Effects of elevated systolic blood pressure on ischemic heart disease: a Burden of Proof study
Supplementary Information: data sources and supplementary results for “Effects of elevated systolic blood pressure on ischemic heart disease: a Burden of Proof study"

This appendix provides detailed information on input data sources and supplementary results for “Effects of elevated systolic blood pressure on ischemic heart disease: a Burden of Proof study.”

Table of Contents

Section 1. Supplementary tables.................................................................................................................. 2
   Supplementary Table 1. PRISMA 2020 checklist.................................................................................. 2
   Supplementary Table 2. PRISMA 2020 abstract checklist................................................................. 5
   Supplementary Table 3. Study name and citation for all input data sources ............................................. 5
   Supplementary Table 4. Mean relative risk measures of IHD risk across systolic blood pressure exposure ........................................................................................................................ 8
   Supplementary Table 5. Burden of proof risk function for high systolic blood pressure exposure and ischemic heart disease........................................................................................................ 9
   Supplementary Table 6. GATHER checklist ......................................................................................... 9
   Supplementary Table 7. Causal criteria extraction template............................................................. 10
   Supplementary Table 8. Study covariates assessed in the analysis ..................................................... 16

Section 2: Data source identification ........................................................................................................... 16
   Section 2.1 Literature studies ........................................................................................................ 17
   Section 2.1.1 PubMed search ........................................................................................................ 17

Section 3: Sensitivity analysis .................................................................................................................... 18
   Section 3.1. Model results based on input data: testing cohort studies vs RCTs............................. 18
Supplementary Table 1. PRISMA 2020 checklist

| Section and Topic | Item # | Checklist item | Location where item is reported |
|-------------------|--------|----------------|---------------------------------|
| **TITLE**         |        |                |                                 |
| Title             | 1      | Identify the report as a systematic review. | This study leveraged a review of the literature as described in the Methods section, “systematic review”. |
| **ABSTRACT**      |        |                |                                 |
| Abstract          | 2      | See the PRISMA 2020 for Abstracts checklist. | See PRISMA 2020 for Abstracts Checklist (Supplementary Table 2) |
| **INTRODUCTION**  |        |                |                                 |
| Rationale         | 3      | Describe the rationale for the review in the context of existing knowledge. | “Main” (intro) paragraphs 1-3 |
| Objectives        | 4      | Provide an explicit statement of the objective(s) or question(s) the review addresses. | “Main” (intro) paragraph 5 |
| **METHODS**       |        |                |                                 |
| Eligibility criteria | 5   | Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses. | Full inclusion and exclusion criteria listed in Methods section “literature review”; reasons for exclusion and number of studies excluded also provided in PRISMA flow diagram (Extended Data Figure 1) |
| Information sources | 6   | Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted. | Methods section “systematic review”; Supplementary Information Section 2.1 |
| Search strategy   | 7      | Present the full search strategies for all databases, registers and websites, including any filters and limits used. | Methods section “literature review”; Supplementary Information Section 2.1 |
| Selection process | 8      | Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process. | Methods section “systematic review” |
| Data collection process | 9 | Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process. | Methods section “systematic review” |
| Data items        | 10a    | List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect. | Title, abstract, methods sections |
|                   | 10b    | List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information. | Methods section “systematic review”; Results section table 2 “Study characteristics” for each included study full list and definitions of all variables are in Supplementary Information Table 7 |
| Study risk of bias assessment | 11 | Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process. | Overview of methods for testing for bias in main text methods section “testing for bias across different study designs and characteristics” |
| Effect measures   | 12     | Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results. | Main methods “overview” and “estimating the burden of proof risk function” sections. |
### Synthesis methods

| 13a | Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)). | Broad description of processes available in methods “literature reviews” |
| 13b | Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions. | Methods section “literature review” |
| 13c | Describe any methods used to tabulate or visually display results of individual studies and syntheses. | Methods sections “literature reviews”, “estimating the shape of the risk-outcome relationship”, Figure 1 |
| 13d | Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used. | Methods sections “estimating the burden of proof risk function”, “quantifying between-study heterogeneity” and results of sensitivity analyses Extended Data Figures 3-10 |
| 13e | Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression). | Methods section “quantifying between-study heterogeneity” and results of sensitivity analyses Extended Data Figures 3-10 |
| 13f | Describe any sensitivity analyses conducted to assess robustness of the synthesized results. | Supplementary Information Section 3: sensitivity results reference to these results found in the main text of the methods and results sections “sensitivity analysis” and Extended Data Figures 3-10 |

### Reporting bias assessment

| 14 | Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases). | Methods for detecting publication or reporting bias found in methods section “evaluating publication and reporting bias” |

### Certainty assessment

| 15 | Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome. | Methods section “quantifying between-study heterogeneity” |

### RESULTS

### Study selection

| 16a | Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram. | PRISMA flow diagram Extended Data Figure 1 |
| 16b | Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded. | Not applicable |

### Study characteristics

| 17 | Cite each included study and present its characteristics. | Results Table 2 (“study characteristics”); Supplemental Information Table S3 (“study name and citation for all input data sources”) citations also provided in the online viz tool. |

### Risk of bias in studies

| 18 | Present assessments of risk of bias for each included study. | Results section “burden of proof risk function” |

### Results of individual studies

| 19 | For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimates and its precision (e.g. confidence/credible interval), ideally using structured tables or plots. | No, we do not present this information in the present manuscript. |

### Results of syntheses

| 20a | For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies. | Results section “burden of proof risk function” and methods section “testing and adjusting for bias related to study attributes” |
| 20b | Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and | Results, Figure 1; Supplemental Information Table 4 and 5; Extended |
| Section | Description |
|---------|-------------|
| 20c | Present results of all investigations of possible causes of heterogeneity among study results. |
| 20d | Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results. |
| 21 | Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed. |
| 22 | Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed. |
| DISCUSSION | Provide a general interpretation of the results in the context of other evidence. Discuss any limitations of the evidence included in the review. Discuss any limitations of the review processes used. Discuss implications of the results for practice, policy, and future research. |
| OTHER INFORMATION | Provide registration information for the review, indicating register name and registration number, or state that the review was not registered. Indicate where the review protocol can be accessed, or state that a protocol was not prepared. Describe and explain any amendments to information provided at registration or in the protocol. Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review. Declare any competing interests of review authors. |
Availability of data, code and other materials

Report which of the following are publicly available and where they can be found template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.

“Data availability” and “code availability” sections in the manuscript; data collection form template; Supplemental Information Table S47

Supplementary Table 2. PRISMA 2020 abstract checklist

| Section and Topic | Item # | Checklist item                                                                 | Reported (Yes/No) |
|-------------------|--------|-------------------------------------------------------------------------------|-------------------|
| TITLE             |        |                                                                               |                   |
| Title             | 1      | Identify the report as a systematic review.                                  | Not applicable    |
| BACKGROUND        |        |                                                                               |                   |
| Objectives        | 2      | Provide an explicit statement of the main objective(s) or question(s) the review addresses. | Yes               |
| METHODS           |        |                                                                               |                   |
| Eligibility criteria | 3     | Specify the inclusion and exclusion criteria for the review.                | Yes, in the main text |
| Information sources | 4     | Specify the information sources (e.g. databases, registers) used to identify studies and the date when each was last searched. | Yes, in the main text |
| Risk of bias      | 5      | Specify the methods used to assess risk of bias in the included studies.    | Yes, in the main text |
| Synthesis of results | 6     | Specify the methods used to present and synthesise results.                | Yes               |
| RESULTS           |        |                                                                               |                   |
| Included studies  | 7      | Give the total number of included studies and participants and summarise relevant characteristics of studies. | Yes, in the main text and Supplementary Information |
| Synthesis of results | 8   | Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favoured). | Yes, the number of included studies and participants is reported in the main text |
| DISCUSSION        |        |                                                                               |                   |
| Limitations of evidence | 9  | Provide a brief summary of the limitations of the evidence included in the review (e.g. study risk of bias, inconsistency and imprecision). | Yes, in the main text |
| Interpretation    | 10     | Provide a general interpretation of the results and important implications. | Yes               |
| OTHER             |        |                                                                               |                   |
| Funding           | 11     | Specify the primary source of funding for the review.                       | Yes, in the main text |
| Registration      | 12     | Provide the register name and registration number.                          | No                |

Supplementary Table 3. Study name and citation for all input data sources

| Study name | Citation |
|------------|----------|
| ABCD-N     | Schrier, R. W., Estacio, R. O., Esler, A. & Mehler, P. Effects of aggressive blood pressure control in normotensive type 2 diabetic patients on albuminuria, retinopathy and strokes. Kidney Int 61, 1086–1097 (2002). |
| Study name | Citation |
|------------|----------|
| ACCORD, Action to Control Cardiovascular Risk in Diabetes Study | ACCORD Study Group et al. Effects of intensive blood-pressure control in type 2 diabetes mellitus. *N Engl J Med* 362, 1575–1585 (2010). |
| ACTION Trial | Poole-Wilson, P. A. *et al.* Effect of long-acting nifedipine on mortality and cardiovascular morbidity in patients with stable angina requiring treatment (ACTION trial): randomised controlled trial. *Lancet* **364**, 849–857 (2004). |
| Active I | ACTIVE I Investigators *et al.* Irbesartan in patients with atrial fibrillation. *N Engl J Med* **364**, 928–938 (2011). |
| ADVANCE | Patel, A. *et al.* Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. *Lancet* 370, 829–840 (2007). |
| CAMELOT | Nissen, S. E. *et al.* Effect of antihypertensive agents on cardiovascular events in patients with coronary disease and normal blood pressure: the CAMELOT study: a randomized controlled trial. *JAMA* **292**, 2217–2225 (2004). |
| CARDIO-SIS | Verdecchia, P. *et al.* Usual versus tight control of systolic blood pressure in non-diabetic patients with hypertension (Cardio-Sis): an open-label randomised trial. *Lancet* **374**, 525–533 (2009). |
| DIABHYCAR | Marre, M. *et al.* Effects of low dose ramipril on cardiovascular and renal outcomes in patients with type 2 diabetes and raised excretion of urinary albumin: randomised, double blind, placebo controlled trial (the DIABHYCAR study). *BMJ* **328**, 495 (2004). |
| DREAM, Diabetes Reduction Assessment with ramipril and rosiglitazone Medication | DREAM Trial Investigators *et al.* Effect of ramipril on the incidence of diabetes. *N Engl J Med* **355**, 1551–1562 (2006). |
| Dutch TIA | The Dutch TIA Trial Study Group. Trial of secondary prevention with atenolol after transient ischemic attack or nondisabling ischemic stroke. *Stroke* **24**, 543–548 (1993). |
| EUROPA, European trial on Reduction of cardiac events with Perindopril in patients with stable coronary artery disease study | Fox, K. M. & EURopean trial On reduction of cardiac events with Perindopril in stable coronary Artery disease Investigators. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study). *Lancet* **362**, 782–788 (2003). |
| EWPHE, European Working Party on High Blood Pressure in the Elderly | Amery, A. *et al.* Mortality and morbidity results from the European Working Party on High Blood Pressure in the Elderly trial. *Lancet* **1**, 1349–1354 (1985). |
| FEVER, Felodipine Event Reduction Study | Liu, L. *et al.* The Felodipine Event Reduction (FEVER) Study: a randomized long-term placebo-controlled trial in Chinese hypertensive patients. *J Hypertens* **23**, 2157–2172 (2005). |
| HOPE-3, Heart Outcomes Prevention Evaluation study 3 | Lonn, E. M. *et al.* Blood-pressure lowering in intermediate-risk persons without cardiovascular disease. *N Engl J Med* **374**, 2009–2020 (2016). |
| HOPE, Heart Outcomes Prevention Evaluation study | Heart Outcomes Prevention Evaluation Study Investigators *et al.* Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med* **342**, 145–153 (2000). |
| HOT, Hypertension Optimal Treatment | Hansson, L. *et al.* Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. *Lancet* **351**, 1755–1762 (1998). |
| HYVET, Hypertension in the Very Elderly Trial | Beckett, N. S. *et al.* Treatment of hypertension in patients 80 years of age or older. *N Engl J Med* **358**, 1887–1898 (2008). |
| Study name | Citation |
|------------|----------|
| MRC 2, Medical Research Council trial of treatment of hypertension | MRC Working Party. Medical Research Council trial of treatment of hypertension in older adults: principal results. *BMJ* **304**, 405–412 (1992). |
| MRFIT, Multiple Risk Factor Intervention Trial | Stamler, J., Neaton, J. D. & Wentworth, D. N. Blood pressure (systolic and diastolic) and risk of fatal coronary heart disease. *Hypertension* **13**, I2 (1989). |
| NAVIGATOR | NAVIGATOR Study Group *et al.* Effect of valsartan on the incidence of diabetes and cardiovascular events. *N Engl J Med* **362**, 1477–1490 (2010). |
| PART 2 The Prevention of Atherosclerosis with Ramipril trial | MacMahon, S. *et al.* Randomized, placebo-controlled trial of the angiotensin-converting enzyme inhibitor, ramipril, in patients with coronary or other occlusive arterial disease. PART-2 Collaborative Research Group. Prevention of Atherosclerosis with Ramipril. *J Am Coll Cardiol* **36**, 438–443 (2000). |
| PATS, Post-stroke Antihypertensive Treatment Study | Liu, L. *et al.* Blood pressure reduction for the secondary prevention of stroke: a Chinese trial and a systematic review of the literature. *Hypertens Res* **32**, 1032–1040 (2009). |
| PEACE, Prevention of Events with Angiotensin Converting Enzyme Inhibition Trial | Braunwald, E. *et al.* Angiotensin-converting-enzyme inhibition in stable coronary artery disease. *N Engl J Med* **351**, 2058–2068 (2004). |
| PHARAO | Lüders, S. *et al.* The PHARAO study: prevention of hypertension with the angiotensin-converting enzyme inhibitor ramipril in patients with high-normal blood pressure: a prospective, randomized, controlled prevention trial of the German Hypertension League. *J Hypertens* **26**, 1487–1496 (2008). |
| PREVENT IT | Asselbergs, F. W. *et al.* Effects of fosinopril and pravastatin on cardiovascular events in subjects with microalbuminuria. *Circulation* **110**, 2809–2816 (2004). |
| PREVENT | Pitt, B. *et al.* Effect of amiodpine on the progression of atherosclerosis and the occurrence of clinical events. PREVENT Investigators. *Circulation* **102**, 1503–1510 (2000). |
| PRoFESS, Prevention Regimen for Effectively Avoiding Second Strokes Study | Yusuf, S. *et al.* Telmisartan to prevent recurrent stroke and cardiovascular events. *N Engl J Med* **359**, 1225–1237 (2008). |
| PROGRESS, The perindopril protection against recurrent stroke study | PROGRESS Collaborative Group. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack. *Lancet* **358**, 1033–1041 (2001). |
| PSC, Prospective Studies Collaboration | Lewington, S. *et al.* Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *The Lancet* **360**, 1903–1913 (2002). |
| QUIET, Quinapril Ischemic Event Trial | Pitt, B. *et al.* The QUinapril Ischemic Event Trial (QUIET): evaluation of chronic ACE inhibitor therapy in patients with ischemic heart disease and preserved left ventricular function. *Am J Cardiol* **87**, 1058–1063 (2001). |
| RENAAL, The Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan Study | Brenner, B. M. *et al.* Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* **345**, 861–869 (2001). |
| SCOPE, Study on Cognition and Prognosis in the Elderly | Lithell, H. *et al.* The Study on Cognition and Prognosis in the Elderly (SCOPE): principal results of a randomized double-blind intervention trial. *J Hypertens* **21**, 875–886 (2003). |
| SPRINT | SPRINT Research Group. A randomized trial of intensive versus standard blood-pressure control. *New England Journal of Medicine* **373**, 2103–2116 (2015). |
| Study name                                           | Citation                                                                                                                                                                                                 |
|-----------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| SPS3, Secondary Prevention of Small Subcortical Strokes trial | SPS3 Study Group et al. Blood-pressure targets in patients with recent lacunar stroke: the SPS3 randomised trial. *Lancet* **382**, 507–515 (2013).                                                                 |
| STOP-Hypertension                                   | Dahlöf, B. et al. Morbidity and mortality in the Swedish Trial in Old Patients with Hypertension (STOP-Hypertension). *Lancet* **338**, 1281–1285 (1991).                                              |
| Syst-China                                           | Liu, L., Wang, J. G., Gong, L., Liu, G. & Staessen, J. A. Comparison of active treatment and placebo in older Chinese patients with isolated systolic hypertension. Systolic Hypertension in China (Syst-China) Collaborative Group. *J Hypertens* **16**, 1823–1829 (1998). |
| Syst-Eur, Systolic Hypertension in Europe Trial      | Staessen, J. A. et al. Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. The Systolic Hypertension in Europe (Syst-Eur) Trial Investigators. *Lancet* **350**, 757–764 (1997). |
| The BBB study                                       | Hannson, L. The BBB Study: the effect of intensified antihypertensive treatment on the level of blood pressure, side-effects, morbidity and mortality in ‘well-treated’ hypertensive patients. Behandla Blodtryck Bättre. *Blood Press* **3**, 248–254 (1994). |
| TOMHS                                               | Neaton, J. D. et al. Treatment of mild hypertension study. Final results. Treatment of Mild Hypertension Study Research Group. *JAMA* **270**, 713–724 (1993).                                    |
| TRANSCEND, Telmisartan Randomized Assessment Study  | Telmisartan Randomised Assessment Study in ACE iNtolerant subjects with cardiovascular Disease (TRANSCEND) Investigators et al. Effects of the angiotensin-receptor blocker telmisartan on cardiovascular events in high-risk patients intolerant to angiotensin-converting enzyme inhibitors: a randomised controlled trial. *Lancet* **372**, 1174–1183 (2008). |
| UKPDS UK, Prospective Diabetes Study (UKPDS 38)     | UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. *BMJ* **317**, 703–713 (1996). |
| VALISH, Valsartan in Eldery Isolated Systolic Hypertension Study | Ogihara, T. et al. Target blood pressure for treatment of isolated systolic hypertension in the elderly. *Hypertension* **56**, 196–202 (2010).                      |

**Supplementary Table 4. Mean relative risk measures of IHD risk across systolic blood pressure exposure**

Relative risk based on the mean relative risk function (95% UI accounting for between-study heterogeneity), presented at every 10 mmHg of systolic blood pressure from 100 to 200 mmHg. The mean RRs are calculated in comparison to a reference SBP level of 100 mmHg. IHD = ischemic heart disease. RR = relative risk. UI = uncertainty interval.

| SBP level (mmHg) | RR (95% UI) |
|------------------|-------------|
| 100              | 1 (ref.)    |
| 107.5*           | 1.06 (1.06 to 1.07) |
| 110              | 1.12 (1.10 to 1.13) |
| 120              | 1.39 (1.34 to 1.44) |
| 130              | 1.81 (1.70 to 1.93) |
| 140              | 2.38 (2.17 to 2.62) |
| 150              | 3.11 (2.75 to 3.52) |
| 160              | 3.99 (3.43 to 4.63) |
| 165*             | 4.48 (3.81 to 5.26) |
| 170              | 4.95 (4.17 to 5.89) |
| 180              | 5.66 (4.69 to 6.82) |
Supplementary Table 5. Burden of proof risk function for high systolic blood pressure exposure and ischemic heart disease.

Burden of proof risk function defined as the 5th quantile risk curve (closest to null)—inclusive of between-study heterogeneity, providing a conservative estimate of effect size and evidence strength—averaged across the data dense 15th–85th percentile range (107.5 to 165 mmHg) of systolic blood pressure (SBP) exposure. The BPRF is calculated in comparison to a reference SBP level of 100 mmHg. Risk outcome score (ROS) calculated as the average log relative risk of the BPRF over the 15th–85th percentile of the SBP exposure range. Star rating summary measure of risk and evidence strength: ROS<0 yields 1 star, 0–15% risk increase yields 2 stars, >15–50% risk increase yields 3 stars, >50–85% risk increase yields 4 stars, and >85% risk increase yields 5 stars. BPRF = burden of proof risk function, ROS = risk outcome score, SBP = Systolic blood pressure.

| SBP level (mmHg) | Relative risk (95% UI) | Exposure-averaged BPRF | ROS | Star rating |
|------------------|------------------------|------------------------|-----|------------|
| 100              | 1 (ref.)               |                        |     |            |
| Averaged over 107.5–165* | 2.01                | 0.70                   | 5   |            |

*15th and 85th percentile of the SBP exposure.

Supplementary Table 6. GATHER checklist

| Item # | Checklist item | Reported on page # |
|--------|----------------|--------------------|
| 1      | Define the indicator(s), populations (including age, sex, and geographic entities), and period(s) for which estimates were made. | Main text (methods and results section); Supplemental Information Section 3 |
| 2      | List the funding sources for the work. | Main text (acknowledgement section) |
| 3      | Describe how the data were identified and how the data were accessed. | Main text (step 1 in methods); Extended Data Figure 1 (PRISMA 2020 flow diagram) |
| 4      | Specify the inclusion and exclusion criteria. Identify all ad-hoc exclusions. | Main text (step 1 in methods); Extended Data Figure 1 (PRISMA 2020 flow diagram) |
| 5      | Provide information on all included data sources and their main characteristics. For each data source used, report reference information or contact name/institution, population represented, data collection method, year(s) of data collection, sex and age range, diagnostic criteria or measurement method, and sample size, as relevant. | Main table 1; Data sources and citations for each risk-outcome pair can be found in the reference list and in Supplementary information Table 3 and can be downloaded from the Burden of Proof visualization tool: http://vizhub.healthdata.org/burden-of-proof |
| 6      | Identify and describe any categories of input data that have potentially important biases (e.g., based on characteristics listed in item 5). | Main text (methods and results sections) |
| 7      | Describe and give sources for any other data inputs. | Not applicable |
| 8      | Provide all data inputs in a file format from which data can be efficiently extracted (e.g., a spreadsheet rather than a PDF), including all relevant meta-data listed in item 5. For any data inputs that cannot be shared because of ethical or legal reasons, such as third-party ownership, provide a contact name or the name of the institution that retains the right to the data. | See Data Availability statement. Data sources and citations can be downloaded from the Burden of Proof visualization tool: http://vizhub.healthdata.org/burden-of-proof |
| 9      | Provide a conceptual overview of the data analysis method. A diagram may be helpful. | Main text (methods overview) |
| 10     | Provide a detailed description of all steps of the analysis, including mathematical formulae. This description should cover, as relevant, data cleaning, data pre- | Main text (methods section) |
processing, data adjustments and weighting of data sources, and mathematical or statistical model(s).

Describe how candidate models were evaluated and how the final model(s) were selected.

Provide the results of an evaluation of model performance, if done, as well as the results of any relevant sensitivity analysis.

Describe methods for calculating uncertainty of the estimates. State which sources of uncertainty were, and were not, accounted for in the uncertainty analysis.

State how analytic or statistical source code used to generate estimates can be accessed.

Provide published estimates in a file format from which data can be efficiently extracted.

Report a quantitative measure of the uncertainty of the estimates (e.g. uncertainty intervals). Risk-outcome scores; star ratings; risk curves with all data points, trimmed data points, and conventional and conservative uncertainty intervals; and an interpretation of the findings are available for all risk-outcome pairs at http://vizhub.healthdata.org/burden-of-proof

Interpret results in light of existing evidence. If updating a previous set of estimates, describe the reasons for changes in estimates.

Discuss limitations of the estimates. Include a discussion of any modelling assumptions or data limitations that affect interpretation of the estimates.

Results and Discussion

Provide published estimates in a file format from which data can be efficiently extracted.

Report a quantitative measure of the uncertainty of the estimates (e.g. uncertainty intervals). Risk-outcome scores; star ratings; risk curves with all data points, trimmed data points, and conventional and conservative uncertainty intervals; and an interpretation of the findings are available for all risk-outcome pairs at http://vizhub.healthdata.org/burden-of-proof

Interpret results in light of existing evidence. If updating a previous set of estimates, describe the reasons for changes in estimates.

Discuss limitations of the estimates. Include a discussion of any modelling assumptions or data limitations that affect interpretation of the estimates.

Code is accessible on GitHub: https://github.com/ihmeuw-msca/burden-of-proof

Supplementary Table 7. Causal criteria extraction template

| Category          | Variable           | Definition                                                                 |
|-------------------|--------------------|-----------------------------------------------------------------------------|
| Source            | seq                |                                                                             |
|                   | underlying_nid     | Underlying NID: Enter the underlying NID of the study (if applicable). Always talk to a data indexer if you don't know if an underlying NID is needed. They may be used for meta-analyses, certain database sources, and in some other specific cases. |
|                   | nid                | Found in GHDx, created through the epi form, or created by Data Indexer       |
|                   | field_citation_value | IHME Zotero format or if source has NID, citation info from GHDx             |
|                   | file_path          | optional; full file path of article; Only needed if source doesn't have NID, to facilitate NID creation. |
| R-O pair          | risk               | Risk: Select the risk factor, if not listed here, contact the causal criteria team |
|                   | risk_mapping       | The relationship between study definition of risk and GBD definition of risk for a particular effect size |
|                   | outcome            | Outcome: Select the outcome.                                                |
|                   | outcome_mapping    | The relationship between study definition of outcome and GBD definition of outcome for a particular effect size |
|                   | location_name      | Location name (from locations tab). Do a fast double-click in this field to get the drop-down menu, then start typing the location_name. For location_names with special characters, you may need to use the scroll bar. |
|                   | location_id        | Autopopulated from location_name                                            |
| Location          | rep_geography      | Were the study participants representative of the geography? 1=yes, 0=no      |
|                   | rep_selection_criteria | If rep_geography is 0, please specify the selection criteria of the study that is used in the analysis |
|                   | rep_prevalent_disease | Is the study aiming to evaluate the risk or mortality of people who have already developed the outcome? 1=yes 0=no (i.e. yes if for SBP-IHD paper, all participants have IHD at baseline and the paper is looking at mortality due to SBP, no if for SBP-IHD paper the participants have other prevalent diseases) |
| Study Population  | year_start_study   | Year the study was started. If not specified, leave blank                   |
|                   | year_end_study     | Year the study was finished (including most recent follow up). If not specified, leave blank |
|                   | age_start          | Ages from 1 and above must be entered as an integer. Ages <1 can be entered as decimal values, e.g., 3 days = 3/365. |
|                   | age_end            | Ages from 1 and above must be entered as an integer. Ages <1 can be entered as decimal values, e.g., 3 days = 3/365. |
| Category       | Variable       | Definition                                                                 |
|----------------|----------------|---------------------------------------------------------------------------|
|                | age_mean       | Mean age                                                                  |
|                | age_sd         | SD of age                                                                  |
|                | age_issue      | 0 = no issue flagged; 1 = issue flagged for modeler; always include       |
|                |                | explanatory notes the note_SR column                                      |
|                | percent_male   | What percent of the population is male (0-1), if pop is all female then   |
|                | sex_issue      | it would be 0                                                              |
| Study Design   | design         | Study design: Specify the design of the study                             |
|                | study_name     | Study Name: Enter the name of the study (e.g., Nurses' Health Study),     |
|                |                | if provided. Do not enter the title of the article.                       |
| Exposure       | exp_assess_level| Level of exposure assessment: The exposure was assessed…                  |
|                | exp_instrument | Exposure assessment instrument: Specify the name of the exposure          |
|                |                | assessment instrument. For self-reported exposures, please specify the     |
|                |                | name of the questionnaire e.g., International Physical Activity           |
|                |                | Questionnaire (IPAQ). If more than one instrument specify all             |
|                | exp_assess_period| What was the frequency of exposure assessment?                            |
|                | exp_assess_num | If multiple, specify the number of times that exposure was assessed        |
|                | exp_method_1   | (excluding baseline)                                                      |
|                | exp_method_2   | Please specify the method of exposure assessment. If there are more than   |
|                | exp_method_3   | 1, please add in the next columns labeled "exp_method_2".                 |
|                | exp_assess_period| This field describes the unit of exposure recall used in data collection  |
|                |                | ONLY for self-report. Select the correct option from the drop-down menu.  |
|                |                | If the unit is days, weeks, months, or years, please enter the number in   |
|                |                | exp_recall_period_value (next column). If the unit is 'lifetime', nothing  |
|                |                | needs to be entered in exp_recall_period_value. For example, if the study  |
|                |                | said the recall period was 4 weeks, enter 4 in exp_recall_period_value,    |
|                |                | and 'weeks' in the field exp_recall_period. If 'other' is selected, please |
|                |                | describe in exp_recall_period_other                                      |
|                | exp_recall_period_value| If you entered days, weeks, months, or years in the field                |
|                |                | 'exp_recall_period', please enter the corresponding integer in this field. |
|                |                | For example, if the study said the recall period was 4 weeks, enter 4 in   |
|                |                | exp_recall_period_value, and 'weeks' in the field exp_recall_period.       |
|                | exp_recall_period_other| If 'other' was selected in exp_recall_period, please describe the         |
|                |                | exposure recall period that the study specified (e.g., recall of exposure   |
|                |                | from 12 to 18 years).                                                     |
|                | exp_type       | Which form of the exposure was included in relative risk estimation        |
|                |                | analysis?                                                                 |
| Outcome        | outcome_def    | Outcome definition: Provide a brief description of the outcome as          |
|                |                | reported in the study.                                                    |
|                | outcome_type   | Outcome type: please specify if the outcome definition included           |
|                |                | incidence of or mortality from a disease endpoint                         |
|                | outcome_assess_1| Method of outcome assessment: Specify the method of assessment of the      |
|                |                | study outcome. If more than 1 are appropriate, enter additional methods in |
|                |                | the next column labeled "outcome_assess_2".                               |
|                | outcome_assess_2| Method of outcome assessment: Specify the method of assessment of the      |
|                |                | study outcome. If more than 2 are appropriate, enter additional methods in |
|                |                | the next column labeled "outcome_assess_3".                               |
|                | outcome_assess_3| Method of outcome assessment: Specify the method of assessment of the      |
|                |                | study outcome.                                                             |
| Follow up      | duration_fup_measure| Type of follow up measure (i.e. mean, median, max, min)                    |
|                | duration_fup_units| Units of follow up duration                                                |
|                | value_of_duration_fup| Enter the length of participant follow-up.                                |
| Confounders    | confounders_age| If controlled for in the relative risk estimation analysis, mark 1 for yes.|
|                |                | Mark 0 for no                                                              |
|                | confounders_sex| If controlled for in the relative risk estimation analysis, mark 1 for yes. |
|                |                | Mark 0 for no                                                              |
|                | confounders_education| If controlled for in the relative risk estimation analysis, mark 1 for yes. |
|                |                | Mark 0 for no                                                              |
|                | confounders_income| If controlled for in the relative risk estimation analysis, mark 1 for yes. |
|                |                | Mark 0 for no                                                              |
|                | confounders_smoking| If controlled for in the relative risk estimation analysis, mark 1 for yes.|
|                |                | Mark 0 for no
| Category | Variable | Definition |
|----------|----------|------------|
|          | confounders_alcohol_use | If controlled for in the relative risk estimation analysis, mark 1 for yes. Mark 0 for no |
|          | confounders_physical_activity | If controlled for in the relative risk estimation analysis, mark 1 for yes. Mark 0 for no |
|          | confounders_dietary_components | If controlled for in the relative risk estimation analysis, mark 1 for yes. Mark 0 for no |
|          | confounders_bmi | If controlled for in the relative risk estimation analysis, mark 1 for yes. Mark 0 for no |
|          | confounders_hypertension | If controlled for in the relative risk estimation analysis, mark 1 for yes. Mark 0 for no |
|          | confounders_diabetes | If controlled for in the relative risk estimation analysis, mark 1 for yes. Mark 0 for no |
|          | confounders_hypercholesterolemia | If controlled for in the relative risk estimation analysis, mark 1 for yes. Mark 0 for no |
|          | confounders_other | For other confounders that are not listed, list here |
|          | page_num_effect_size | Page number (where you found effect_size) from literature, or survey question where you found effect_size; Use page number(s) of article, not page # of pdf |
|          | effect_size_measure | Effect size measure: Specify the measure of effect size |
|          | effect_size | Effect size estimate: Provide the effect size estimate |
|          | lower | Provide the lower limit of the confidence interval. Enter on a "per 1" basis. (If the CI is reported as a percent, you must convert to a decimal.) These 3 fields must all be filled in if any of them are filled in: lower, upper, uncertainty_type_value. |
|          | upper | Provide the upper limit of the confidence interval. Enter on a "per 1" basis. (If the CI is reported as a percent, you must convert to a decimal.) These 3 fields must all be filled in if any of them are filled in: lower, upper, uncertainty_type_value. |
|          | CI_uncertainty_type_value | This field is required if 'lower' & 'upper' are entered. This column represents the confidence level which is reported at (Eg. 95, 90, 99). These 3 fields must all be filled in if any of them are filled in: lower, upper, uncertainty_type_value. |
|          | nonCI_uncertainty_value | Numerical value of the nonCI_uncertainty_type entered in that column. For example, if SD=5.3, you'd put 5.3 in this column, and choose SD from the drop-down menu in nonCI_uncertainty_type. |
|          | nonCI_uncertainty_type | Enter SE or SD if appropriate. For example, if SD=5.3, you'd put 5.3 in nonCI_uncertainty_value, and choose SD from the drop-down menu in this column (nonCI_uncertainty_type). |
|          | uncertainty_issue | Mark with a 1 if no uncertainty is reported, if some sort of uncertainty is reported, mark 0 |
|          | subgroup_analysis | 1 if RR is from main analysis (all participants), 0 if sub-analysis (only males, or among a specific age group, etc.) |
|          | subgroup_analysis_free_text | If a sub-analysis, describe it (i.e., age, sex, etc.) |
|          | effect_size_multi_location | 1 if the reported effect size is from a multi-country study and only one effect size has been reported for all locations, otherwise 0 |
|          | effect_size_multi_location_specify | Which geography level is the RR for |
|          | pooled_cohort | 1 if the reported effect size is from a pooled analysis and only pooled effect size has been reported, otherwise 0 |
|          | dose_response | Does the study support a dose-response relationship between the exposure and the outcome? (1= yes, 0=no) |
|          | dose_response_detail | If "1" was specified in the dose_response field, please specify in this field the type of evidence supporting the dose-response relationship. For example, "statistically significant p value for linear trend". |
|          | cohort_person_years_exp | Please specify the person-years of follow up in the exposed group |
|          | cohort_person_years_unexp | Please specify the person-years of follow up in the unexposed group |
|          | cohort_person_years_total | Enter the total person-years of follow-up if person-years of follow up in exposed and unexposed not reported |
|          | cohort_number_events_exp | Please specify the number of events in the exposed group |
|          | cohort_number_events_unexp | Please specify the number of events in the unexposed group |
|          | cohort_number_events_total | Enter the total number of events/cases if number of events in exposed and unexposed not reported |
|          | cohort_sample_size_exp | Please specify the number of people in the exposed group if person-years of follow up in exposed not reported |
| Category | Variable | Definition |
|----------|----------|------------|
| cohort_sample_size_unexp | Please specify the number of people in the unexposed group if person-years of follow up in unexposed not reported |
| cohort_sample_size_total | Please specify the number of people included in the analysis if total person-years of follow up is not reported |
| cohort_dropout_rate | Dropout rate: Specify the dropout rate (%) at the end of the study. Enter on a "per 1" basis. For example: 23% is entered as .23. |
| cohort_dropout_assess | Specify how dropout rate was defined in the study. |
| cohortExposed_def | Exposed group definition: Provide a brief description of the exposed group (i.e., the comparison group) as used in estimation of the relative risk (e.g., never smokers) |
| cohortExp_unit_rr | Exposure unit (for continuous risks): Specify the unit of exposure (e.g., grams/day). |
| cohortExp_level_rr | Exposure level in the exposed group (for continuous risks): Specify the mean/median level of exposure in the exposed group. |
| cohortUnexp_def | Unexposed group definition: Provide a brief description of the unexposed group (i.e., the comparison group) as used in estimation of the relative risk (e.g., never smokers) |
| cohortUnexp_unit_rr | Exposure unit (for continuous risks): Specify the unit of exposure (e.g., grams/day) for the unexposed group. |
| cohortUnexp_level_rr | Exposure level in the unexposed group (for continuous risks): Specify the mean/median level of exposure in the unexposed group. |
| ccCommunity | Were the controls selected from the community? 1 = yes, 0 = no |
| cc_cases | Number of cases |
| ccControl | Number of controls |
| ccExposed_def | Exposed group definition: Provide a brief description of the exposed group for which the relative risk is reported (e.g., current smokers) |
| ccExp_unit_rr | Exposure unit (for continuous risks): Specify the unit of exposure (e.g., grams/day). |
| ccExp_level_rr | Exposure level in the exposed group (for continuous risks): Specify the mean/median level of exposure in the exposed group. |
| cc_unexposed_def | Unexposed group definition: Provide a brief description of the unexposed group (i.e., the comparison group) as used in estimation of the relative risk (e.g., never smokers) |
| cc_unexp_unit_rr | Unexposed unit (for continuous risks) |
| cc_unexp_level_rr | Exposure level in the unexposed group (for continuous risks): Specify the mean/median level of exposure in the unexposed group. |
| ccExp_level_dr | Exposure level in for dose-repose RRs (for continuous risks): If the study reports dose-repose RR, please specify the level of exposure for the reported RR |
| int_intervention_description | Intervention definition: Provide a brief description of the intervention as reported in the study. |
| int_control_description | Control definition: Provide a brief description of the control as reported in the study. |
| int_intervention_multi_rf | Does this intervention simultaneously target more than one risk? (1 = yes, 0 = no) |
| int_intervention_multi_rfSpecify | Specify the risks that are targeted by the intervention |
| int_intervention_level | Level of intervention: The intervention was implemented … |
| intAdhere_assess | Specify how adherence was defined in the study. |
| intAdhere_rate_intervention | Adherence rate in the intervention group; Enter on a "per 1" basis. For example: 23% is entered as .23. |
| intAdhere_rate_control | Adherence rate in the control group; Enter on a "per 1" basis. For example: 23% is entered as .23. |
| int_dropout_rate_intervention | Dropout rate in the intervention group: Specify the dropout rate (%) at the end of the study. Enter on a "per 1" basis. For example: 23% is entered as .23. |
| int_dropout_rate_control | Dropout rate in the control group: Specify the dropout rate (%) at the end of the study. Enter on a "per 1" basis. For example: 23% is entered as .23. |
| int_dropout_assess | Specify how dropout rate was defined in the study. |
| int_blinding | For interventional studies. Blinding: The trial was … (select 1) |
| int_exp_unit | For trials, specify the unit of exposure (e.g., mmol/l) |
| Category | Variable                                | Definition                                                                                                                                 |
|----------|-----------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------|
|          | int_baseline_exp_int                    | For trials, specify the exposure level in the intervention group at baseline                                                                |
|          | int_baseline_exp_comp                   | For trials, specify the exposure level in the comparison group at baseline                                                                  |
|          | int_fup_exp_int                         | For trials, specify the exposure level in the intervention group at the end of the follow-up time                                               |
|          | int_fup_exp_comp                        | For trials, specify the exposure level in the comparison group at the end of follow up time                                                  |
|          | int_fup_exp_int_difference              | For trials, please specify the difference of exposure level between baseline and follow up time for the intervention group                   |
|          | int_fup_exp_comp_difference             | For trials, please specify the difference of exposure level between baseline and follow up time for the comparison group                   |
|          | int_person_years_int                    | Please specify the number of person years of follow up for the intervention group                                                           |
|          | int_person_years_comp                   | Please specify the number of person years of follow up in the comparison group                                                             |
|          | int_number_events_int                   | For trials, specify the number of cases in the intervention group at the end of follow up                                                    |
|          | int_number_events_comp                  | For trials, specify the number of cases in the control group at the end of follow up                                                        |
|          | int_sample_size_int_group_baseline      | For trials, specify the sample size in the intervention group at baseline                                                                    |
|          | int_sample_size_comparison_group_baseline| For trials, specify the sample size in the comparison group at baseline                                                                     |
|          | int_sample_size_int_group_follow_up     | For trials, specify the sample size in the intervention group at the end of the follow-up time                                               |
|          | int_sample_size_comparison_group_follow_up| For trials, specify the sample size in the comparison group at the end of follow up time                                                    |
| Other    | note_modeler                            | For modelers only, audience is modeler, not for correspondence                                                                               |
|          | note_sr                                 | notes related to extraction, including assumptions, data adjustment, problems with source, any other notes that may be relevant, etc.       |
|          | extractor                               | Identifier (uwnet id) of person who extracted the data                                                                                      |
| Custom   | custom_exp_meas_num                     | If the exposure level was assessed multiple times at a given time point (e.g., systolic blood pressure), specify the number of measurements at each time point. |
|          | custom_exp_biomarker                    | If the exposure level was assessed via a biomarker, specify the full name of the biomarker.                                                 |
|          | custom_exp_kilometer                    | Specify the geographical unit of measurement in kilometer (if applicable, e.g., satellite data).                                           |
|          | custom_exp_level_lower                  | If don't have a mean/midpoint exposure level can use this column in conjecture with the custom exp_level_upper to enter in a range         |
|          | custom_exp_level_upper                  | If don't have a mean/midpoint exposure level can use this column in conjecture with the custom exp_level_lower to enter in a range         |
|          | custom_unexp_level_lower                | If don't have a mean/midpoint exposure level can use this column in conjecture with the custom outcome_level_upper to enter in a range     |
|          | custom_unexp_level_upper                | If don't have a mean/midpoint exposure level can use this column in conjecture with the custom outcome_level_lower to enter in a range     |
|          | custom_prospective_lag                  | Specify lag time between exposure assessment and outcome                                                                                  |
|          | custom_age_demographer                  | A binary flag to identify if ages are presented in demographer notation or not in the source. This value is currently not used to adjust any age_start or age_end values, but in the future, that is the intention; 0 = article does not use demographer notation (4 = 4.00 not 4.99); 1 = article uses demographer notation (4=4.99 not 4.00) |
|          | custom_bmi_menopause_free_text          | Free text field for bmi team                                                                                                                |
|          | custom_cvd_outcome                      | Used for mapping cvd outcomes, free text field                                                                                             |
|          | custom_dm_type                          | Used for documenting diabetes type                                                                                                          |
|          | custom_dm_case_defn                     | Used for documenting diabetes definitions, free text                                                                                       |
|          | custom_pmid                             | Document PubMed id                                                                                                                         |
|          | custom_cvd_rep_high_risk                | CVD-specific, binary, if the study only includes people at high risk for CVD (1 for example if it is only among diabetics)                |
|          | custom_drug_class                       | Class of drug being used in intervention, free text                                                                                       |
|          | custom_outcome_primary                  | Outcome is the primary outcome of RCT (1=yes, 0=no)                                                                                       |
|          | custom_outcome_prespecified             | Outcome is the prespecified outcome of RCT (1=yes, 0=no)                                                                                   |
|          | custom_multipollutant                   | Are any other pollutants controlled for in the model? 0=no, 1=yes                                                                            |
|          | custom_pollutants_controlled            | If custom_multipollutant=1, list the pollutants controlled for                                                                               |
| Category                  | Variable                        | Definition                                                                 |
|---------------------------|---------------------------------|---------------------------------------------------------------------------|
|                           | custom_PM2.5_model_type         | Describe the model used for exposure                                      |
|                           | custom_assign_method            | How do researchers assign participants to exp? (ex: by home address,      |
|                           |                                 | by city, nearest zipcode centroid, etc.)                                  |
|                           | custom_PM2.5_def                | What metric are they using to measure PM2.5 (ex: mean of annual          |
|                           |                                 | PM2.5 averages for 35-1 year prior to study)                              |
|                           | custom_lag                      | Do the authors take into account lag? If so, how?                        |
|                           | custom_PM2.5_min                | All of these have to do with the spread of the PM2.5 exposure covered    |
|                           |                                 | by the study. Minimum                                                     |
|                           | custom_PM2.5_5th                | 5th percentile                                                            |
|                           | custom_PM2.5_25th               | 25th percentile                                                            |
|                           | custom_PM2.5_50th               | Median/50th percentile                                                    |
|                           | custom_PM2.5_75th               | 75th percentile                                                            |
|                           | custom_PM2.5_95th               | 95th percentile                                                            |
|                           | custom_PM2.5_max                | Maximum                                                                   |
|                           | custom_PM2.5_mean               | Mean                                                                       |
|                           | custom_PM2.5_stddev             | Standard deviation                                                         |
|                           | custom_PM2.5_other_measure      | Any other measures of the distribution of PM2.5 amongst participants?     |
|                           | custom_PM2.5_other_measure_description | If so, what are they? (e.g., 10th, 90th, IQR)                            |
Supplementary Table 8. Study covariates assessed in the analysis

| Domain                      | Covariate name          | Definition                                                                                     | Completeness (%)* |
|-----------------------------|-------------------------|------------------------------------------------------------------------------------------------|-------------------|
| Representativeness          | Representativeness      | Scored 0 for studies whose results are likely generalizable to the general population because the sample was based on the general population with reasonable exclusions for pre-existing disease states and 1 for analyses in sub-groups such as high-risk groups | 100               |
| Exposure measurement        | Exposure population     | Scores 0 for individual level exposure and 1 for population level exposure                     | 100               |
|                             | Exposure self-report    | Scores 0 for measurements based on assays, tests or physician observation and 1 for self-report | 100               |
|                             | Exposure study          | Scores 0 if exposure was measured multiple times and 1 for only a baseline measurement. In RCTs score the study as 0 | 100               |
| Outcome measurement         | Outcome self-report     | Scores 0 if the outcome measurement was based on death certificates or medical records and scores 1 if based on self-report | 100               |
|                             | Outcome unblinded       | Scores 0 if the assessment of outcome is blind to the individual level of exposure or vice versa for outcome and 1 if unblinded | 100 (of RCTs)     |
|                             | Outcome definition      | One dummy variable per definition of the outcome including ischemic heart disease, coronary heart disease angina, revascularization, was generated. | 100               |
|                             | Outcome type            | Incidence or mortality                                                                         | 100               |
| Reverse causation           | Reverse causation       | Scores 0 if there is minimal or no risk of reverse causation and 1 if there is a risk of reverse causation. | 64                |
| Control for confounding     | Confounding_nonrandom   | Scores 0 for a randomized study and 1 for a non-randomized study                                | 95.3              |
|                             | Confounding_uncontrolled | Scores 0 for randomization or for a non-randomized study but the outcome is controlled for all major known confounders including age, sex, smoking, education, income, body mass index and/or cholesterol measurements and other critical determinants of that outcome. Scores 1 for non-randomized with control for age, sex, and other critical determinants of that outcome. Scores 2 if only controls for age and sex and select determinants | 44.4              |
|                             | Blinding                | Scores 0 for RCTs double or triple blinded, 1 for single blinding and 2 for no blinding         | 100               |
| Selection bias              | Selection bias          | Scores 0 for greater than 95% follow-up, scores 1 for follow up of 85-95% and scores 2 for less than 85% follow up | 92                |
| Study type                  | Trials                  | Scores 0 for RCTs and 1 for other study types                                                   | 100               |
|                             | Cohorts                 | Scores 0 for cohorts or pull cohorts and 1 for other study types                               | 100               |
| Risk measurement            | Risk measurement        | Dummy variables were created to identify studies reporting hazard ratios, relative risks and odds ratio. | 100               |

*Completeness of a covariate was defined as the percentage of studies included in the analysis reporting relevant information.

Section 2: Data source identification
The data used for this study includes randomized control trials (RCTs) and pooled cohort studies. More detailed information on data inputs is provided in the online viz tool: http://vizhub.healthdata.org/burden-of-proof.
Section 2.1 Literature studies
We conducted a literature review to obtain input data from randomized control trials evaluating the relationship between systolic blood pressure levels and ischemic heart disease. We also searched citation lists of the most recent systematic reviews of clinical trials.

Section 2.1.1 PubMed search
A literature search was performed on PubMed using the following search string. Inclusion and exclusion criteria are described in the Methods section of the main text.

Search string
("blood pressure"[Title/Abstract] OR "blood pressure"[MeSH Terms] OR "antihypertensive"[Title/Abstract] OR "blood pressure-lowering"[Title/Abstract] OR "blood pressure-lowering"[Title/Abstract] OR "antihypertensive agents"[MeSH Terms] OR "Ambrisentan"[Text Word] OR "Bosentan"[Text Word] OR "Diazoxide"[Text Word] OR "iloprost"[Text Word] OR "Minoxidil"[Text Word] OR "Sildenafil"[Text Word] OR "sodium nitroprusside"[Text Word] OR "Tadalafil"[Text Word] OR "Methyldopa"[Text Word] OR "Clonidine"[Text Word] OR "moxonidine"[Text Word] OR "Guanethidine"[Text Word] OR "Doxazosin"[Text Word] OR "Indoramin"[Text Word] OR "Prazosin"[Text Word] OR "Terazosin"[Text Word] OR "Phenoxybenzamine"[Text Word] OR "Phentolamine"[Text Word] OR "Atenolol"[Text Word] OR "Metoprolol"[Text Word] OR "Pindolol"[Text Word] OR "Timolol"[Text Word] OR "Oxyprenolol"[Text Word] OR "Nebivolol"[Text Word] OR "Nadolol"[Text Word] OR "Labetalol"[Text Word] OR "Celiprolol"[Text Word] OR "Carvedilol"[Text Word] OR "Bisoprolol"[Text Word] OR "Propranolol"[Text Word] OR "Hydrochlorothiazide"[Text Word] OR "Trichlormethiazide"[Text Word] OR "Spirolonactone"[Text Word] OR "Chlortalidone"[Text Word] OR "Indapamide"[Text Word] OR "Captopril"[Text Word] OR "Cilazapril"[Text Word] OR "Enalapril"[Text Word] OR "Enalapril"[Text Word] OR "Imidapril"[Text Word] OR "Lisinopril"[Text Word] OR "Moexipril"[Text Word] OR "Perindopril"[Text Word] OR "Quinapril"[Text Word] OR "Ramipril"[Text Word] OR "Trandolapril"[Text Word] OR "Azilsartan"[Text Word] OR "Candesartan"[Text Word] OR "Eprosartan"[Text Word] OR "Irbesartan"[Text Word] OR "Losartan"[Text Word] OR "Olmesartan"[Text Word] OR "Telmisartan"[Text Word] OR "Valsartan"[Text Word] OR "Aliskiren"[Text Word] OR "Amlodipine"[Text Word] OR "Diltiazem"[Text Word] OR "Felodipine"[Text Word] OR "Isradipine"[Text Word] OR "Lacidipine"[Text Word] OR "Lercanidipine"[Text Word] OR "Nicardipine"[Text Word] OR "Nifedipine"[Text Word] OR "Nisoldipine"[Text Word] OR "Verapamil"[Text Word] OR "Nitrendipine"[Text Word]) AND "clinical trial"[Publication Type] AND 2018/2/1:2020/4/1[Date - Publication]
Section 3: Sensitivity analysis

Section 3.1. Model results based on input data: testing cohort studies vs RCTs

To estimate the shape of the risk-outcome relationship directly from the data and to validate using evidence from both prospective cohort studies and RCTs, we performed a sensitivity analysis as follows. We first modeled a non-linear curve including only data from cohort studies without monotonicity constraints, not assuming a log-linear relationship. We then fit a similar model from RCT data only (see figures below). We decided to use all available data combining evidence from different study designs given that 1) RCTs are a rich source of exposure and outcome information, 2) most of the SBP population evidence typically comes from populations at high IHD risk and/or with treated high blood pressure, 3) cohort studies account for populations with normal and below normal SBP levels, and 4) the shape of the relationship without constraints was remarkably similar across all models. See Extended Data Figures 6–9 for results.