Associations with high blood pressure in young adults: protocol for a systematic review and meta-analysis

Abstract

Introduction Hypertension is a leading cause of cardiovascular diseases worldwide and its prevalence is expected to rise among young adults. Although a risk-increasing association of high blood pressure (BP) with cardiovascular risk has been demonstrated in middle-aged or elderly adults, whether cumulated exposure to elevated BP during young adulthood contributes to higher risks of cardiovascular events in later life is largely unraveled. Therefore, in this protocol, we outlined a systematic review and meta-analysis to quantify the relationship between BP and the future risk of cardiovascular events in young adults and to assess if elevations in systolic (SBP) and diastolic blood pressure (DBP) differentially impacted clinical outcome.

Methods and analysis The following electronic databases will be searched: Medline, Embase and Web of Science. Grey literature and unpublished eligible studies will be searched on several trial registries and Google Scholar, CNKI, Wanfang datasets. Cohort studies investigating the adverse outcomes of individuals with increased blood pressure and aged 18–45 years old will be eligible. The primary study outcome will be the cardiovascular events. Coronary artery disease (CHD), stroke, and all-cause mortality will be examined as the secondary outcomes. Two investigators will independently review each article included in the final analysis. Data will be extracted by using an electronic data extraction table. Pooled analyses will be conducted using the random or fixed-effects model and expressed with 95% confidence intervals (CIs). Dose-response relationships between BP and individual outcomes will be assessed by a restricted cubic spline model. Publication bias will be assessed by visual inspection of funnel plots and by Begg's or Egger's statistical tests. Between-studies heterogeneity will be measured using the I^2 test ($p<0.05$). Sources of heterogeneity will be explored by sensitivity, subgroup and metaregression analyses.

Ethics and dissemination This is the first meta-analysis that will ascertain the associations of high blood pressure and future risks of cardiovascular events in young

adults. Findings will be shared through scientific conferences. Results will be used to inform the current guidelines for diagnosis and management of hypertension in young adults by demonstrating the importance of implementing age-specific recommendations.
Key words high blood pressure, young adults, cardiovascular events, coronary heart disease, stroke

Introduction

Cardiovascular events are responsible for approximately one-third of all global deaths, killing more than 18 million people each year (1, 2). High blood pressure (BP) is a well-recognized remediable risk factor for cardiovascular events. Although hypertension is traditionally a more prevalent disease in the elderly, recent epidemiological studies have shown that the incidence is progressively rising among the young (3). However, studies of cardiovascular event risks in this age group are quite limited (4). Most randomized outcome studies have involved participants who are at high risk or are over the age of 55 (5); thus, frequently used risk prediction models or guidelines are mainly based on studies among the old (6-8), whereas the relationship of BP to cardiovascular event risks among young adults is under studied. Assessment of the burden of cardiovascular events in young adults with increased BP is important as a guide to the early diagnosis and management of hypertension.

To this end, we are going to conduct a systemic review and meta-analysis of published studies to quantify the relationship between BP and the future risk of cardiovascular events in young adults and to assess if elevations in systolic (SBP) and diastolic blood pressure (DBP) differentially impacted clinical outcome.

Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) reporting guidelines were used to prepare this protocol. This study will be conducted under the recommendations of the Cochrane handbook and reported in accordance with the PRISMA statement(9). Additionally, the grading quality of this meta-analysis

was evaluated by using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach(10).

Eligibility criteria

Inclusion and exclusion criteria are summarized in Table 1.

Study design. Empirical studies using quantitative methods will be eligible for our study. We will expressly target longitudinal cohort studies (both retrospective and prospective). Cross-sectional studies, intervention studies, case reports/series, randomized controlled trials comparing efficacy of antihypertensive medications and review articles (including systematic reviews) will be excluded. There was no restriction based on publication data, gender, location, languages, or duration of follow-up, with a search end date of 6th, March 2020.

Population. Studies must involve adults within the age range of 18 to 45 years old with increased BP. Studies involving children or adults above 45 years old, animals, critically ill or hospitalized patients, pregnant women, participants with other overt diseases, like cancer, hyperthyroidism, diabetes, kidney disease, connective tissue diseases, rheumatoid arthritis will be excluded.

Exposure. The exposure of interest is the presence of increased BP (≥120/80 mmHg) in young adults. We will include studies that assess the relationship between increased BP and our outcomes of interest. Studies that focus solely on adverse outcomes associated with presence or absence of hypertension will be excluded as this meta-analysis is interested in the associations of BP categories and adverse study outcomes.

Comparator. Participants with optimal BP (<120/80 mmHg) will act as the comparator/control/reference group.

Outcomes. The primary study outcome is cardiovascular events. Coronary artery disease (CHD), stroke, and all-cause mortality will be examined as secondary outcomes. Studies which provide data on any of these outcomes will be included.

Data sources

The following electronic medical databases will be searched: MELINE, EMBASE and Web of Science. We will also search the reference lists of relevant publications,

review articles, and included studies and contact experts in the field to request additional data. The grey literature, such as government reports, conference proceedings, and dissertations, will be searched through Google Scholar, NCKI or Wanfang datasets. Ongoing or unpublished eligible studies will be searched on the website of ClincalTrials.gov or the World Health Organization International Clinical Trials Registry Platform.

Search strategy

The search strategy will combine the following search terms or keywords: 1) hypertension, 2) high blood pressure, 3) cardiovascular disease, 4) coronary artery disease, 5) coronary heart disease, 6) myocardial infarction, 7) ischemic heart disease, 8) acute coronary syndrome, 9) stroke, 10) cerebrovascular accident, 11) cerebrovascular disease,12) age, 13) young, 14) cardiovascular events, 15) cardiovascular deaths,16) heart failure, 17) chronic kidney disease, 18) chronic renal disease,19) renal failure, 20) kidney failure, 21) end-stage renal disease, 22) diabetes. Each database will be searched individually with the search strategy adapted to reflect the differing subject index terms and keywords used by each database. Advanced search features, such as multi-field search, operators, truncation/wildcards and limits, will be combined with the appropriate Boolean terms to create our search strategy.

Study records

Data management. The results of the literature search will be downloaded to EndNote and duplicates removed. The remaining studies will be prepared for the selection process.

Study selection. Two reviewers (D.L and Y.C) will screen all titles that meet the inclusion criteria. This will be followed by a screen of the remaining abstracts. The full manuscripts will be screened by the same reviewers to make the final decision for all included studies. Articles screened from the references will be included if the inclusion criteria are met. Any disagreements are resolved by consensus.

Data extraction process. Data from included studies will be extracted and recorded in a predefined data extraction form. The form will cover Population, Exposure, Comparator and Outcomes (Table 1). Study characteristics will also be included to

record study design, setting, study time period and aims and objectives. The data extraction form will be piloted and any modifications to the form will be made by the review team. Data extraction will be carried out in duplicate by independent reviewers and discrepancies will be resolved by discussion and/or consultation with a third reviewer.

Data items

Study characteristics. Details relating to study design, setting, period of study and study aims and objectives will be extracted.

Population. Study population characteristics, such as sample size, sex, age, occupation, treated or untreated status, will be extracted. Population recruitment and sampling for each study will be recorded, as will the individual inclusion/exclusion criteria.

Exposure. Details of different BP strata/categories will be recorded for each included study. Methods on how BP is measured will be recorded as well. BP will stratified into 5 subgroups: optimal BP (SBP <120 and DBP <80 mmHg), normal BP (SBP 120-129 and/or DBP 80-84 mmHg), high-normal BP (SBP 130-139 and or DBP 85-89 mmHg), grade 1 hypertension (SBP 140-159 and/or DBP 90-99 mmHg), and grade 2 hypertension (SBP ≥160 and/or DBP≥ 100 mmHg) based on the 2018 European Guideline (8).

Comparator. Details of the optimal BP stratum will be extracted.

Outcome. We will record how outcomes of cardiovascular diseases/events are defined and measured by each included study. Length of follow-up and statistical analyses used by the authors to evaluate the relationship between increased BP and the study outcomes will be extracted

Statistical methods. We will also record the statistical methods used, reported results, nature of association reported along with the corresponding effect sizes and adjusting confounders used in the model.

Risk of bias in individual studies

Newcastle-Ottawa scores (NOS) will be used to assess the characteristics and quality of included studies. Briefly, the NOS scale is based on a “star” system and includes

three broad perspectives: the "selection" of the study groups, the "comparability" of the groups, and the ascertainment of the "outcome" of interest (11). Similarly, two independent reviewers, D.L and Y.C, will perform each quality assessment, consulting a third reviewer when necessary. Studies will be considered of good quality if the total score is ≥7/9. No studies will be excluded based on the risk of bias assessment. Publication bias will be assessed by visual inspection of funnel plots and by Begg's or Egger's statistical tests, if at least ten studies are available. $P<0.05$ will be considered evidence of small study effects.

Data synthesis and analysis

The STATA version 15.0 (Stata Corp, College Station, Texas) software package will be employed to conduct random-effects or fixed-effects meta-analysis using the inverse variance method for pooling log risk ratios (RRs). Pooled RRs are expressed with 95% confidence intervals (CIs). The absolute risk difference (RD) is calculated by: $[(RR-1) *I_0]$, where RR indicates pooled RRs and I_0 is the incidence of cardiovascular events among young adults with optimal BP (12). In the dose-response analysis, restricted cubic splines are used to assess the pooled dose-response relationship between BP and individual outcomes.

To assess the potential benefit of initiating or adding treatments, a number needed to treat (NNT) will be estimated. The estimates are based on the absolute risk difference (RD) we calculated previously and derived from the reciprocal of the absolute risk reduction(13). Additionally, we will use the formula of "pdi*[(RR-1)/RR]" to calculate the population-attributable fractions (PAFs) for each categorical BP level in comparison to the reference category of optimal BP, where pdi here represents the proportion of total cases in the population arising from the ith exposure category(14). To assess heterogeneity across studies, the chi-square heterogeneity test will be used and expressed as an I^2 statistic. Values of 0–25% represents minimal heterogeneity, 26% to 75% represents moderate heterogeneity, and greater than 75% represents substantial heterogeneity (15). Sources of heterogeneity will be explored by sensitivity, subgroup and metaregression analyses.

Ethics approval and dissemination

This meta-analysis will not contain individual patient data therefore ethics approval is not required. The findings from this review will be shared through scientific conferences. Results will be used to inform the current guidelines for diagnosis and management of hypertension in young adults by demonstrating the importance of implementing age-specific recommendations.

Discussion

The associations between high blood pressure and cardiovascular risk have long been recognized and found to be age-specific, but most of the outcome studies were carried out in the middle-age or elderly population. Whether cumulated exposure to elevated BP during young adulthood contributes to higher risks of cardiovascular events in later life is largely unraveled. Previous cohorts and overviews have demonstrated that, for middle-aged or elderly populations, high BP is robustly associated with increased risk of total cardiovascular events and all-cause mortality (1, 16-19). Each 10 mmHg decrement in systolic pressure was predicted to result in about a 25–40% reduction in cardiovascular events (20). However, cardiovascular risks associated with high BP in young adults remain unclear.

It's been demonstrated that the pathophysiological basis of high blood pressure in young adults and the elderly is different (2, 5). White-coat hypertension, a hyperadrenergic state, a higher prevalence of secondary hypertension, hypertension due to peripheral BP amplification, etc. are more commonly seen in young adults. Conversely, loss of arterial compliance and increased arterial stiffness are often found in the elderly concurrent with increasing SBP and decreasing DBP (4, 5, 21). Whether these distinct pathologic phenotypes may have varying effects on blood vessels, causing distinctive risks among different age groups is unanswered. Additionally, whether the association of SBP/ DBP with different disease outcome differs among different age groups remained to be determined.

Without a defined relationship between high BP and cardiovascular risks, it is difficult to develop and implement standardized treatment advice and guidelines that are inclusive to young adults. Although ongoing studies for young adults are currently being investigated, most are still at very initial stage and long-term impact for

cardiovascular end points remain to be determined (22-24). Therefore, this meta-analysis will provide insights into the associations of high BP and future risks of cardiovascular events in young adults, which might prompt refinement of the diagnostic threshold and management recommendation used in hypertension guidelines.

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Table 1. Summary of inclusion and exclusion criteria to be used during the study selection process.

Category	Inclusion criteria	Exclusion criteria
Study design	Longitudinal cohort studies (retrospective and prospective)	Cross-sectional studies, intervention studies, case reports/series, randomized controlled trials comparing efficacy of antihypertensive medications and review articles
Population	Adults aged between 18 to 45 years old	Studies involving children or adults above 45 years old, animals, critically ill or hospitalized patients, pregnant women, participants with other overt diseases, like cancer, hyperthyroidism, diabetes, kidney disease, connective tissue diseases, rheumatoid arthritis
Exposure	Presence of increased BP(≥120/80 mmHg)	None
Comparator	Within optimal BP level (<120/80 mmHg)	None
Outcomes	Cardiovascular events, CHD, stroke, and all-cause mortality	None

Abbreviation: BP: blood pressure; CHD: coronary artery disease.