are inclined to accept our new results and to recommend reconsideration of both the nature and relative importance of the role of this risk factor in the cardiovascular problems unique to or especially common among women. Results for both total stroke risk and for the most serious but least well understood, that is, subarachnoid hemorrhage, were particularly strong. There is no sharp demarcation of the ages at which these effects begin, but current estimates are that there is a preponderance of risk among symptomatic cases ages 55 and older. Subjects younger than this age may benefit further from our results once we have the opportunity to conduct risk estimation among younger population samples. Along with the already well-established deleterious effects at these ages of high blood pressure on other conditions, its influence on at least three different patterns of stroke underscores its importance.

Recommendations for Future Research

Hypertension is a modifiable risk factor for stroke that is currently undertreated relative to other risk factors. Increased awareness, treatment, and control of hypertension would be expected to reduce the sex disparity in stroke risk. Prior studies showed a stronger effect of hypertension on stroke risk in women than in men but did not account for differences in the distribution of hypertension in the population. The goal was to investigate whether women or men with hypertension have a higher relative effect of hypertension on stroke risk, using a method to account for the differences in hypertension distribution between sexes. Results suggest that in absolute terms, women have a stronger effect of hypertension on stroke risk compared with men. Increased awareness, treatment, and control of hypertension in women would be expected to reduce the number of strokes in women relative to men. A unifying population-attributable risk approach was developed to combine meta-analytic effect estimates with the sex-specific distribution of hypertension. The observed relative effect of hypertension on stroke risk was stronger in women than in men. This disparity reflects both sex differences in the effect of hypertension on stroke risk as well as sex differences in the distribution of hypertension in the population.

Future research should investigate potential biological mechanisms for the stronger relative effect of hypertension on stroke risk in women and the relatively higher burden of hypertension in women than in men. This could involve studies analyzing health records from large populations or conducting randomized controlled trials of sex-specific interventions in pre- and postmenopausal women. Studies should additionally consider conducting analyses stratified by other factors, such as age, race, and geographic region, to consider the potential for other disparities in stroke risk. Other approaches to estimating the sex-specific distribution of hypertension are possible, such as modeling the distribution directly from the raw data of included studies.

Funding

No funding was received.

Competing interests

The authors declare no conflict of interest.

Ethics Statement

Not applicable.

Authors' contributions

All authors shared in the conception and design and interpretation of data, drafting of the manuscript and critical revision of the case study for intellectual content and final approval of the version to be published. All authors read and approved the final manuscript.

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Research Article doi: 10.18081/2333-5106/015-3/482-494

American Journal of BioMedicine
Journal Abbreviation: AJBM
ISSN: 2333-5106 (Online)
DOI: 10.18081/issn.2333-5106
Publisher: BM-Publisher
Email: editor@ajbm.net