

# Blood pressure, hypertension and the risk of heart failure: A systematic review and meta-analysis of cohort studies.

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## ABSTRACT

**Background:** Hypertension is a major risk factor for several cardiovascular diseases including heart failure, atrial fibrillation, coronary heart disease, stroke, and all-cause mortality. Several studies have investigated the association between hypertension and risk of heart failure, but not all the studies have shown an increased risk and studies and differed with regard to the strength of the observed association. The objective of this systematic review and meta-analysis was to summarize the available data from cohort studies on the association between hypertension, systolic and diastolic blood pressure and the risk of heart failure.

**Methods:** PubMed and Embase databases were searched for relevant articles from inception up to May 2020. Cohort studies on hypertension or blood pressure causing heart failure were included. Random effect models were used to calculate summary relative risks (RRs) and 95% confidence intervals (CIs) for the association between hypertension or blood pressure and heart failure risk.

**Results:** A total of 36 cohort studies were included in the meta-analysis. The summary RR was 1.67 (95% CI: 1.46-1.90,  $I^2 = 92.8\%$ ,  $P_{\text{heterogeneity}} < 0.0001$ ) for hypertension vs.no hypertension (n=23 studies, 20233 cases, 643694 participants ), 1.31 (95% CI: 1.20-1.44,  $I^2 = 94.6\%$ ,  $P_{\text{heterogeneity}} = 0.0001$ ) per 20 mmHg of systolic blood pressure (13 studies, 22159 cases, 2159707 participants) and 1.14 (95% CI: 1.01-1.30,  $I^2 = 96.7\%$ ,  $P_{\text{heterogeneity}} = 0.0001$ ) per 10 mmHg of diastolic blood pressure (6 studies, 14024 cases and 284177 participants). There was evidence of nonlinear association between SBP and DBP and heart failure with a steeper increase in the risk at higher levels. There was no indication of publication bias and the association between hypertension and heart failure persisted across all subgroup analyses.

**Conclusion:** The findings of this meta-analysis suggest a strong positive association between hypertension and systolic and diastolic blood pressure and the risk of heart failure. Any further studies should clarify the shape of the dose-response relationship between blood pressure and heart failure.

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## ABBREVIATIONS

HPT	Hypertension
SBP	Systolic blood pressure
DBP	Diastolic blood pressure
CVD	Cardiovascular disease
DALYs	Disability adjusted life
CHF	Congestive heart disease
BP	Blood pressure
HF	Heart failure
CHD	Coronary heart disease
RR	Relative risk
CI	Confidence interval
CDC	Center for disease control
RAAS	Renin-angiotensin-aldosterone system



MR	Mendelian randomization
OR	Odd ratio
DM	Diabetes mellitus
IHD	Ischemic heart disease.
CO	Cardiac output
MRI	Magnetic Resonance Imaging

## **1. INTRODUCTION**

Heart failure remains a major public health concern, and is a major cause of morbidity and mortality worldwide. In the United States about 1 million persons are hospitalized every year due to heart failure<sup>(1, 2)</sup> The prevalence of heart failure has increased considerably the last few decades with aging, increased prevalence of hypertension, obesity, physical activity, underlying heart conditions and other lifestyle factors<sup>(3)</sup>. When heart failure is left untreated, it can lead to a life-threatening complication like stroke, thromboembolism, heart attack which generally increases the burden of the disease on public health and globally<sup>(4)</sup>.

### **1.1 BACKGROUND**

#### **1.1.1 Heart failure**

Heart failure is a condition where the heart is unable to pump blood around the body properly and usually occurs because the heart has become too weak or stiff. This clinical syndrome can occur in a variety of heart conditions, and established risk factors includes, age, sex<sup>(5)</sup>, history of ischemic heart disease<sup>(6)</sup>, atrial fibrillation<sup>(7)</sup>, overweight and obesity<sup>(8)</sup>, smoking<sup>(9)</sup>, diabetes/elevated blood glucose<sup>(10)</sup> and low physical activity<sup>(11)</sup>. The most common cause is hypertension with ventricular hypertrophy and results from fluid buildup within the heart muscles which affects the pumping power of the heart muscles, in other ways deprives other peripheral organ blood due to a reduced cardiac output<sup>(12)</sup>. Congestive heart failure (CHF) which also known as heart failure, not only has severe consequences for the patients and their families but also places serious public health burden, as patients with CHF have a poorer quality of life and shorter life expectancy compared with those of the same age in the general population<sup>(13, 14)</sup>. Heart failure can be diagnosed based on physical examination, looking out for either a swelling of

the leg, bulging of neck vein, chest X-rays, heart MRI, nuclear scan, stress exam and echocardiogram is used to confirm the presence of heart failure (4).

### **1.1.2 Global burden of Heart Failure**

Heart failure has been an emerging epidemic over the past 25 years (15). In the study by Ziaieian et al, there was an estimated prevalence of over 37.7 million heart failure cases globally in 2011 (16). The prevalence in Western countries is 1–2% in adults and increases to around 10% in individuals over 70 years of age (17). Heart failure is a major public health concern, mortality in heart failure remains high, between 20% and 40% (18, 19) Heart failure is accountable for 1 in 9 annual deaths in the United States and has been estimated to cost approximately \$30.7 billion (20). There is a relatively significance of numerous risk factors to heart failure development, however, this still remains debatable. In a study of Swedish men, the prevalence of heart failure was 2.1% at age 50 and 13.0 % at age 67 (21).while the incidence was 1.5 per 1,000 population per year at age 50/54 years and 10.2 per 1,000 population per year at age 61-67 years in the same study.

### **1.1.3 Risk factors for heart failure**

According to an analysis from the Strong Heart Study, heart failure affects from 2% to 10% of persons over the age of 70, and the underlying causes differ depending on sex, age, ethnicity, comorbidities including diabetes (22). Even though most causes of heart failure are preventable through modification of lifestyle factors, and even through appropriate management can reduce the morbidity and mortality, heart failure still remains a life-threatening medical emergency despite advancements in treatments available (23, 24) . Due to a growing and ageing population, the total number of cases continues to rise with men having a significantly higher incidence rate

of heart failure compared with women (1). In the United States, compared with other races/ethnic groups, African Americans have the highest prevalence and incidence of heart failure, and this typically manifests at a younger age (25, 26). In another study it was found that racial differences in heart failure risk were to a large degree explained by differences in established risk factors including BMI, hypertension, diabetes, myocardial infarction, chest pain, and smoking (27).

In a Mendelian Randomization on modifiable lifestyle factors and heart failure risk, smoking was associated with increased risk for heart failure, but no associations were observed in relation to alcohol consumption, coffee consumption, or physical activity (3). In population-based study, the most common risk factor for heart failure was hypertension, which accounted for around 66 percent of the cases followed by smoking with 51 percent (28). An analysis of the National Health and Nutrition Examination Survey 1 found suggested prevalence of hypertension, obesity, and smoking increased overtime and was related to increased risk of heart failure, and risk was particularly high for patients with coronary disease and diabetes with odds ratios (95% confidence intervals) of 3.05 (2.36–3.95) and 2.65 (1.98–3.54) respectively. However, the population attributed risk (PAR) for heart failure was highest for patients with coronary heart disease and hypertension; accounting for 62 and 17% of heart failure cases in the population, respectively (6)

In a small Greek cohort study BMI was found not to be a significant factor for heart failure, but persons with the metabolic syndrome had 2-3 fold increase in risk of heart failure, (hazard ratio [HR]: 2.5, 95% confidence interval [CI]: 1.68 to 3.40). Obese persons with the metabolic syndrome had a higher systolic blood pressure increasing the chances of developing heart failure (29). Meta-analyses have found that both higher BMI, and abdominal adiposity as well as diabetes or high blood glucose are risk factors for heart failure, suggesting the importance of both adiposity and metabolic health as determinants of heart failure (8, 10). Diabetes has been demonstrated to be an

independent risk factor for heart failure among African Americans and generally westernized countries (30, 31)

..

#### **1.1.4 Pathophysiology of heart failure**

There is a reduction in the effectiveness of the contracting of the heart muscles caused from a damage or overload of the heart muscles, and this overload may develop due to hypertension, where there is an overload of fluid (blood) in the ventricles which causes an increased activity for the heart muscles, misfolded proteins begins to build up in the heart muscles and the flow of blood to muscles is cut off causing irreversible heart muscle damage as a result of the lack of oxygen to the heart muscles causing it to stiffen and later begins to fail over time (32).

The best pathological model for new-onset HF included the combination of N-terminal pro-B-type natriuretic peptide, troponin and responsible for heart failure especially reduced ejection fraction (33).

Any cardiac ailment that causes myocardial dysfunction causes aberrant myocyte development, which stimulates cardiac remodeling through a cascade of gene activation. Myocardial cell hypertrophy and ventricular dilatation with enhanced interstitial matrix production are hallmarks of cardiac remodeling. After a cutoff threshold, this compensatory mechanism to sustain contraction capability becomes a maladaptive process, contributing to the worsening of heart failure as myocardial degeneration progresses. Myocyte loss that is necrotic, apoptotic, or autophagic may aggravate cardiac failure and cause left ventricular remodeling (34).

### **1.1.5 Hypertension**

Hypertension, or high blood pressure, is an important risk factor for cardiovascular diseases (CVDs), and the leading cause of death and disability-adjusted life-years worldwide according to the Global Burden of disease Study (35). Hypertension affects around one billion individuals worldwide, making it a very common risk factor for development of heart failure (36). Hypertension remains a major public health concern and puts tremendous constraints on nations both medically and financially, this includes the cost of health care services, and medications to treat high blood pressure<sup>(37-39)</sup> .

The CDC currently defines hypertension as having a systolic and diastolic blood pressure of 130/80 mmHg or higher, however It is classified into different stages, stage 1 hypertension is defined as a systolic blood pressure of 130-139 mmHg or diastolic 80-90 mmHg; stage 2 hypertension is defined as systolic blood pressure  $\geq 140$  mmHg and /or a diastolic BP  $\geq 90$  mmHg, stage 3 hypertension is defined as a systolic blood pressure of 140-159 mmHg and diastolic blood pressure of 90-99 mmHg and stage 4 hypertension is defined as a systolic blood pressure level at 160 mmHg or higher and a diastolic at 100 mmHg or higher (40) .

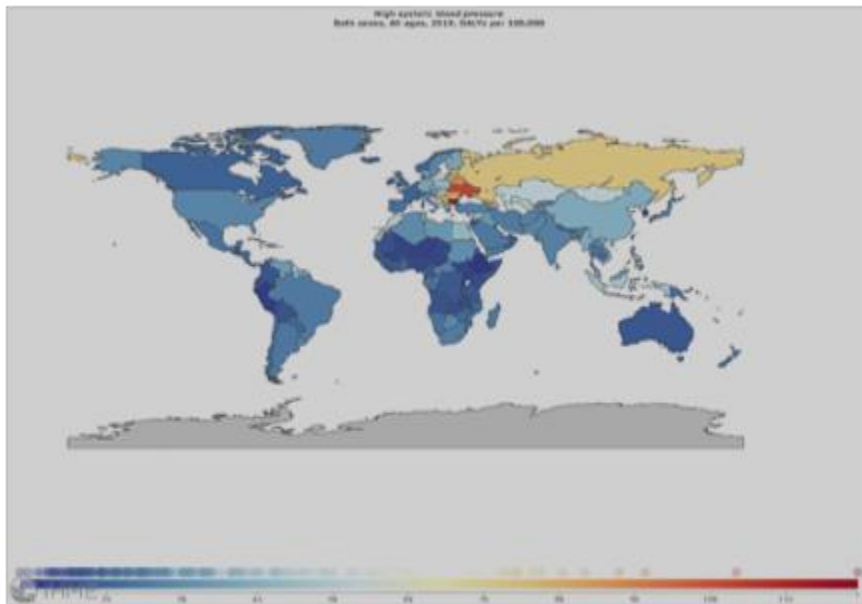
Epidemiological studies have reported some manifestation of CVDs to be associated with stage 1 hypertension, but there has not been any evidence of a medication to prevent CVDs at this stage, which makes the proportion of CVD events that could be prevented with effective control of stage 1 hypertension unknown (41).

A community-based study found that a blood pressure of 115/75 mmHg was associated with minimal mortality and appeared to be the optimal level of blood pressure (42). Such blood pressure levels are infrequent in westernized societies. The threshold for determining the presence of

hypertension is defined as the level of blood pressure above which treatment has been shown to reduce the development or progression of disease (43).

June et al demonstrated a higher prevalence of hypertension among women, in a rural and urban communities (44) . An inception cohort study of men and women indicated that hypertension was a strong predictor of various cardiovascular disease progression. A higher body mass index, age, prevalence of diabetes, physical inactivity and diet is proven to be a related factor for the developing a high blood pressure (39, 45). Studies conducted in the United States stipulates an increase in hypertension rate which results from higher systolic level compared to diastolic blood pressure (25). A slight change in the blood pressure levels can predict the incidence of heart failure according to some researches (31, 46)

FIGURE 1.1 Global risk of high systolic blood pressure (GBD compare data visualization)(35)



## 1.2 Hypertension and the risk of heart failure

Although hypertension elevated blood pressure is an established risk factor for a range of cardiovascular disease outcomes, data on blood pressure in relation to the risk of heart failure have not been summarized previously. Data regarding blood pressure and heart failure risk have also not been incorporated in the Global Burden of Disease Study, which potentially could lead to underestimation of the disease and mortality burden attributable to high blood pressure. A large number of studies have investigated the association between hypertension and heart failure risk(1, 2, 6, 12-14, 21, 22, 26-28, 30, 31, 33, 46-51) . In a small Swedish cohort study of 973 men aged 50 years, there was a 70% increase in risk of heart failure among persons with hypertension compared to those without hypertension (1, 2, 6, 12-14, 22, 26, 30, 31, 33, 46-48, 50, 51). The National Health and Nutrition Examination Survey 1 reported a 50% increase in risk of heart failure among persons with hypertension (1, 2, 6, 13, 14, 22, 26, 30, 31, 33, 46-48, 50), while the UK General Practice Research Database found a 70% increase in risk of heart failure among hypertensives (1, 2, 6, 12-14, 22, 26, 30, 31, 33, 46-48, 50). In the Southern Community Cohort Study, it was observed that hypertension was more strongly related to heart failure among black men when compared to white men (HR=2.07 vs. 1.45), while the association was similar among black women and white women (HR=1.64 vs. 1.61) while in the Women's Health Initiative the association between hypertension and heart failure was slightly stronger among black women (HR=2.83) than among white women (HR=2.45), but it was strongest among Hispanics (HR=5.18) and Asians (HR=8.16). All in all (1, 2, 22, 27, 30, 31, 46-48, 50), the vast majority of the studies published have reported a significant increase in risk of heart failure among persons with hypertension (1, 21, 22, 26-28, 30, 31, 48, 50, 51) compared to persons without hypertension, while a few studies did not detect a significant association(33, 46, 47, 49)



. In most of these studies the relative risk has ranged between 1.4 and 2.7, so there has been some heterogeneity with regard to the size of the association across studies.

Several additional studies have reported on systolic blood pressure (20, 24, 25, 42, 52-60) and diastolic blood pressure (25, 52, 55-57, 59) and the risk of heart failure. An analysis from a large UK cohort study of 1.9 million participants and 10437 incident heart failure cases reported a 27% (95% CI: 23-32%) and a 23% (95% CI: 19-28%) increase in the relative risk of heart failure per 20 mmHg increase in systolic blood pressure and per 10 mmHg increase in diastolic blood pressure, respectively (56). An analysis from the Chicago Heart Association Detection Project reported a relative risk of 1.32 (95% CI: 1.28-1.36) and 1.34 (95% CI: 1.29-1.39) per 18.5 mmHg increase in systolic blood pressure and per 11.6 mmHg increase in diastolic blood pressure, respectively (59). In a community of 5888 people over the age of 65, the development of heart failure was directly related to systolic blood pressure. All in all, most of the studies on systolic blood pressure and heart failure have shown an increased risk (20, 24, 25, 42, 52, 54-59), and only one study showed a significant reduction in risk (53), however, again the available studies have differed with regard to the strength of the observed associations, with relative risks ranging between an 8% increase in risk and a 62% increase in risk for high systolic blood pressure. Studies on diastolic blood pressure and heart failure have shown more mixed results with three cohort studies showing a significant increase in risk (25, 56, 59), while two studies reported no significant association (52, 55), and another one reported a weak inverse association (57)

### **1.2.1 Rationale of the study**

Hypertension is likely to be a significant risk factor for the development of heart failure, with various mechanisms contributing to both systolic and diastolic dysfunction (61). Although many studies have investigated the association between hypertension or elevated systolic or diastolic blood pressure and the risk of heart failure (9-11, 19) , the available studies have not yet been summarized in a meta-analysis. In addition, the strength of the associations and the shape of the dose-response relationships between systolic and diastolic blood pressure and heart failure needs to be clarified. Heart failure has so far not been included in the estimates of the disease burden related to elevated blood pressure by the Global Burden of Disease study<sup>(35)</sup>. A meta-analysis of the available epidemiological data could therefore contribute to improved estimates of the disease burden due to hypertension and elevated blood pressure globally and clarify potential sources of heterogeneity in the results between studies. This project therefore aims to summarize the results from published cohort studies on blood pressure or hypertension and the risk of heart failure.

### **1.2.2 Research objectives**

The main objective of the study was to conduct a systematic review and meta-analysis of cohort studies on blood pressure, hypertension, and the risk of heart failure.

Objectives

- i. To estimate the strength of the association between hypertension and the risk of heart failure.
- ii. To identify the shape of the dose-response relationship between systolic and diastolic blood pressure and the risk of heart failure.
- iii. To clarify if the association between hypertension and blood pressure and heart failure is consistent across subgroups stratified by age, sex, geographic location, study size, study quality, and adjustment for confounding factors.

## 2. METHODS

Standard criteria for reporting meta-analyses such as the Moose criteria were adopted (62)

### 2.1 Search strategy for identification of studies

Relevant studies were identified by searching PubMed and Embase databases. There was construction of Medical Subject Heading (MeSH) and keywords on the review. Search strings were constructed using a combination of MeSH terms (“Blood pressure” or Hypertension” AND “Heart Failure” AND (“Cohort OR prospective OR “case-control“ OR “cross-sectional” OR “relative risk” OR “hazard ratio” OR “incidence rate ratio”). Search strings were modified to suit the corresponding database interface. Relevant articles were screened, referenced, and adopted through the Reference Manager.

Table 1 Search strategy for each database

Database	Search strategy
PubMed	“Blood pressure” or Hypertension” AND “Heart Failure” AND “Cohort OR prospective OR “case-control“ OR “cross-sectional” OR “relative risk” OR “hazard ratio” OR “incidence rate ratio”
Embase	“Blood pressure” or Hypertension” AND “Heart Failure” AND (Cohort OR prospective OR “case-control“ OR “cross-sectional” OR “relative risk” OR “hazard ratio” OR “incidence rate ratio”

## **2.2 Study selection and inclusion criteria**

Published retrospective cohort studies, prospective cohort studies, case-cohort studies and nested case-control studies within cohort studies that investigated the association between hypertension, blood pressure and the risk of heart failure were included. The studies had to report adjusted estimates of relative risk (RR), such as hazard ratios, odds ratios, or incidence rate ratios, with 95% confidence intervals (CIs). For the dose-response analysis, the RRs for at least three categories of blood pressure, as well as the number of cases and, number of participants, or person-years per category, or a risk estimate on a continuous scale were required for the studies to be included. For studies reporting the total number of cases, but not per category, these were estimated based on a previously described method (8) . Studies published in English were considered, while conference, abstracts, grey literature and unpublished studies were not considered because information published in such formats is often too crude for study quality to be assessed and for the data to be included in dose-response analysis. Retrospective case-control and cross-sectional were excluded because of potential biases that can affect these studies including recall bias and selection bias in case-control studies and because of the difficulty in establishing the temporal relation between the exposure and the outcome in cross-sectional studies.

References were screened manually, PubMed was screened by myself and Embase screening was done by Shalu Jain (SJ) a coworker. Some studies included in the first stage were later excluded as they were duplicates or did not report on the exposures and/or outcome of interest.

## **2.3 Data extraction and synthesis**

The following data were extracted from each study into a table; the author's name, publication year and country, study name, study period, number of participants and cases, age and sex of participants, exposure (hypertension or blood pressure) and subgroups (e.g., by sex, ethnicity), comparison, RR and 95% CI, and lastly adjustment for confounders (Table 2 and 3)

## **2.4 Quality assessment of included studies**

The quality of studies included in the meta-analysis was assessed using the New castle Ottawa quality assessment scale for cohort studies (63) . Studies were assessed under three main categories and each category with sub-probing questions.

- Selection
  - Representativeness of exposure
  - Selection of the non- exposed cohort
  - Ascertainment of exposure
  - Demonstration that outcome of interest was not present at the start of study
- Comparability
  - Control for confounder (Age)
  - Control for more than one confounder
- Outcome
  - Assessment of outcome
  - Long follow up period (stars were allocated to studies with follow up period 3 years or more)
  - Adequacy of follow up (was rated 10% or less)

## **2.5 Statistical analysis**

Random effects models, which takes into account heterogeneity within and between studies were used to estimate summary RRs (95% CIs) for the association between hypertension or blood

pressure and the risk of heart failure (64) . The method of Greenland and Longnecker was used for the linear dose-response analysis of blood pressure and heart failure risk and study specific slopes (linear trends) and 95% confidence intervals were estimated across categories of blood pressure (65). When studies reported means or medians of systolic or diastolic blood pressure per category, these values were used directly, and when studies reported ranges of blood pressure, we calculated the mean of the upper and lower range. When the lowest or highest category was open-ended, we used the width of the adjacent category to estimate a lower or higher cut-off value for the category.

Fractional polynomial models were used for the nonlinear dose–response analysis of blood pressure and heart failure (66). The best fitting second order fractional polynomial regression model, defined as the one with the lowest deviance, was determined. A likelihood ratio test was used to assess the difference between the nonlinear and linear models to test for nonlinearity (66)

Heterogeneity between studies was evaluated with Q and I<sup>2</sup> statistics (67) . Subgroup and meta-regression analyses were stratified by study characteristics including duration of follow-up, sex, geographical location, number of cases, study quality and adjustment for confounding factors to investigate the potential sources of heterogeneity. Publication bias was assessed with Egger's test (68), and by inspection of the funnel plots. Sensitivity analyses excluding one study at a time from the analysis were conducted to assess whether the observed summary estimates were robust to the influence of each included study. All statistical analyses were performed with STATA version 15.0 (Stata Corp LP, College Station, TX).

## **2.6 Ethical considerations**

No ethical approval was necessary because the project used already published studies.

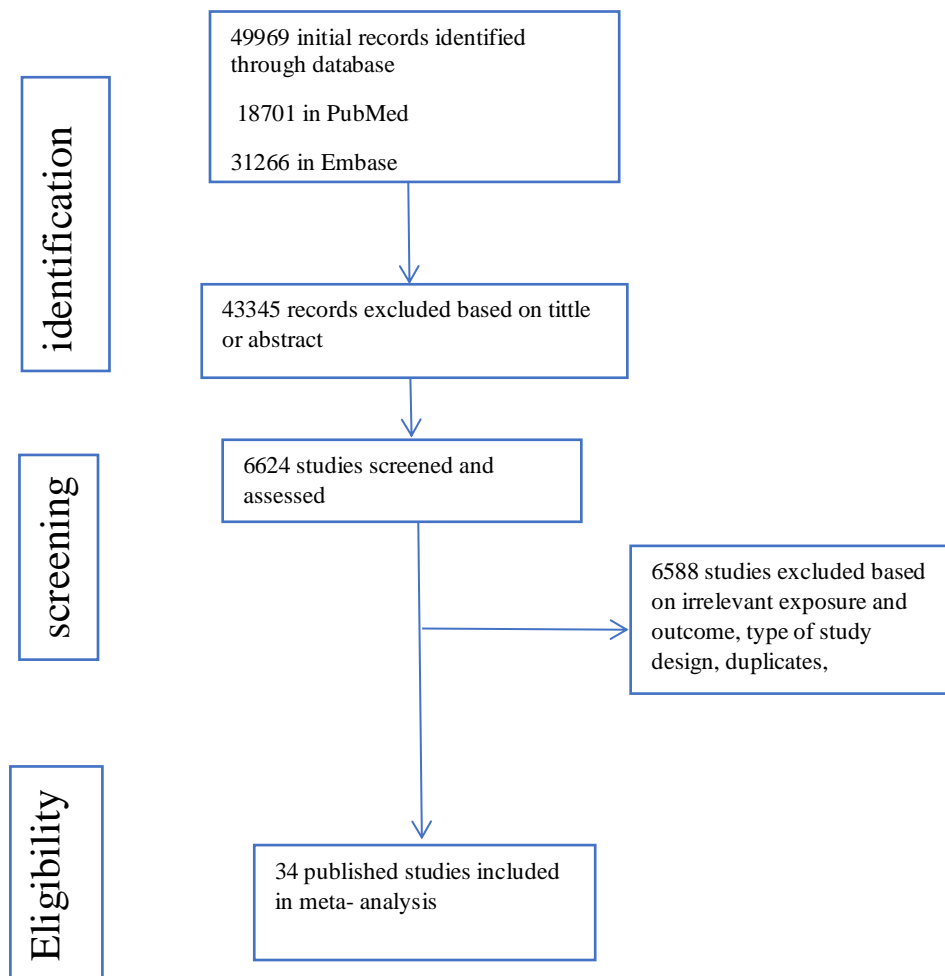
### **3. RESULTS**

#### **3.1 Characteristics of included studies**

The literature search retrieved a total of 49967 records including 18701 records from PubMed and 31266 from Embase (Figure 3.1). The first part of the screening based on inspection of abstract and title excluded 43345 records, leaving 6624 potentially relevant articles. Further inspection of these studies led to the final inclusion of a total of 36 studies (33 cohort studies and 1 nested case-control study) (1, 2, 6, 12-14, 21, 26-28, 30, 31, 33, 42, 46-54, 59, 60) with a total of 2729668 participants and 41169 cases (Figure 1, Table 1 and 2). The age of the participants in the included studies ranged between 40-100 years. Twenty- nine studies included both men and women, three studies included only men, and one study included only women. Nine studies were from Europe and 24 were from North- America. The mean (median) study quality as measured by the Newcastle-Ottawa scale was 6.9 (7) out of 9 across all studies included.



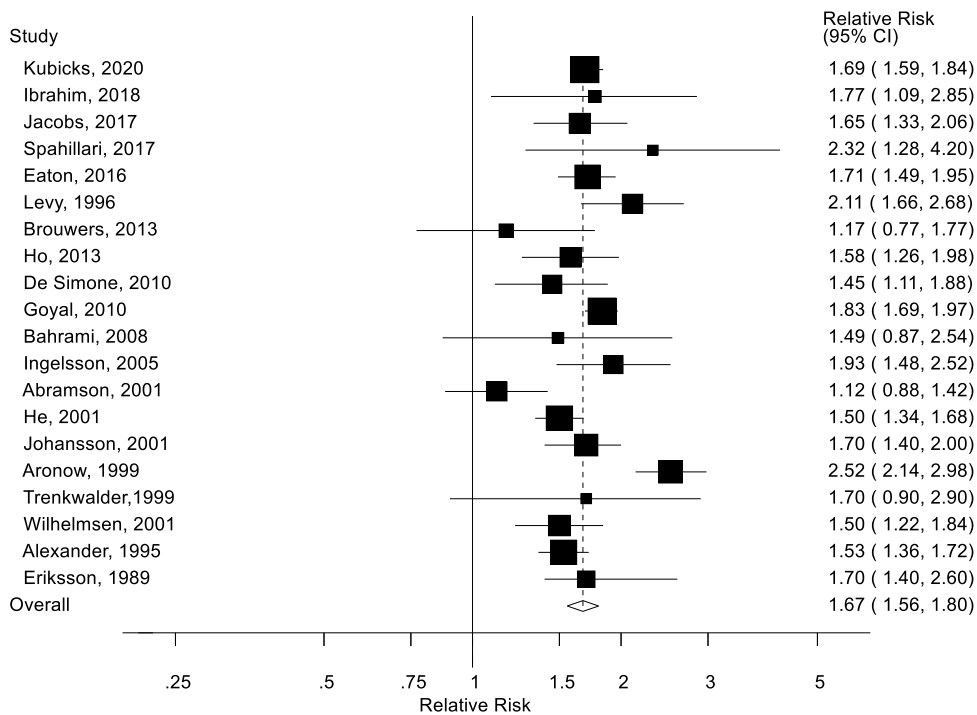
FIGURE 3.1: Flow diagram of the study the selection for the systematic review and meta-analysis of cohort studies on blood pressure, hypertension, and the risk of heart failure.



### 3.2 Hypertension and heart failure

Twenty studies (1, 2, 6, 12-14, 21, 22, 26-28, 30, 31, 33, 46-51) were included in the analysis of the association between hypertension and the risk of heart failure, including 19010 cases and 569961 participants. Among all the studies, 6 studies were conducted in Europe and 14 studies conducted in North America. The summary RR of heart failure in people with hypertension vs. without hypertension was 1.67 (95% CI:1.56-1.80,  $I^2=66.4\%$ ,  $p_{\text{heterogeneity}} < 0.0001$ ) (Figure 2). When individual studies were excluded one at a time, the summary RRs ranged from 1.63 (1.54-1.73) when the study by Aronow et al.(28) was excluded to 1.71 (1.59-1.82) when the study by Abramson et al. (47)was excluded. (Appendix D). There was no evidence of publication bias with Egger’s test ( $p=47$ ) or by inspection of the funnel plot. (*See appendix D*)

FIGURE 3.2. Forest plot for hypertension and the risk of heart failure



### 3.3 Systolic blood pressure and heart failure

Thirteen studies (20, 24, 25, 42, 52-60) were included in the analysis for systolic blood pressure with 22159 cases and 2159707 participants. Ten studies were from the North America and three from Europe. Twelve studies had both men and women included while one study was conducted in men only. The summary RR per 20 mmHg increases in systolic blood pressure was 1.31 (95% CI: 1.20 -1.44),  $I^2 = 94.6\%$ ,  $p_{\text{heterogeneity}} = 0.0001$ ) (Figure3). There was no evidence of publication bias with Egger's test ( $p=0.43$ ) or by inspection of the funnel plot (see appendix D). The summary RRs ranged from 1.26 (95% CI: 1.16-1.38) when the study by Pierdomenico et al (54) was excluded to 1.34 (95% CI:1.22-1.48) when the study by Nichols et al (57) was excluded. (See Appendix). There was evidence of non-linear relationship between SBP and heart failure ( $P_{\text{nonlinearity}} < 0.0001$ ) with a steeper increase in risk at 150 mmHg and above than below (supplementary table 5).

FIGURE 3.3 Forest plot for systolic blood pressure and heart failure

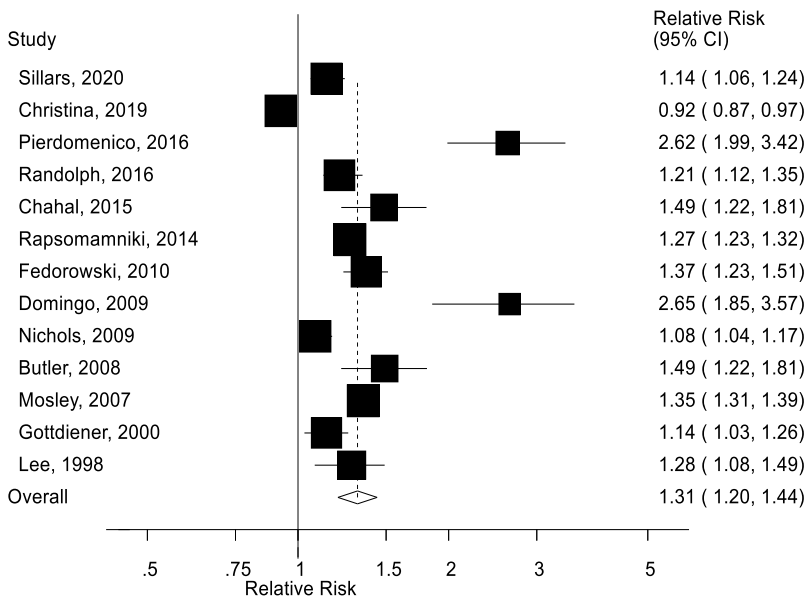
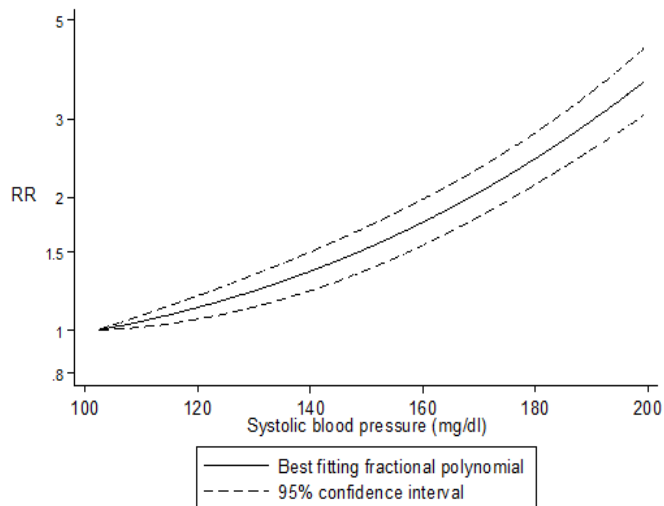


Figure 3.4. Nonlinear dose-response analysis of systolic blood pressure and risk of heart failure



### 3.4 Diastolic blood pressure and heart failure

Six studies(25, 52, 55-57, 59) were included in the analysis of diastolic blood pressure and risk of heart failure<sup>36,48,51,55,56,57</sup>. Including 14024 cases and 284177. Four studies were from North America and two studies were from Europe. All studies included both men and women. The summary RR per 10mmHg increase in diastolic blood pressure was 1.14 (95% CI: 1.01-1.30,  $I^2 = 96.7%$ ,  $P_{\text{heterogeneity}} = 0.0001$ ). There was no evidence of publication bias with Eggers's test ( $p = -0.81$ ). or by inspection of the funnel plot, (see appendix D). The summary RRs ranged from 1.07 (95% CI: 0.94-1.22) when the study by Domingo et al (25) was excluded to 1.19 (95% CI: 1.06-1.34) when the study by Nichols et al (57) was excluded. There was evidence of non-linear relationship between DBP and heart failure with a steeper increase in risk from around 80 mmHg and above than below (Supplementary table 5).

Figure 3.5. Forest plot for diastolic blood pressure and heart failure

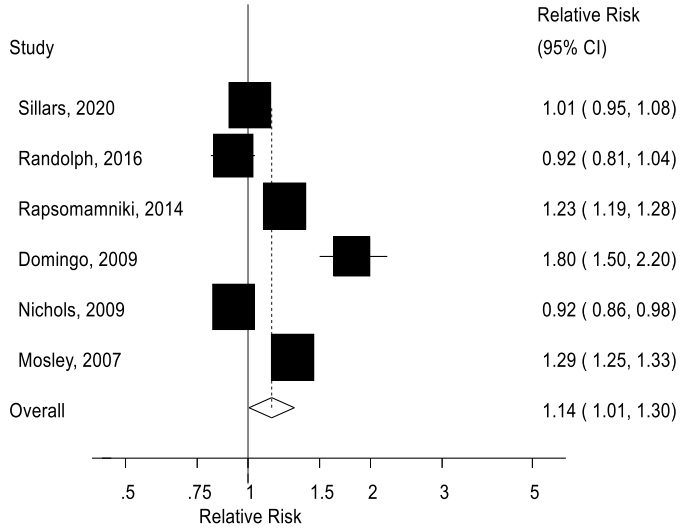
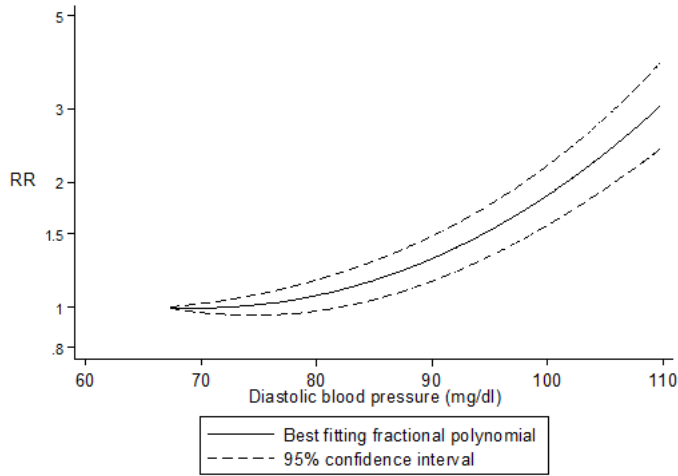


Figure 3.6. Nonlinear dose-response analysis of diastolic blood pressure and risk of heart failure



### **3.5 Subgroup and sensitivity analyses**

Table 4 shows the results of the subgroup analyses. The positive association between hypertension and heart failure persisted across all the subgroups that were considered including duration of follow-up, sex, geographical location, number of cases, study quality, and adjustment for a range of confounding factors (Table 2 and 3). The majority of analyses revealed significant heterogeneity within each subgroup, with the exception of the subgroups of males and European studies, which showed no and low heterogeneity, respectively.

## **4. Discussion**

### **4.1 Primary findings**

In this meta-analysis of 36 cohort studies on hypertension, blood pressure and heart failure risk there was a 67% increase in the relative risk of heart failure among people with hypertension compared to those without hypertension. Further, there was a 31 % and 14% increase in relative risk of heart failure per 20 mmHg increase in systolic blood pressure and per 10 mmHg increase in diastolic blood pressure, respectively. The association between hypertension and heart failure was consistent across subgroup analyses and there was little evidence of heterogeneity between subgroups, and the summary estimates was robust to the influence of individual studies. The analysis of diastolic blood pressure and heart failure was limited by the few studies included. The analyses involved an overall good-high quality from two continents with 42392 heart failure cases and 2.8 million participants.

#### **4.1.1 Comparison to previous pooled analyses**

The findings of this meta-analysis are consistent with a pooled analysis of 61 prospective studies on blood pressure and mortality from heart failure which found a HR of 0.53 (95% CI: 0.48-0.59) for a 20 mmHg lower systolic blood pressure, and a pooled analysis of four cohort studies of elderly participants which found a 20% increase in heart failure risk per 20 mmHg increase in systolic blood pressure, and-a pooled analysis of six studies, which found a systolic blood pressure (>150mmHg) to be associated with a 80% (56) increase in heart failure risk, however no association was observed with diastolic blood pressure. Results are also consistent with a pooled analysis of three cohort studies which found HRs in the range of 1.43-3.02 from older to younger age for participants with hypertension compared to those without hypertension

## 4.2 Strengths/limitations

This systematic review and meta-analysis has both strengths and limitations. Inclusion of cohort studies ensured that the blood pressure was assessed before the occurrence of heart failure, avoiding the potential for recall bias, and reducing the potential for selection bias and reverse causation to have impact on the results. With a total 2.8 million participants and >42000 cases included in the analyses, there was sufficient statistical power to detect even a modest association between hypertension or blood pressure and heart failure. Further strengths include the high study quality of the included studies, as well as the detailed subgroup and sensitivity analyses, which showed that the observed associations were robust in different strata and to the influence of any individual studies. The current meta-analysis also has some limitations, including potential confounding, errors in the exposure and outcome assessment, and heterogeneity between studies. Although only cohort studies with adjusted RR estimates were included in the meta-analysis, residual confounding cannot completely be excluded, however some studies may also have over-adjusted by including mediating factors on the pathway from elevated blood pressure to heart failure in the multivariable models, such as coronary heart disease and atrial fibrillation. However, the observed associations persisted across a range of subgroup analyses by adjustment for various confounding factors including age, alcohol, smoking, BMI, physical activity, serum cholesterol, and diabetes as well as by adjustment for potential intermediate factors such as coronary heart disease, valvular heart disease, atrial fibrillation and left ventricular hypertrophy, and there was no indication between subgroup heterogeneity in these analyses. The findings were also further supported by a recent Mendelian randomization (MR) study, which reported an OR of heart failure of 1.38 (95% CI: 1.25-1.53) per 10 mmHg increase in genetically predicted systolic blood pressure



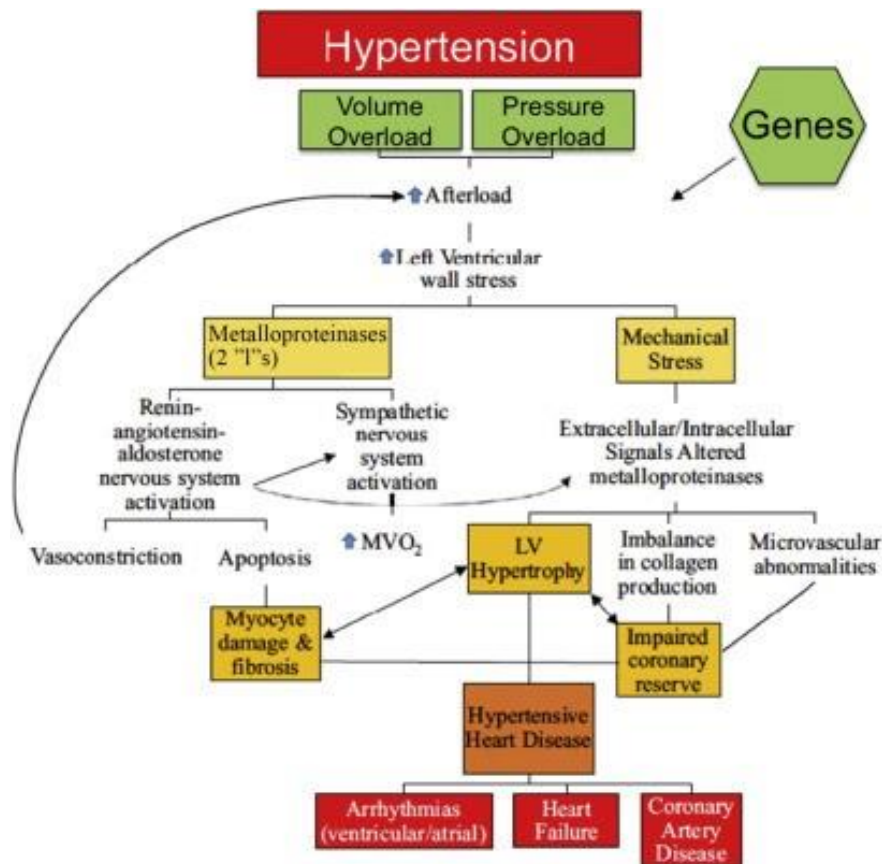
, while the current analysis showed a 31% in risk per 20 mmHg in systolic blood pressure (69), which is directionally similar, but weaker than what was observed in the MR study. It is possible that the difference in the strength of the association could partly be due to 1) some of the observational cohort studies included in the current analysis having adjusted for potentially intermediate factors, 2) regression dilution bias where a single measurement of blood pressure at baseline does not take into account changes in blood pressure during follow-up, or 3) the impact of lifelong elevated blood pressure, which may be better assessed in the MR studies, and which could have a stronger adverse impact on heart failure than blood pressure measured in middle age, or 4) a combination of some or all these. Blood pressure was measured in most of the included studies, while hypertension status was additionally based on medical history of elevated blood pressure or treatment for high blood pressure with medication in many studies. Changes in blood pressure or hypertension status during follow-up were not usually assessed as most of the included studies only had a baseline assessment, however, any changes in exposure status would most likely have led to regression dilution bias, and if anything, underestimation of the observed associations. The outcome was assessed by linkages of medical records and/or death records across studies and any inaccuracies in such records would most likely lead to underestimation of the observed association as the analysis was based on cohort studies. Although there was high heterogeneity in the analysis as measured by  $I^2$ , the heterogeneity was driven by differences in the strength of the association than differences in the direction of the observed association, as all the included studies reported RRs above 1. This is less problematic than when there is heterogeneity with respect to the direction of the observed associations. Although publication bias can affect meta-analysis of published studies, there was no indication of publication bias across the analyses, however, given that only six out of the 12 studies in the analysis of systolic blood pressure reported on diastolic

pressure, there might have been selective reporting of the results for the latter. Any further studies should clarify the association between diastolic blood pressure and heart failure.

### **4.3 Biological mechanisms**

A multitude of mechanisms could explain the association between high blood pressure (or hypertension) and an increased risk of heart failure. Long-term high blood pressure produces adaptive structural changes in the myocardium, which in turn generates a cascade of morphological and functional changes that lead to left ventricular hypertrophy, where the chamber of heart is thickened and not pumping blood effectively (70). The change in the myocardium happens as a result of an increase or decrease in the contractility which later damages the cardiomyocytes and preload disorder is when the length of the sarcoma is more or below the optimal and afterload due to fluid retention in the body. Due to the increase in the contractility, there is a shifting of ventricular function. Causing a decreased cardiac output (CO), in relation to diastolic and levels of systolic blood pressure, normal neurohumoral control is changed and creates pathologic neuro mechanisms (activation of RAAS, high release of angiotensin causing retention of Na and increasing the blood volume,) hypertrophy of the of ventricles (a structural abnormality) as a result of the high blood volume increases the percentage of non-myocytic cells in the myocardium (71). This left ventricular hypertrophy develops in relation higher blood pressure is associated with increased risk of coronary heart disease as well as atrial fibrillation, conditions that have been associated with a strong increase in risk of heart failure (72). The walls of the left ventricles lose its elasticity and weakens, the remodelling process includes a systemic hypertension (73)

Figure 4.1. Mechanism of hypertension leading to heart failure. *Slivnick, 2019 (36)*



#### 4.4 Public health implications

The current systematic review and meta-analysis provide strong support for the role of high blood pressure in the development of heart failure. Some of the main determinants for elevated blood pressure include high BMI, low physical activity, dietary factors like high intakes of salt, and low intakes of fruit and vegetables and medication use and could be targets for interventions to reduce blood pressure for the primary prevention of heart failure. Given the epidemic of obesity and inactivity globally and the relationship between obesity and low physical activity and increased heart failure risk (11, 74), policies to reduce adiposity and increase physical activity are likely to be important not only for preventing heart failure, but a range of other cardiovascular and chronic

diseases. This is likely to be of major importance for public health given the ageing population and increasing rates of adiposity and physical inactivity. In addition, appropriate use of blood pressure-lowering medications is an important target that clinicians can intervene on.

#### **4.5 Future research**

More studies are needed to better understand the link between diastolic blood pressure and heart failure, as well as the shape of the dose- response relationship between both systolic and diastolic blood pressure and heart failure. Because the majority of the studies considered were from Europe and America, more research is needed to confirm these relationships in other geographic locations. Only studies from the general population were included in this systematic review and meta-analysis, thus the findings are generalizable to generally health population mainly in Europe and North America. Further studies are also needed to examine potential interactions between blood pressure and other risk factors (e.g., adiposity, physical activity, diet, and medication use) in relation to heart failure risk.

#### **4.6 Conclusion**

In this meta-analysis of 36 cohort studies there was a 67% increase in the relative risk of heart failure for persons with hypertension compared to those without hypertension and a 31% and 14% increase in the relative risk of heart failure per 20 mmHg increase in systolic blood pressure and per 10 mmHg increase in diastolic blood pressure respectively. These findings provide strong

evidence that hypertension and elevated systolic and diastolic blood pressure increases the risk of heart failure. Any further studies should clarify the shape of the dose-response relationship between systolic and diastolic blood pressure and heart failure, and further studies from other geographic location than Europe and North America are also needed. Nevertheless, these findings provide support for interventions to reduce the blood pressure level in the general population, with lifestyle and blood pressure-lowering medications to reduce the incidence of heart failure.

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## APPENDIX A: CHARACTERISTICS OF INCLUDED STUDIES

TABLE 2. Prospective studies of hypertension and heart failure

First author, publication year, country	Study name or description	Study period	Number of participants, number of cases	Exposure, subgroup	Comparison	Relative risk (95% confidence interval)	Adjustment for confounders
Eriksson H et al, 1989, Sweden	The Study of Men Born in 1913	1963-1980-NA 17 years follow-up	973 men, age 50 years: 1020 HF cases	Hypertension	Yes vs. no	1.7 (1.4-5.7)	Smoking, body weight, heart volume, ECG T-wave, heart rate variability, peak flow, Fy-antigen, stress
Alexander M et al, 1995, USA	Northern California Kaiser Permanente Medical Care Program	1978-1984 - 1991, 9.5 years follow-up	64877 men and women, age $\geq$ 40 years: 1330 HF cases	Hypertension, uncontrolled, women age <60 years Hypertension, controlled Hypertension, unrecognized Hypertension, uncontrolled, men age <60 years Hypertension, controlled Hypertension, unrecognized Hypertension, age 60+ years Hypertension, controlled Hypertension, unrecognized	Yes vs. no Yes vs. no Yes vs. no Yes vs. no Yes vs. no Yes vs. no Yes vs. no Yes vs. no Yes vs. no	2.06 (1.07-3.95) 1.32 (0.84-2.07) 2.67 (1.32-5.42) 2.90 (1.78-4.70) 1.51 (1.05-2.17) 0.88 (0.32-2.42) 1.53 (1.16-2.01) 1.34 (1.09-1.65) 1.50 (1.14-1.97)	Age, sex, race/ethnicity, education, diabetes, smoking, MI, chest pain, total cholesterol, BMI, creatinine, uric acid, urine protein, left ventricular hypertrophy, alcohol

Levy D et al, 1996, USA	Framingham Heart study	NA-NA, 20 years of follow up	2334 men and 2809 women, 40-89 years: 392 HF cases	Hypertension men  Hypertension women	Yes vs.no  Yes vs.no	1.84 (1.35-2.51)  2.60 (1.77-3.81)	Myocardial infarcti on, left ventricular hypertrophy, angina pectoris, diabetes
Aronow WS et al, 1999, USA	New York	NA-NA, 3.6 years follow-up	2737 men and women, age 60-103 years: 739 HF cases	Hypertension	Yes vs. no	2.52 (2.14-2.98)	Age, sex, diabetes, coronary artery disease
Trenkwalder, P. et al., 1999, Germany	The prospective STEPHY II Study	1992-1995, -NA, 2.7 years of follow-up	647 men and women, 60-99 years: 60 HF cases	Hypertension, all	Yes vs. no	1.17 (0.9-2.9)	Age, sex, acute myocardial infarction,
Wilhelmsen L et al, 2001, Sweden	The Multifactor Primary Prevention Study	1970-1973 - 1996, 25.2 years follow-up	7495 men, age 47-55 years: 754 HF cases	Antihypertensive treatment or blood pressure of $\geq 175/\geq 115$	Yes vs. no	1.50 (1.22-1.84)	Age, MI in brothers or sisters, diabetes, chest pain, smoking, coffee, alcohol abuse, BMI
Abramson J et al, 2001, USA	Established Populations for the Epidemiolog ic Study of the Elderly Program (EPESE) - New Haven	1982- 1996, 14 years follow-up	2235 men and women, mean age 73.7 years: 281 HF cases	Hypertension	None Stage 1 Stage 2	1.00 1.04 (0.72-1.50) 1.18 (0.86-1.63)	Age, sex, race/ethnicity, education, alcohol, MI history, smoking, angina, diabetes, pulse pressure, BMI
He J et al, 2001, USA	NHANES I - Epidemiolog	1971-1975 - 1992, 19	13643 men and women, age 25-74	Hypertension, all Hypertension, men Hypertension, women	Yes vs. no Yes vs. no Yes vs. no	1.50 (1.34-1.68) 1.44 (1.25-1.67) 1.58 (1.36-1.82)	Age, sex, race/ethnicity, education, physical

	ic Follow-up Study	years follow-up	years: 1382 HF cases				activity, smoking, alcohol, BMI, diabetes, valvular heart disease, coronary heart disease
Johansson S et al, 2001, United Kingdom	UK General Practice Research Database	1996-1996, -NA, 1 year follow-up	Nested case-control study: 938 HF cases 5000 controls Age 69-100	Hypertension Hypertension, men Hypertension, women	Yes vs. no Yes vs. no Yes vs. no	1.7 (1.4-2.0) 1.6 (1.2-2.0) 1.8 (1.4-2.2)	Age, sex, smoking, BMI, hyperlipidemia, dyspnoea, prior comorbidities - CHD, valvular disease, diabetes, other cardiac disease, chronic respiratory disease, other diseases (anemia, renal failure, hyperthyroidism)
Ingelsson E et al, 2005, Sweden	Uppsala Longitudinal Study of Adult Men (ULSAM) cohort	1970-1974 - NA, 28.8 years follow-up	2321 men, age 50 years: 259 HF cases	Hypertension	Yes vs. no	1.93 (1.48-2.52)	Serum cholesterol, BMI, ECG-LVH, smoking, diabetes, prior AMI, serum uric acid, beta-carotene, triglycerides, apolipoprotein B/A-1 ratio, LDL cholesterol, HDL cholesterol
Hsia J et al., 2007, USA	The Women's Health Initiative	1978-1983, -NA 7.7 years of follow-up	60785 post-menopausal women, age 60-70 years: 1336 HF cases	Hypertension, all Hypertension, white Hypertension, black Hypertension, Hispanic Hypertension, Asian	Yes vs.no Yes vs.no Yes vs.no Yes vs.no Yes vs.no	2.53 (2.26-2.84) 2.45 (2.17-2.76) 2.83 (1.76-4.53) 5.18 (2.30-11.65) 8.16 (2.40-27.80)	Age, smoking, BMI, diabetes, hypercholesterolemia and alcohol

Bahrami et al 2008, USA	The MESA study	2000-2002-NA 4 years follow up	6814 men and women, age 45-84 years: 79 HF cases	Hypertension	Yes vs. no	1.49 (0.87-2.54)	Age, sex, BMI, diabetes, smokers
De Simone G et al, 2010, USA	Strong Heart Study	1989-1992 - NA, 11.9 years follow-up	2740 men and women, age 45-74 years: 291 HF cases	Hypertension	Yes vs. no	1.45 (1.11-1.88)	Age, sex, HF risk factors, HbA1c, smoking, alcohol, education, physical activity
Goyal A et al, 2010, USA	Kaiser Permanente Georgia data Study	2000 - 2005, -NA 6 years follow-up	168551 men, and 191396 women ≥18 years: 4001 HF cases	Hypertension	Yes vs. no Yes vs. no	2.03 (1.84–2.37) 1.71 (1.55-1.89)	Age, hypertension, diabetes mellitus, coronary artery disease, atrial fibrillation, and valvular heart disease.
Brouwers F et al, 2013, Netherlands	Prevention of Renal and Vascular End-stage Disease (PREVEND)	1997-1998 - 2010, 11.5 years follow-up	8592 men and women, age 28-75 years: 374 HF cases	Hypertension	Yes vs. no	1.17 (0.77-1.77)	Age, sex, obesity, diabetes, smoking, MI, atrial fibrillation, hypercholesterolemia, cystatine, UAE, hs-CRP, NT-proBNP, hs-TnT
Ho JE et al, 2013, USA	Framingham Heart Study	1981-2008, NA~15.4 years follow-up	6340 men and women, mean age 59.4 years: 512 HF cases	Hypertension Hypertension, HFpEF Hypertension, HFrEF	Yes vs. no Yes vs. no Yes vs. no	1.58 (1.26-1.98) 1.87 (1.33-2.64) 2.45 (1.79-3.34)	Age, sex, smoking, BMI, heart rate, previous MI, previous CHD, DM, valvular disease, HDL cholesterol, atrial

							fibrillation, left ventricular hypertrophy, left bundle-branch block
Eaton CB et al, 2016, USA	Women's Health Initiative	1993-1998 - 2015, 13.2 years follow-up	42170 postmenopausal women, age 50-79 years: 1952 HF cases	Hypertension, HFpEF Hypertension, HFrEF Hypertension, whites, HFpEF Hypertension, whites, HFrEF Hypertension, African Americans, HFpEF  Hypertension, African Americans, HFrEF Hypertension, Hispanics, HFpEF Hypertension, Hispanics, HFrEF	Yes vs. no Yes vs. no Yes vs. no  Yes vs. no Yes vs. no  Yes vs. no Yes vs. no Yes vs. no	1.57 (1.33-1.86) 1.99 (1.59-2.51) 1.57 (1.30-1.90)  2.07 (1.58-2.71) 1.80 (1.22-2.67)  1.60 (1.01-2.54) 1.22 (0.57-2.60) 4.24 (1.25-14.32)	Age, study component, race/ethnicity, income, education, diabetes, heart rate, MI, CHD other than MI, stroke, smoking, dyslipidemia, oophorectomy, cancer, BMI, smoking, physical activity, chronic lung disease, anemia, atrial fibrillation, beta-blocker use, aspirin use, hormone therapy, alcohol, insurance, interim CHD - not MI, interim DM, interim cancer
Jacobs L et al, 2017, UK	The Heart "OMics" in AGEing (HOMAGE) study (The Health Aging and	1997-1998 2007-2010 1997-1999 3.5 years follow-up	10236 men and women, mean age 74.5 years: 470 HF cases	Antihypertensive medication use	Yes vs. no	1.65 (1.33-2.06)	Age, sex, BMI, smoking, CAD, diabetes, SBP, heart rate, serum creatinine

	Body Composition Study, The PREDICTOR Study, PROSPER)						
Spahillari A et al, 2017, USA	Jackson Heart Study	2000-2004 - 2012, 9.9 years follow-up	4195 black men and women, mean age 54.4 years: 239 HF cases	Hypertension	Yes vs. no	2.32 (1.28-4.20)	Age, sex, BMI, nutrition, physical activity, smoking, fasting plasma glucose, total cholesterol
Ibrahim E et al, 2018, USA	The Casablanca Study	2008-2011, 3.8-8years follow up	1251 participants: 177 HF cases	Hypertension	Yes vs. no	1.77 (1.09-2.85)	Age, sex, Race, diabetes, Atrial fibrillation
Kubicks M et al, 2020, USA	Southern Community Cohort study	2002-2009-NA 5.2-6.7years follow up	27078 men and women, age 56 years: 4341 HF cases	Hypertension	Yes vs. no	1.69 (1.59-1.84)	Age, sex, race, smoking, BMI, poor diet, diabetes, high cholesterol, physical activity

ARIC=Atherosclerosis Risk in Communities Study, BMI =Body mass index, NA= not available



TABLE 3. Prospective studies of blood pressure and heart failure

First author, publication year, country	Study name or description	Study period	Number of participants, number of cases	Exposure, subgroup	Comparison	Relative risk (95% confidence interval)	Adjustment for confounders
Lee S, et al 1998, USA	Framingham Heart Study	1998-2004 3.2 years follow-up	3362 men and women, mean age 62 years: 518 HF cases	Systolic blood pressure	Per 10 mmHg	1.13 (1.04-1.22)	Age, sex, atrial fibrillation, BMI, DM,
Gottdiener, J. et al 2000, USA	Cardiovascular Health Study,	1989-1990-1994-1995, 6.3 years of follow up	5,625 men and women, age 65-100 years: 597 HF cases	Systolic blood pressure	Per 20 mmHg	1.14 (1.03-1.26)	Age, stroke, male gender, race, smoking, diabetes, CHD, atrial fibrillation,
Mosley WJ et al, 2007, USA	Chicago heart Association Detection project study	1967-1973-2002, 33 years of follow up	36314 men and women, mean age 13 to39 years: 599 HF cases	Systolic blood pressure, Diastolic blood pressure	Per 18.5 mmHg Per 11.6mmHg	1.32 (1.28-1.36) 1.34 (1.29-1.39)	Age, sex, pulse pressure, BMI, smoking, total cholesterol
Butler J et al, 2008, USA	Health ABC Heart Failure Score	1997-1998 - NA, 6.5 years follow-up	2935 men and women, mean age 73.6 years: 258 HF cases	Systolic blood pressure	Per 1 mmHg	1.02 (1.01-1.02)	Age, CHD, smoking status, creatinine, heart rate, albumin, glucose, VHD, left ventricular hypertrophy
Nichols GA et al, 2009, USA	Kaiser Permanente Northwest medical records	1997-1998 - 2005, 6.5 years follow-up	10113 men and women, age ≥50 years: 809 HF cases	Systolic blood pressure Diastolic blood pressure	Per 5 mmHg Per 5 mmHg	1.02 (1.01-1.04) 0.96 (0.93-0.99)	Age, sex, fasting glucose, BMI, CVD diagnosis, total cholesterol, smoking, estimated GFR, ACE/ARB inhibitor use, beta-blocker use, statin use, hydrochlorothiazide use, diabetes

Domingo B, et al, 2009, USA	The CARDIA study	1985-1986-NA 20years of follow up	5115 black men and women, age 18-30 years: 27 HF cases	Systolic blood pressure  Diastolic blood pressure	Per 10.9 mmHg  Per 10.0 mmHg	1.7 (1.4-2.0)  1.8 (1.5-2.2)	Age, sex diabetes, BMI, cholesterol, alcohol, LVH, smoking
Fedorowski A et al, 2010. Sweden	Malmö Preventive Project	1992-1974 2006,24 years of follow -up	33346 men and women, mean age: 45 years: 1293 HF cases	Systolic blood pressure	Per 10 mmHg	1.17(1.11-1.23)	Age, gender, antihypertensive treatment, hypertension, cholesterol, diabetes, BMI, smoking
Rapsomaniki E et, 2014, UK	The CALIBER study	1997-2010-NA, 5.2 years follow up	1937360 men and women, Age range 30-100 years, 104371 HF cases	Systolic blood pressure  Diastolic blood pressure	Per 20mmHg  Per 10mmHg	1.27(1.23-1.32)  1.23(1.19-1.28)	Age, sex, myocardial infarction, angina, abdominal aortic aneurysm
Chahal A et al, 2015, USA	The Multi-Ethnic Study of Atherosclerosis	2000-NA, 4.7 years follow-up	6814 men and women, mean age 64 years: 176 HF cases	Systolic blood pressure	Per 1 mmHg	1.02 (1.01-1.02)	Age, sex, ethnicity, BMI, smoking, heart rate, DM, total cholesterol, HDL cholesterol, creatine, LVH, smoking
Randolph C et al, 2016, USA	Jackson Heart Study	2000-2011-12 months follow up	5280 men and women, median age 56 years: 340 HF cases	Systolic blood pressure  Diastolic blood pressure	Per 10mmHg  Per 10mmHg	1.10 (1.06-1.16)  0.92 (0.81-1.04)	Age, diabetes, BMI, LVH, high cholesterol
Pierdomenico S et al, 2016, USA	A study of elderly men	1992-2012-NA, 9.1-20 years of follow up	1191 elderly men, age $\geq$ 60 years: 123 HF cases	24 hours systolic blood pressure	Per 10mmHg	1.62 (1.41-1.85)	Age, sex, atrial fibrillation, smoking, BMI, diabetes
Christina M et al 2019 USA	A subcohort of the BiomarCaRE consortium study	NA- NA 12.7years follow up	78,657 individuals, age range 24.1 to 98.7 years: 5,170 HF cases	systolic blood pressure	Per 21 mmHg	0.92 (0.86–0.97)	Diabetes, smoking, BMI, myocardial infarction, history of stroke, sex

Sillars A et al,2020, UK	The UK Biobank study	2007-2010-NA, 8.2 years follow up,	33595 men and women, age 40-60 years: 1812 HF cases	Systolic blood pressure  Diastolic blood pressure	$\leq 125$ mmHg $>125$ to 138 $>138$ to 152 $>152$  $\leq 75$ mmHg $>75$ to 82 $>82$ to 89 $>89$	1.00 1.34 (0.94-1.93) 1.31 (0.94-1.83) 1.28 (0.92-1.76)  1.00 1.05 (0.78-1.43) 1.27 (0.95-1.69) 1.31 (0.98-1.75)	Age, diabetes BMI, pulse pressure, women, sleep duration, smoking, physical activity
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Abbreviations

HF Heart failure

NA Not applicable

USA United States of America

BMI Body mass index

LVH Left ventricular Hypertrophy

**APPENDIX B: SUBGROUP ANALYSES OF HYPERTENSION AND HEART FAILURE, BLOOD PRESSURE AND HEART FAILURE**

TABLE 4

	Hypertension and heart failure				
	<i>n</i>	RR (95%CI)	<i>I</i> <sup>2</sup> (%)	<i>P</i> <sub>h</sub> <sup>1</sup>	<i>P</i> <sub>h</sub> <sup>2</sup>
All studies	20	1.67 (1.56-1.80)	66.4%	<0.0001	
Sex					
Men	2	1.83 (1.49-2.24)	0.0	0.54	0.67
Women	1	1.71 (1.49-1.95)	0.0	0	
Men, women	17	1.66 (1.52-1.80)	71.2	<0.0001	
Follow-up					
<10 years	11	1.76 (1.60-1.93)	66.2	0.001	0.21
≥10 years	9	1.58 (1.40-1.77)	60.9	0.01	
Geographic location					
Europe	6	1.68 (1.51-1.87)	0.0	0.55	0.97
America	16	1.68 (1.53-1.83)	75.2	<0.0001	
Asia	0				

Number of cases						
Cases <250	5	1.60 (1.35-1.88)	0.0	0.71	0.70	
Cases 250-<500	6	1.55 (1.26-1.91)	72.6	0.003		
Cases 500-<1000	3	1.90 (1.42-2.56)	86.5	0.001		
Cases ≥1000	6	1.66 (1.55-1.78)	55.2	0.05		
Study quality						
0-3 stars	0				0.46	
4-6 stars	5	1.75 (1.61-1.91)	17.2	0.31		
7-9 stars	15	1.67(1.52-1.83)	71.2	<0.0001		
Adjustment for confounding factors <sup>3</sup>						
Age	Yes	19	1.65 (1.54-1.78)	66.2	<0.0001	0
	No	1	2.11 (1.66-2.68)	0.0	0.04	
Alcohol	Yes	4	1.46 (1.26-1.70)	68.0	0.025	0.04
	No	16	1.75 (1.62-1.89)	59.3	0.001	
Smoking	Yes	14	1.59 (1.49-1.69)	35.8	0.089	0.089
	No	6	1.92 (1.63-2.27)	72.4	0.003	
BMI or obesity	Yes	14	1.59 (1.49-1.69)	35.4	0.09	0.25
	No	6	1.93 (1.63-2.28)	70.7	0.004	
Physical activity	Yes	4	1.60 (1.45-1.77)	41.5	0.16	0.45
	No	16	1.69 (1.54-1.86)	69.1	<0.0001	
Cholesterol	Yes	7	1.64 (1.53-1.77)	19.7	0.28	0.73
	No	13	1.68 (1.51-1.88)	74.7	<0.0001	
Diabetes	Yes	16	1.68 (1.55-1.81)	72.2	<0.0001	0.76
	No	4	1.62 (1.35-1.1.95)	0.0	0.53	
	Yes	11	1.62 (1.44-1.82)	77.6	<0.0001	0.21

Coronary heart disease	No	9	1.76 (1.67-1.84)	0.0	0.46	
Valvular heart disease	Yes	4	1.66 (1.48-1.86)	65.3	0.04	0.91
	No	16	1.68 (1.52-1.85)	68.6	<0.0001	
Atrial fibrillation	Yes	5	1.72 (1.56-1.89)	30.3	0.219	0.74
	No	15	1.64 (1.52-1.85)	71.1	<0.0001	
Left ventricular hypertrophy	Yes	4	1.73 (1.48-2.02)	57.8	0.07	0.64
	No	16	1.66 (1.52-1.81)	69.4	<0.0001	

*n* denotes the number of studies

<sup>1</sup>P for heterogeneity within each subgroup

<sup>2</sup> P for heterogeneity between subgroups with meta-regression analysis

<sup>2</sup> P for heterogeneity between men and women (excluding studies with both genders) with meta-regression analysis

BMI, body mass index

Table 4. Subgroup analyses of systolic and diastolic blood pressure and heart failure

	Systolic blood pressure (per 20 mmHg)					Diastolic blood pressure (per 10mmHg)				
	<i>n</i>	RR (95%CI)	<i>I</i> <sup>2</sup> (%)	<i>Ph</i> <sup>1</sup>	<i>Ph</i> <sup>2</sup>	<i>n</i>	RR (95% CI)	<i>I</i> <sup>2</sup> (%)	<i>Ph</i> <sup>1</sup>	<i>Ph</i> <sup>2</sup>
All studies	13	1.31 (1.20-1.44)	94.6	<0.0001	0.024	6	1.14 (1.01-1.30)	96.6	<0.0001	0.04
Sex										
Men	1	2.62 (1.99-3.42)			<0.0001	0				NC
Women	0					0				
Men, Women	12	1.26 (1.16-1.38)	94.7	0.0001		6	1.14 (1.01-1.30)	96.6	<0.0001	
Follow-up										
<10 years	8	1.22 (1.14-1.31)	79.5	<0.0001	0.06	4	1.02 (0.89-1.20)	96.2	<0.0001	0.04
≥10 years	5	1.56 (1.22-2.00)	98.0	<0.0001		2	1.50 (1.09-2.08)	91.2	0.001	
Geographic location										
Europe	3	1.25 (1.15-1.36)	77.8	0.01	0.28	2	1.12 (0.95-1.35)	96.4	<0.0001	0.76
America	10	1.37 (1.19-1.57)	96.0	<0.0001		4	1.17 (0.92-1.49)	97.5	<0.0001	

Asia		0					0				
Number of cases											
<250		3	2.15 (1.42-3.26)	86.7	0.001	0.05	1	1.80 (1.49-2.18)			<0.0001
250-<500		2	1.32 (1.08-1.61)	71.4	0.06		1	0.92 (0.81-1.04)			
500-<1000		4	1.21 (1.05-1.39)	93.9	<0.0001		2	1.09 (0.78-1.52)	98.8	<0.0001	
≥1000		4	1.16 (0.97-1.39)	97.1	<0.0001		2	1.12(0.92-1.35)	96.4	<0.0001	
Study quality											
0-3 stars		0				0.37	0				0.76
4-6 stars		3	1.45 (1.18-1.78)	94.2	<0.0001		2	1.12 (0.92-1.35)	96.4	<0.0001	
7-9 stars		10	1.29 (1.15-1.46)	95.5	<0.0001		4	1.17 (0.92-1.49)	97.5	<0.0001	
Adjustment for confounding factors <sup>3</sup>											
Age	Yes	12	1.34(1.24-1.44)	90.1	<0.0001	<0.0001	6	1.14 (1.01-1.30)	96.6	<0.0001	NC
	No	1	0.92 (0.87-0.97)				0				



Alcohol	Yes	1	2.65 (1.91-3.68)			<0.0001	1	1.80 (1.49-2.18)			<0.0001
	No	12	1.27 (1.16-1.40)	94.9	0.000		5	1.07 (0.94-1.22)	96.9	0.000	
Smoking	Yes	10	1.36 (1.20-1.56)	96.2	<0.0001	0.26	4	1.19 (0.97-1.47)	97.7	<0.0001	0.55
	No	3	1.26 (1.22-1.30)	0.0	0.63		2	1.07 (0.81-1.42)	94.8	<0.0001	
BMI or obesity	Yes	10	1.35 (1.19-1.54)	96.1	<0.0001	0.40	5	1.13 (0.94-1.37)	97.2	<0.0001	0.40
	No	3	1.26 (1.13-1.40)	70.4	0.03		1	1.23 (1.19-1.28)			
Physical activity	Yes	2	1.02 (0.83-1.26)	94.8	<0.0001	0.01	1	1.01 (0.95-1.08)			0.05
	No	11	1.36 (1.26-1.47)	90.2	<0.0001		5	1.17 (1.02-1.35)	96.7	<0.0001	
Cholesterol	Yes	8	1.34 (1.20-1.48)	90.7	<0.0001	0.77	4	1.17 (0.92-1.49)	97.5	<0.0001	0.76
	No	5	1.29 (1.07-1.57)	97.0	<0.0001		2	1.12 (0.92-1.35)	96.4	<0.0001	
Diabetes	Yes	10	1.33 (1.17-1.51)	93.7	<0.0001	0.98	4	1.09 (0.91-1.30)	93.2	<0.0001	0.12
	No	3	1.32 (1.25-1.40)	75.7	0.02		2	1.26 (1.20-1.32)	73.7	0.051	
Coronary heart disease	Yes	2	1.29 (0.99-1.67)	82.2	0.02	0.83	0				NC
	No	11	1.33 (1.20-1.47)	95.7	<0.0001		6	1.14 (1.01-1.30)	96.6	<0.0001	

Valvular heart disease	Yes	1	1.49 (1.22-1.81)			0.24	0					NC
	No	12	1.31 (1.19-1.44)	95.3	<0.0001		6	1.14 (1.01-1.30)	96.6	<0.0001		
Atrial fibrillation	Yes	3	1.53 (1.05-2.24)	93.7	<0.0001	0.37	0					NC
	No	11	1.28 (1.16-1.42)	95.6	<0.0001		6	1.14 (1.01-1.30)	96.6	<0.0001		
Left ventricular heart disease	Yes	5	1.41 (1.08-1.83)	95.4	<0.0001	0.51	2	1.28 (0.66-2.47)	97.0	<0.0001	0.67	
	No	8	1.28 (1.18-1.39)	91.9	<0.0001		4	1.10 (0.96-1.27)	97.4	<0.0001		

denotes the number of studies

<sup>1</sup>P for heterogeneity within each subgroup

<sup>2</sup> P for heterogeneity between subgroups with meta-regression analysis

<sup>2</sup> P for heterogeneity between men and women (excluding studies with both genders) with meta-regression analysis

BMI, body mass index, NC, not calculable

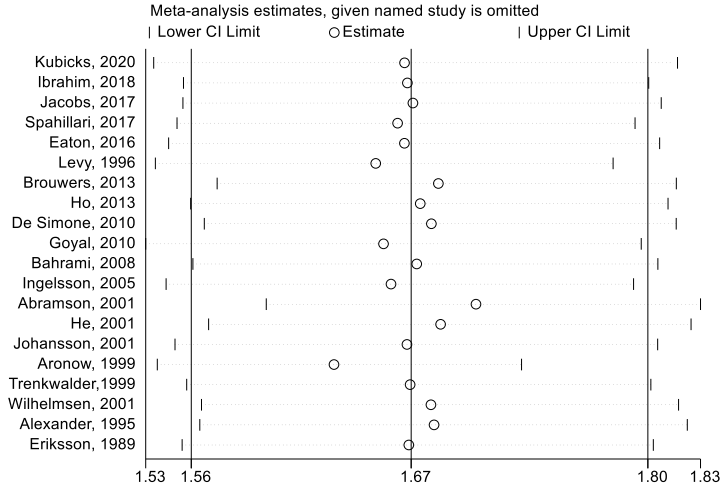
**SUPPLEMENTARY TABLE FOR NONLINEAR DOSE RESPONSE OF SYSTOLIC AND DIASTOLIC BLOOD PRESSURE**

TABLE 5

SBP		DBP	
mmHg	RR (95% CI)	mmHg	RR (95% CI)
102	1.00	67	1.00
110	1.05 (1.02-1.08)	70	1.00 (0.97-1.02)
120	1.13 (1.06-1.20)	75	1.02 (0.96-1.08)
130	1.23 (1.13-1.34)	80	1.07 (0.98-1.16)
140	1.36 (1.23-1.50)	85	1.16 (1.04-1.30)
150	1.53 (1.37-1.71)	90	1.31 (1.15-1.48)
160	1.75 (1.56-1.98)	95	1.53 (1.33-1.77)
170	2.05 (1.81-2.32)	100	1.86 (1.58-2.19)
180	2.44 (2.13-2.79)	105	2.34 (1.92-2.85)
190	2.98 (2.56-3.46)	110	3.07 (2.42-3.91)
200	3.70 (3.10-4.41)		
$P_{\text{nonlinearity}}$	<0.0001	$P_{\text{nonlinearity}}$	<0.0001

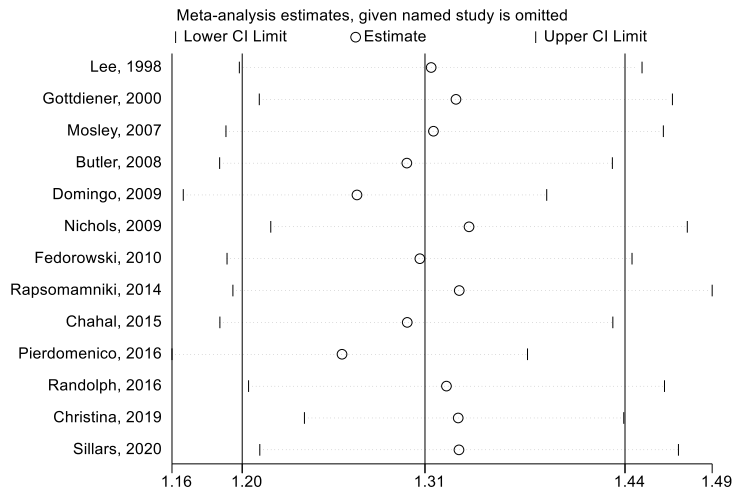
## APPENDIX C: GRAPHS AND OUTPUT FROM STATA FOR SENSIVITY ANALYSIS

### (i) Hypertension and the risk of heart failure



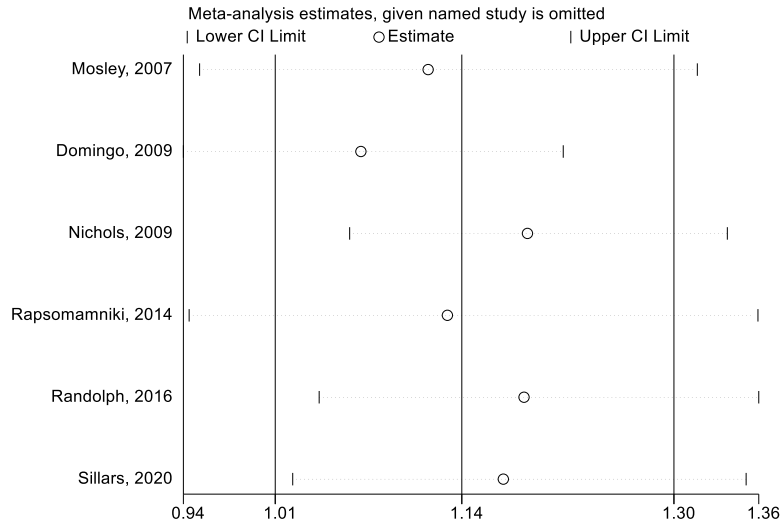
Study omitted	Estimate	[95% Conf. Interval]
Kubicks, 2020	1.6703894	1.5352457 1.8174294
Ibrahim, 2018	1.6719198	1.5512923 1.8019272
Jacobs, 2017	1.6748862	1.5510006 1.8086671
Spahillari, 2017	1.6666371	1.5478208 1.7945739
Eaton, 2016	1.6703252	1.5432925 1.8078142
Levy, 1996	1.6548638	1.5361495 1.7827524
Brouwers, 2013	1.6885992	1.5694396 1.8168061
Ho, 2013	1.6788369	1.5551628 1.8123462
De Simone, 2010	1.6848316	1.5625046 1.8167355
Goyal, 2010	1.6590546	1.5309297 1.7979023
Bahrani, 2008	1.6769472	1.5563821 1.806852
Ingelsson, 2005	1.6630932	1.5419344 1.7937722
Abramson, 2001	1.7088642	1.5958923 1.8298331
He, 2001	1.6898041	1.564851 1.8247346
Johansson, 2001	1.6716919	1.5467278 1.8067522
Aronow, 1999	1.6323639	1.5372022 1.7334167
Trenkwalder, 1999	1.6733902	1.5530286 1.80308
Wilhelmsen, 2001	1.6846136	1.5610073 1.8180076
Alexander, 1995	1.6862923	1.5600809 1.8227143
Eriksson, 1989	1.6726896	1.5505787 1.8044168
Combined	1.6739652	1.5554888 1.8014656

(ii) Systolic blood pressure and risk of heart failure



Study omitted	Estimate	[95% Conf. Interval]	
Lee, 1998	1.3188009	1.1998247	1.4495752
Gottdiener, 2000	1.3341726	1.2122015	1.4684165
Mosley, 2007	1.3202101	1.1915214	1.4627976
Butler, 2008	1.3037143	1.1875962	1.4311858
Domingo, 2009	1.2727717	1.1650487	1.3904551
Nichols, 2009	1.3422801	1.2193091	1.4776531
Fedorowski, 2010	1.3117785	1.1921881	1.4433653
Rapsomamniki, 2014	1.3362021	1.1958145	1.4930712
Chahal, 2015	1.3039364	1.1877635	1.4314719
Pierdomenico, 2016	1.2634972	1.1580452	1.3785518
Randolph, 2016	1.3282704	1.2055304	1.4635072
Christina, 2019	1.3355561	1.24019	1.4382557
Sillars, 2020	1.3360403	1.212504	1.4721631
Combined	1.3149549	1.2015918	1.4390132

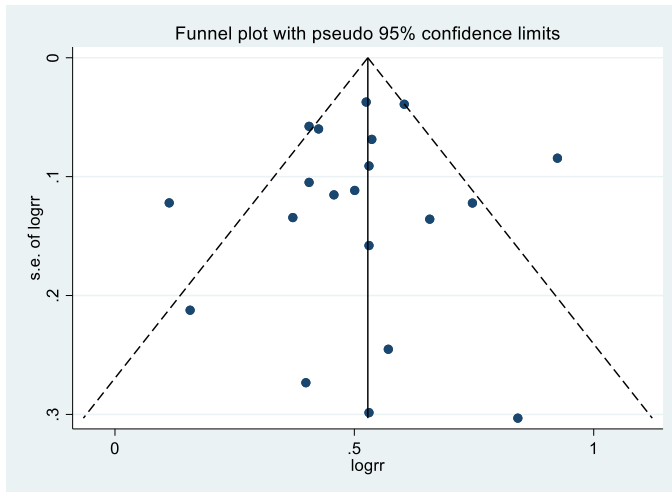
(i) Diastolic blood pressure and risk of heart failure



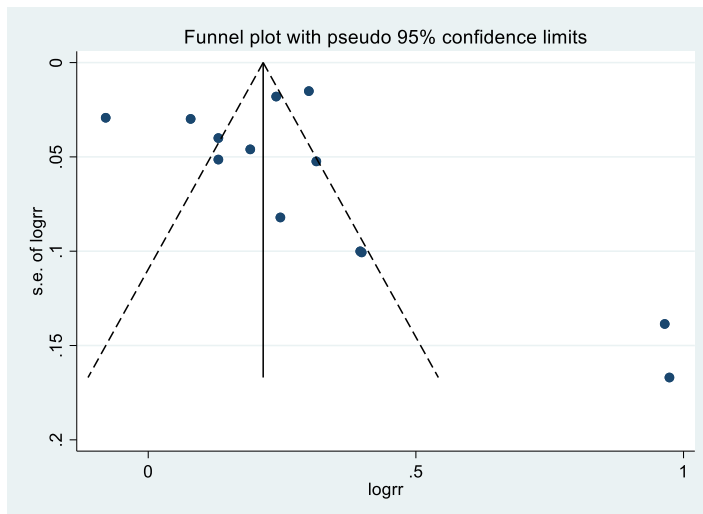
Study omitted	Estimate	[95% Conf. Interval]
Mosley, 2007	1.1187558	.94989181 1.3176391
Domingo, 2009	1.0690745	.9379124 1.2185791
Nichols, 2009	1.1921365	1.0607466 1.3398012
Rapsomamniki, 2014	1.1329787	.94216681 1.3624345
Randolph, 2016	1.1895995	1.0382409 1.3630238
Sillars, 2020	1.1743054	1.0186973 1.3536832
Combined	1.143625	1.0057864 1.3003539

## APPENDIX D: FUNNEL PLOT ANALYSIS TO DETECT RISK OF PUBLICATION BIAS

### (i) Hypertension and the risk of heart failure



### (ii) Systolic blood pressure and risk of heart failure



(i) Diastolic blood pressure and risk of heart failure

