

Disclaimer: The manuscript and its contents are confidential, intended for journal review purposes only, and not to be further disclosed.

URL: <https://circ-submit.aha-journals.org/>

Manuscript Number: CIRCULATIONAHA/2021/056546R3

Title: Blood Pressure, Hypertension and The Risk of Aortic Dissection Incidence and Mortality: results from the Japan-Specific Health Checkups Study, the UK Biobank Study and a Meta-analysis of Cohort Studies

Authors:

Makoto Hibino (St Michael's Hospital, University of Toronto)
Yoichiro Otaki (Yamagata University School of Medicine)
Elsa Kobeissi (American University of Beirut, Beirut, Lebanon)
Han Pan (Imperial College London)
Hiromi Hibino (Imperial College London)
Henock Taddese (Imperial College London)
Azeem Majeed (Imperial College London)
Subodh Verma (St Michael's Hospital, University of Toronto)
Tsuneo Konta (Yamagata University School of Medicine, Yamagata, Japan)
Kunihiro Yamagata (University of Tsukuba)
Shouichi Fujimoto (University of Miyazaki)
Kazuhiko Tsuruya (Nara Medical University)
Ichiei Narita (Niigata University Medical and Dental Hospital)
Masato Kasahara (Nara Medical University Hospital)
Yugo Shibagaki (St Marianna University School of Medicine)
Kunitoshi Iseki (Nakamura Clinic)
Toshiki Moriyama (Osaka University)
Masahide Kondo (University of Tsukuba)
Koichi Asahi (Iwate Medical University)
Tsuyoshi Watanabe (Fukushima Medical University)
Tetsu Watanabe (Yamagata University School of Medicine)
Masafumi Watanabe (Yamagata University School of Medicine)
Dagfinn Aune (Imperial College London)

Blood Pressure, Hypertension and The Risk of Aortic Dissection Incidence
and Mortality: results from the Japan-Specific Health Checkups Study, the
UK Biobank Study and a Meta-analysis of Cohort Studies

Running title: BP, Hypertension and Risk of Aortic Dissection

Makoto Hibino, MD, PhD^{1,2,3,4}, Yoichiro Otaki, MD, PhD⁵, Elsa Kobeissi, MPH³, Han Pan, MPH³,
Hiromi Hibino, MD, MPH⁴, Henock Taddese, PhD⁴, Azeem Majeed, MD⁴, Subodh Verma, MD, PhD^{1,2},
Tsuneo Konta, MD, PhD⁶, Kunihiro Yamagata, MD, PhD⁶, Shouichi Fujimoto, MD, PhD⁶, Kazuhiko
Tsuruya, MD, PhD⁶, Ichiei Narita, MD, PhD⁶, Masato Kasahara, MD, PhD⁶, Yugo Shibagaki, MD, PhD⁶,
Kunitoshi Iseki, MD, PhD⁶, Toshiki Moriyama, MD, PhD⁶, Masahide Kondo, MD, PhD⁶, Koichi Asahi,
MD, PhD⁶, Tsuyoshi Watanabe, MD, PhD⁶, Tetsu Watanabe, MD, PhD⁵, Masafumi Watanabe, MD,
PhD⁵ Dagfinn Aune, MSc, PhD^{3,7,8,9}

¹ Division of Cardiac Surgery, St Michael's Hospital, University of Toronto, 30 Bond St, Toronto, ON

M5B 1W8, Canada

² Department of Surgery, University of Toronto, 27 King's College Cir, Toronto, Ontario, M5S 1K1,

Canada

³ Department of Epidemiology and Biostatistics, School of Public Health, Imperial College London,

St. Mary's Campus, Norfolk Place, London, W2 1PG, UK

1 ⁴ Department of Primary Care and Public Health, School of Public Health, Imperial College London,
2 Charing Cross Campus, St Dunstan's Road, London, W6 8RP, UK

3 ⁵ Department of Cardiology, Pulmonology, and Nephrology, Yamagata University School of
4 Medicine, Japan

5 ⁶ The Japan Specific Health Checkups study (J-SHC study) Group, Japan

6 ⁷ Department of Nutrition, Bjørknes University College, Oslo, Norway

7 ⁸ Department of Endocrinology, Morbid Obesity and Preventive Medicine, Oslo University Hospital,
8 Oslo, Norway

9 ⁹ Unit of Cardiovascular and Nutritional Epidemiology, Institute of Environmental Medicine,
10 Karolinska Institutet

12 Corresponding author: Makoto Hibino, MD, MPH, PhD. Tel 1-416-864-5997, Fax 1-416-864-5881

13 email mhibino-ngy@umin.org

14 30 Bond St, Toronto, Ontario, M5B1W8, Canada

15 Word Count =4778

16

1 **Abstract**

2 **Background**

3 Hypertension or elevated blood pressure (BP) is an important risk factor for aortic dissection (AD);
4 however, few prospective studies concerning this topic have been published. We investigated the
5 association between hypertension/elevated BP and AD in two cohorts and conducted a
6 meta-analysis of published prospective studies, including these two studies.

7 **Methods**

8 We analyzed data from the Japan Specific Health Checkups (J-SHC) Study and UK Biobank, which
9 prospectively followed 534,378 and 502,424 participants, respectively. Multivariable Cox
10 regression was used to estimate hazard ratios (HRs) and 95% confidence intervals (95% CIs) for the
11 association of hypertension/elevated BP with AD incidence in the UK Biobank and AD mortality in
12 the J-SHC Study. In the meta-analysis, summary relative risks (RRs) were calculated using random
13 effects models. A potential nonlinear dose-response relationship between BP and AD was tested
14 using fractional polynomial models, and the best-fitting second-order fractional polynomial
15 regression model was determined.

16 **Results**

17 In the J-SHC Study and UK Biobank, there were 84 and 182 ADs during 4- and 9-year follow-up, and
18 the adjusted HRs of AD were 3.57 (95% CI, 2.17-6.11) and 2.68 (95% CI: 1.78-4.04) in hypertensive

individuals, 1.33 (95% CI: 1.05-1.68) and 1.27 (95% CI: 1.11-1.48) per 20-mmHg increase in systolic BP (SBP), and 1.67 (95% CI: 1.40-2.00) and 1.66 (95% CI: 1.46-1.89) per 10-mmHg increase in diastolic BP (DBP), respectively. In the meta-analysis, the summary RRs were 3.07 (95% CI 2.15-4.38, $I^2=76.7\%$, $n=7$ studies, 2,818 ADs, 4,563,501 participants) for hypertension and 1.39 (95% CI: 1.16-1.66, $I^2=47.7\%$, $n=3$) and 1.79 (95% CI: 1.51-2.12, $I^2=57.0\%$, $n=3$) per 20-mmHg increase in SBP and per 10-mmHg in DBP, respectively. The AD risk showed a strong, positive dose-response relationship with SBP and even more so with DBP. The risk of AD in the nonlinear dose-response analysis was significant at SBP >132 mmHg and DBP >75 mmHg.

Conclusions

Hypertension and elevated SBP and DBP are associated with a high risk of AD. The risk of AD was positively dose-dependent, even within the normal BP range. These findings provide further evidence for the optimization of BP to prevent AD.

Keywords

Blood pressure, Hypertension, Aortic dissection, Cohort study, Dose response, Meta-analysis

Non-standard Abbreviations and Acronyms

- 1 AD: aortic dissection
- 2 BP: Blood pressure
- 3 BMI: Body mass index
- 4 CI: Confidence interval
- 5 DBP: Diastolic blood pressure
- 6 DM: Diabetes mellitus
- 7 NHS: National Health Service
- 8 PARp: Population-attributable risk percentage
- 9 RR: Relative risk
- 10 SBP: Systolic blood pressure

11

12 **Clinical Perspective**

13 1) What is new?

14 -The association of hypertension and systolic and diastolic blood pressure with incidence and
15 mortality of aortic dissection is robust and exponentially dose-dependent.

16 -The risk of aortic dissection was significant at systolic blood pressure >132 mmHg and diastolic
17 blood pressure >75 mmHg in the meta-analysis.

18 2) What are the clinical implications?

1 -Within the hypertension range, a low blood pressure may be associated with a low risk of aortic
2 dissection.

3 -Ideal blood pressure targets to reduce risk of aortic dissection may be even lower than the
4 threshold of hypertension.

5

Disclaimer: The manuscript and its contents are
confidential, intended for journal review purposes
only, and not to be further disclosed.

1 **Introduction**

2 Aortic dissection (AD) is a relatively rare but serious disease that often leads to catastrophic
3 complications or death.¹ The reported incidence of AD is 3-6 cases per 100,000 persons per year in
4 Europe and the United States.² To date, results from only a few epidemiological cohort studies
5 have been published on risk factors for AD because of the low incidence of the disease, which
6 would require large sample sizes and/or long follow-up periods to accrue sufficient numbers of
7 cases for statistical analyses. This has in turn limited our understanding regarding primary
8 prevention routes.

9 Hypertension is associated with aortic wall stress and is a risk factor for AD. A high prevalence
10 of hypertension was reported in patients who developed AD (67.3% to 76.6%).^{3,4} Most of the
11 previous studies which investigated the association of AD with hypertension were based on case
12 series.^{1,3,4} Only a few prospective cohort studies have assessed the association between blood
13 pressure (BP) or hypertension and AD⁵⁻⁸; however, these studies were often small in scale with a
14 limited number of AD cases and therefore had limited power to investigate the dose-response
15 relationship between systolic blood pressure (SBP) or diastolic blood pressure (DBP) and AD across
16 the full range of BP values. It is therefore important to clarify both the strength and shape of the
17 association between elevated BP or hypertension and the risk of AD, both from a clinical and
18 public health perspective as well as for risk assessment.

In the Global Burden of Disease Project, results regarding the association between elevated BP and aortic aneurysm have been incorporated in the most recent risk assessment⁹, but data regarding elevated BP and AD were not included, most likely due to the limited cohort data available as well as a lack of any meta-analyses summarizing the available evidence. To fill in these gaps, we analyzed data from two prospective cohort studies, each of which consists of approximately a half-million participants, conducted in Japan and the United Kingdom (UK). We then summarized the evidence from these two cohort studies along with previously published cohort studies in a systematic review and meta-analysis of prospective studies.

Methods

Japan Specific Health Checkups (J-SHC) study

The J-SHC study data can be accessed by researchers by submitting an application (Department of Chronic Kidney Disease Initiatives; Fukushima Medical University School of Medicine; 1-Hikarigaoka, Fukushima 960-1295, Japan; Phone & Fax: +81-24-547-1898; E-mail: dckdi@fmu.ac.jp) and receiving approval.

The J-SHC Study was based on individual risk assessments determined by the Specific Health Checkup for all inhabitants of Japan between 40 and 74 years old, which is covered by the

1 Japanese national health insurance system.¹⁰ The purpose of the Specific Health Checkup is to
2 maintain a healthy life through the prevention of life-style diseases, and it excludes people who
3 have been hospitalized for more than six months or who are living in a support facility or nursing
4 home. With permission from the Ministry of Health, Labour and Welfare, participant deaths were
5 identified by linking data from this study to a death certificate database that records all deaths that
6 occur in Japan. All participants were prospectively followed until they reached 75 years old.

7 Data used in this study were obtained from 664,927 men and women who participated in
8 health checkups from 2008 to 2015 in eastern and western Japan. Among the 664,927 individuals,
9 130,549 were excluded from this study due to a lack of essential data, including the SBP, DBP, body
10 mass index (BMI), smoking habit, alcohol consumption habit and antihypertensive and
11 antihyperglycemic medication. Therefore, 534,378 men and women were included in the statistical
12 analyses. The outcome was AD death, which was determined based on a review of the death
13 certificates and classified based on the death code until April 1, 2015 (I710 in International
14 Classification of Diseases, 10 code). At health checkups, participants were seated with back
15 support, and the BP was measured two times without conversation after resting for at least five
16 minutes. BP was determined by an average of two BP readings. Hypertension was defined as
17 SBP/DBP of $\geq 140/90$ mmHg or the use of antihypertensive medication. Diabetes mellitus (DM) was
18 defined as fasting plasma glucose ≥ 126 mg/dL and glycosylated hemoglobin A1c (HbA1c) $\geq 6.5\%$ or

1 use of antihyperglycemic medication. Dyslipidemia was defined as high-density lipoprotein
2 cholesterol (HDL-C) <40 mg/dL, low-density lipoprotein cholesterol (LDL-C) ≥140 mg/dL, and
3 triglycerides ≥150 mg/dL or use of lipid-lowering medication. The history of coronary artery
4 disease was determined based on self-report.

5 All procedures performed in the studies involving human participants were done in accordance
6 with the guidelines of the institutional ethics committee (Yamagata University, 2008, no. 103)
7 and/or the national research committee (the Ethical Guidelines for Medical and Health Research
8 Involving Human Subjects enacted by the Ministry of Health, Labour and Welfare of Japan;
9 [http://www.mhlw.go.jp/file/06-Seisakujouhou-10600000-Daijinkanboukouseikagakuka/000008027](http://www.mhlw.go.jp/file/06-Seisakujouhou-10600000-Daijinkanboukouseikagakuka/0000080278.pdf)
10 [8.pdf](http://www.mhlw.go.jp/file/06-Seisakujouhou-10600000-Daijinkanboukouseikagakuka/0000080278.pdf)). In the context of this guidance, the investigators were not required to obtain informed
11 consent, but we publicized information concerning this study on the web
12 (https://www.fmu.ac.jp/univ/sangaku/data/koukai_r02/2771.pdf) and ensured opportunities for
13 the research participants to refuse the use of their personal information.

14 Statistical analyses were performed using the JMP software program, version 12 (SAS Institute.,
15 Cary, NC, USA), and R 3.0.2 with additional packages including Rcmdr, Epi, pROC and PredictABEL.
16 Continuous and categorical variables were compared using a *t*-test and chi-square test,
17 respectively. Cox proportional hazard analysis was performed to obtain hazard ratios of AD death
18 for SBP and DBP (ordinal categorical and continuous variables) and hypertension adjusted for the

1 age, sex, BMI, smoking, region, dyslipidemia, diabetes mellitus and coronary artery disease. For
2 ordinal BP categories, the p-value for linear trend was also calculated using the Wald test. The
3 population-attributable risk percentage (PARp) was calculated as the percent of the incidence rate
4 of AD death in the entire population that could be attributed to an exposure. A p-value <0.05 was
5 considered statistically significant.

7 **UK Biobank**

8 The UK Biobank study data can be accessed by researchers by submitting an application
9 (<http://www.ukbiobank.ac.uk/register-apply/>) and receiving approval.

10 The UK Biobank was a large-scale prospective cohort study conducted to improve the
11 prevention, diagnosis and treatment of a range of diseases, and the data included in this study
12 were obtained from 502,424 participants ranging from 40-69 years of age from 2006 to 2010.¹¹
13 The UK Biobank received ethical approval from the North West Multi-Center Research Ethics
14 Committee (11/NW/03820). Participants were recruited using contact information obtained from
15 the National Health Service (NHS) in the UK. Invitations to participate in the study were sent via
16 post to 9 million people, and the UK Biobank enrolled voluntary participants, irrespective of their
17 health status, following the receipt of their written informed consent.

Following the enrollment of participants, the UK Biobank collected health-related data using questionnaires, physical examinations and biological samples in the initial assessment. Participants with a history of AD (n=63) were excluded from this analysis. The follow-up of the cohort was conducted through the linkage of routinely available national health records, such as death registrations and hospital inpatient episodes. The primary outcome of this study was the incidence of AD recorded as The International Classification of Disease 10 code I710 in the hospital admission or death record. The BP was measured at the initial assessment via a predetermined method (supplementary method), and hypertension was defined as BP $\geq 140/90$ mmHg or a diagnosis in the past. The medical history was determined based on self-reports at the initial assessment. Deprivation was based on the Townsend area deprivation index derived from UK census: positive and negative scores correspond to higher and lower levels of deprivation, respectively, than the national averages¹². Data were censored at the date of the AD diagnosis or death, death from any other cause, loss to follow-up or February 16, 2018, for England and Wales and December 16, 2017, for Scotland, whichever occurred first.

Statistical analyses were conducted using the software package Stata, version 14.1 (StataCorp, College Station, TX, USA). To compare participant's baseline characteristics, *t*-tests were used for continuous variables, and chi-squared tests were used for categorical variables. A chi-squared test for trend was used for ordinal categorical variables. Associations between the BP/hypertension and

1 risk of AD were investigated using Cox proportional hazards models with adjusting for the age, sex,
2 smoking status, connective tissue disease, BMI and DM. For ordinal BP categories, p-values for
3 linear trend were also calculated using the Wald test. Age- and sex-adjusted PARps were
4 subsequently calculated using the PUNAF Stata module.¹³ Associations between SBP and DBP and
5 the risk of AD adjusted using multivariable Cox proportional hazards regression models were
6 explored using restricted cubic splines with three knots, and nonlinearity of the associations was
7 tested. If the association was nonlinear, the exponential dose-response was tested. Adjusted
8 hazard ratios and 95% confidence intervals (CIs) for each unit of BP were computed and plotted
9 against the reference values: 120 mmHg for SBP and 80 mmHg for DBP. A p-value of <0.05 was
10 considered statistically significant.

11

12 **Systematic review and meta-analysis**

13 The systematic review and meta-analysis were conducted in accordance with the preferred
14 reporting items for systematic reviews and meta-analyses (PRISMA) guidelines. The study protocol
15 of our review was registered in PROSPERO, the international database of prospectively registered
16 systematic reviews (CRD42018096916). Three authors (MH, HH and DA) used PubMed and
17 EMBASE databases to search for relevant publications from the inception of the databases up to
18 May 17, 2021, and the search returns were screened by two of those authors (MH, HH). Details

concerning the search terms used can be found in Supplementary Table I.

One study⁸, which analyzed the association between type 2 DM and the incidence of AD but also contained data on hypertension, was identified in a separate search. Published retrospective or prospective cohort studies and nested case-control studies within prospective studies were eligible for inclusion. Publications with relative risk estimates (risk ratios, incidence rate ratios, odds ratios, or hazard ratios) for the association between BP and/or hypertension and the risk of AD adjusted for at least one confounding variable were included. For one study⁶ where the AD incidence data were available for hypertension and categorical BP stratified by a confounding variable, the Mantel–Haenszel method was used to calculate weighted-average relative risks for hypertension adjusted for the confounding variable with the 95% CI and logistic regression was used to calculate the adjusted odds ratio for each BP category. The results from the present J-SHC Study and UK Biobank analyses were included alongside the previously published studies in the meta-analysis.

The Random effects model by DerSimonian and Laird,¹⁴ which accounts for both within- and between-study variance, was used to calculate the summary relative risks (RRs) for the association between hypertension and BP and AD. As all the studies included in the analyses of SBP/DBP reported risk estimates on a continuous scale, these risk estimates were used directly for the nonlinear dose-response meta-analysis. A potential nonlinear dose-response relationship between

BP and AD was tested using fractional polynomial models, and the best-fitting second-order fractional polynomial regression model was determined.¹⁵ A likelihood ratio test was used to test nonlinearity by comparing the nonlinear and linear models.¹⁵ Asymmetry in the funnel plot was assessed by a visual inspection. The quality of the studies was evaluated with the relevant Newcastle-Ottawa scale.¹⁶ Subgroup analyses were conducted to clarify if the results were consistent across study characteristics (e.g. sex, duration of follow-up, geographic location, study quality, study outcome definition and adjustment for confounding factors) and random effects meta-regression analyses were used to test for differences between subgroups. To ensure that the results were not driven by one very large study or a study with an extreme result, sensitivity analyses were conducted by omitting one study at a time from the analyses and assessing the effect on the overall results.

Results

J-SHC Study

Among 534,378 participants, 84 died from AD during a median of 4.0 years follow-up (interquartile range: 2.7-5.0). The AD death rate was 4.18 per 100,000 person-years. Participants who died from AD were older and more likely to be male and smokers and had a higher SBP and DBP and higher prevalence of hypertension than participants without AD (Table 1). In the age- and sex-adjusted

1 Cox proportional hazards model, there were significant associations between the SBP, DBP,
2 hypertension and incidence of AD deaths, with hazard ratios of 2.23 (95% CI: 1.14-4.67) for an SBP
3 of ≥ 140 vs. < 120 mmHg, 4.00 (95% CI: 2.36-6.75) for a DBP of ≥ 90 vs. < 80 mmHg, and 3.58 (95% CI:
4 2.19-6.11) for hypertension (Table 2). These associations persisted in the multivariable models
5 with further adjustment for the BMI, smoking status, region, dyslipidemia, DM and coronary artery
6 disease, with hazard ratios of 2.37 (95% CI: 1.21-5.03) for an SBP of ≥ 140 vs. < 120 mmHg, 3.80
7 (95% CI: 2.25-6.45) for a DBP of ≥ 90 vs. < 80 mmHg and 3.57 (95% CI: 2.17-6.11) for hypertension.
8 The estimated PARp was 58% for individuals with hypertension compared to those without, 52%
9 for SBP above the reference category (≥ 120 mmHg) and 61% for DBP above the reference category
10 (≥ 80 mmHg). In the sensitivity analyses with participants without antihypertensive drugs at
11 baseline, these associations were preserved with mildly or moderately high hazard ratios
12 (Supplementary Table IIa).

14 **UK Biobank**

15 Among the 502,424 participants without a history of AD, 182 participants developed AD during a
16 median of 9.0 years of follow-up (interquartile range: 8.3-9.7), during which time 63 of those
17 participants died as a result of AD. The incidence of AD was 4.1 per 100,000 person-years.
18 Participants who developed AD were older and more likely to be male and current smokers and

1 had a higher SBP and DBP and higher prevalence of hypertension and connective tissue disease
2 than participants without AD (Table 3). In the age- and sex-adjusted Cox proportional hazards
3 model, there were significant associations between SBP, DBP, hypertension and the incidence of
4 AD, with hazard ratios of 4.77 (95% CI: 1.92-11.87) for an SBP of ≥ 180 vs. < 120 mmHg, 12.43 (95%
5 CI: 6.80-22.72) for a DBP of ≥ 110 vs. < 80 mmHg, and 2.70 (95% CI: 1.80-4.05) for hypertension
6 (Table 4). The estimated PARp was 53% for individuals with hypertension compared to those
7 without, 62% for SBP above the reference category (≥ 120 mmHg) and 36% for DBP above the
8 reference category (≥ 80 mmHg). The significant associations persisted in the multivariable models
9 with further adjustment for the smoking status, connective tissue disease, BMI and DM with
10 hazard ratios of 4.69 (95% CI: 1.88-11.68) for an SBP of ≥ 180 vs. < 120 mmHg, 11.82 (95% CI:
11 6.43-21.72) for a DBP of ≥ 110 vs. < 80 mmHg and 2.68 (95% CI: 1.78-4.04) for hypertension (Table
12 4).

13 We conducted a further sensitivity analysis excluding participants with antihypertensive drugs
14 at baseline and a sensitivity analysis with AD death outcomes, and the results were nearly identical,
15 except for unstable estimates in the AD death analysis due to the low number of AD deaths
16 (Supplementary table IIb and IIc). Associations between the SBP and DBP and the AD adjusted for
17 the age, sex, smoking status, connective tissue disease, BMI and DM in Cox regression were
18 modelled using restricted cubic spline with three knots (Supplementary Figure I, Supplementary

Table III). The associations between the SBP and DBP and the AD were nonlinear ($p_{\text{nonlinearity}}=0.0030$ and <0.0001 , respectively) and showed an exponential dose-response curve (both $p\text{-values}<0.0001$). The positive relationship between the risk of AD and DBP was steeper than that between the risk of AD and SBP, consistent with the categorical analyses.

Systematic review and meta-analysis

A total of 3,283 publications (1,244 publications from PubMed and 2,038 publications from EMBASE databases, and 1 publication⁸ from a separate search) were identified by the literature search (Figure 1). A total of 692 duplicates were excluded, as were 2,591 unique records because they were deemed irrelevant based on their titles or abstracts. The full-text articles of 153 potentially relevant publications were thus further examined, and 6 publications were ultimately included in the systematic review and meta-analysis in addition to the current analysis of the J-SHC study and UK Biobank (Table 5).^{5-8,17,18}

Adjusted relative risks were calculated for the Whitehall study⁶ (Supplementary Table IV). The average Newcastle-Ottawa scale score was 7.3 out of 9 (Supplementary Table V). Two studies (Whitehall Study and J-SHC Study) reported on AD mortality while the remaining studies included both hospital admissions and deaths from AD. All of the included studies found that hypertension or a high BP at baseline was a significant risk factor for AD.

Hypertension and AD

Seven cohort studies⁵⁻⁸ (2,818 AD cases and 4,563,501 participants) were included in the meta-analysis of hypertension and the risk of AD. The summary relative risk of AD for individuals with hypertension versus individuals without hypertension was 3.07 (95% CI: 2.15-4.38, $I^2=76.7\%$, $p_{\text{heterogeneity}} < 0.001$) (Figure 2). In the sensitivity analysis, the summary RR was not substantially altered when each of the studies was omitted from the analyses sequentially (Supplementary Figure II). While an inspection of the funnel plot indicated asymmetry (Supplementary Figure III), this was attenuated when a large Swedish registry-based study conducted by Avdic et al.⁸, which found a weaker association than the other studies, was excluded (Supplementary Figure IV). This study⁸ also explained the observed heterogeneity, and the summary RR was 3.40 (95% CI: 2.73-4.22, $I^2=0\%$, $p_{\text{heterogeneity}}=0.69$) when it was excluded.

Subgroup and meta-regression analyses were carried out to explore potential sources of heterogeneity (Supplementary Table VI). The positive association between hypertension and risk of AD persisted across all subgroup analyses, including subgroups defined by the duration of follow-up (<10 vs. ≥ 10 years), sex, geographic location of the study, study quality score assessed by the Newcastle-Ottawa scale, study outcome definition (AD mortality vs. AD incidence) and adjustment for confounding variables (smoking status, lipid status, coronary artery disease, DM,

BMI and education level) (Supplementary Table VI). There was no evidence of heterogeneity between subgroups, except for the subgroups with and without adjustment for education level (p for heterogeneity=0.005); however, the only study with such adjustment was the study conducted by Avdic et al.⁸.

BP and AD

Three studies¹⁷ including the present studies (289 cases and 1,044,484 participants) were included in the meta-analysis of SBP and the risk of AD, and three studies⁶ (including the present ones; 304 cases and 1,055,205 participants) were included in the meta-analysis of DBP and AD. The summary RR of AD per 20-mmHg increment of SBP was 1.39 (95% CI: 1.16-1.66, $I^2=47.7\%$ and $p_{\text{heterogeneity}}=0.15$) and that per 10-mmHg increment of DBP was 1.79 (95% CI: 1.51-2.12, $I^2=57.0\%$ and $p_{\text{heterogeneity}}=0.10$) (Figure 2). In the nonlinear dose-response analyses, there was evidence of nonlinearity ($p_{\text{nonlinearity}}=0.0007$) and a very strong dose-response relationship between SBP and AD (Figure 3, Supplementary Table VII). There was a very strong dose-response relationship between DBP and AD, and the test for nonlinearity showed statistical significance ($p_{\text{nonlinearity}}=0.0008$). The 95% CIs of the RRs were above 1.0 at SBP >132 mmHg and DBP >75 mmHg, suggesting a risk of AD even within a high “normal” BP range.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18

Discussion

Our analyses include two of the largest cohort studies conducted to date concerning the association between BP and the risk of AD. This is also the first systematic review and meta-analysis of cohort studies on the association between hypertension and BP and the risk of AD. The risk of AD was 2- and 5-fold higher than the reference group with an elevated SBP and 4- and 12-fold higher than the reference group with an elevated DBP in the J-SHC study and UK Biobank, respectively. Importantly, there was a 2- to 3-fold higher risk of AD, even within the "normal" SBP and DBP categories, than in the lowest reference category, suggesting that the optimal BP value may be considerably lower than what is considered normal BP for the prevention of AD. In addition, a roughly 3-fold higher-than-reference group risk was observed for persons with hypertension in the UK Biobank, the J-SHC study and our meta-analysis. In the UK Biobank, estimates of the population attributable risk suggested that an SBP above the reference category (≥ 120 mmHg) may account for 62% of AD cases, while a DBP above the reference category (≥ 80 mmHg) may account for 36% of AD cases; hypertension was deemed to account for 53% of cases. In the J-SHC study, hypertension was deemed to account for 53% of cases as well, and the corresponding estimates for an SBP and DBP ranged between 52% and 61%. This suggests that a substantial proportion of AD cases could be prevented if the prevalence of hypertension or elevated BP in the general

1 population could be reduced.

2 In the meta-analysis for hypertension, significant associations between hypertension and AD
3 persisted in subgroup and sensitivity analyses, suggesting that the result was robust and
4 independent of other risk factors that were adjusted for, including the smoking habit, lipid status,
5 coronary artery disease, DM and BMI. There was some suggestion of funnel plot asymmetry and
6 was likely due to the inclusion of the study with the largest sample size and weakest association⁸.
7 Although there were a few studies in each of the meta-analyses for BP, they both showed a
8 positive dose-response relationship between increasing SBP or DBP and the risk of AD, with a
9 notably steeper association with DBP. Of note, we observed some risk of AD even within the
10 “normal” BP range.

11 Two biological mechanisms have been suggested to contribute to the development of AD when
12 patients are exposed to elevated BP. One mechanism is AD with few pathological changes of
13 atherosclerosis, which is commonly seen in type A AD.^{19,20} In this mechanism, the hypertensive
14 status is associated with a loss of elastic fibers in the aortic media and unstable connections
15 between each elastic lamina, which results in AD before or after aortic aneurysm formation.^{21,22}
16 Hypertension has also been shown to be related to dilatation of the ascending aorta without
17 evidence of atherosclerosis.²³⁻²⁵ Such ascending aortic aneurysmal changes increase aortic wall
18 stress²⁶ and have been reported to increase the risk of AD drastically.²⁷ The vulnerability of the

1 ascending aorta to suffering dissection or contracting an aneurysm by exposure to hypertension
2 has been suggested to be driven by genetic factors.¹⁹ Another mechanism from elevated BP that
3 may contribute to the development of AD is atherosclerosis, which is commonly seen in type B
4 AD.^{28,29} Hypertension has been reported to be a major cause of atherosclerosis and aneurysmal
5 formation by impairing repair processes.³⁰

6 There is uncertainty regarding the predictive reliability between SBP and DBP. In the study of
7 Strachan et al., the DBP was a stronger predictor of aortic diseases, including AD, than the SBP;
8 however, Reed et al. found a stronger association in the SBP than with the DBP.^{6,17} Regarding
9 vascular mortality, a meta-analysis of prospective studies suggested that the SBP and DBP were
10 similarly predictive across all ages, with an effect size about two-fold higher in DBP than in SBP.³¹ In
11 addition, a meta-analysis on BP and the risk of abdominal aortic aneurysm showed significant
12 associations for both the SBP and DBP, albeit with a considerably stronger association for DBP,³²
13 which is consistent with the current findings. The dose-response relationship between DBP and AD
14 was exponential in shape in the UK Biobank, but the nonlinearity was less pronounced in our
15 meta-analysis. These findings highlight the importance of BP management. The associations
16 between hypertension and BP with AD, which were reinforced in this meta-analysis, provide
17 further impetus to support public health promotion to reduce and control hypertension. Although
18 the risk of AD in certain populations is also determined by unmodifiable factors, hypertension

remains a major modifiable risk factor for AD, and populations can reduce the risk of AD through the prevention and management of hypertension.

The prospective large-scale cohort study design based on the general population is a major strength of both the J-SHC study and UK Biobank, as it reduces the possibility for information bias.

However, several limitations associated with the present studies warrant mention. First, neither cohort was not representative of the general population with regard to several participant characteristics; therefore, they cannot be used to provide representative disease prevalence and incidence rates. Specifically, a “healthy volunteer” selection bias in the UK Biobank has been reported, with the participants more likely to live in less socioeconomically deprived area and to thus have a healthier lifestyle.³³ However, a valid assessment of exposure-disease relationships can nevertheless be obtained. Second, there were no data on the history of AD at baseline in the J-SHC study and for this reason we were unable to exclude participants with prevalent AD; however, we believe that the impact of this was limited, as AD is a rare and highly fatal disease. Third, the inclusion of AD deaths without capture of AD incidence is a limitation in the J-SHC study. The richness of the baseline data allowed us to explore possible confounders and to adjust for the effects of additional variables in the UK Biobank study. Fourth, misclassification of both the exposure and outcome, such as due to coding inaccuracy in administrative or medical databases, is another possible limitation of our cohort studies as well as the studies included in the

1 meta-analysis. However, if such misclassification occurred, it would most likely have been
2 non-differential with regard to the exposure and outcome status because of the prospective design
3 of the studies, so the calculated risk estimates would tend to be biased towards the null and thus
4 underestimated.³⁴ Fifth, the hypertension status or BP was assessed at baseline in the cohort
5 studies but may have changed over the follow-up period, so using the baseline measurement may
6 not have adequately represented the exposure level during follow-up, leading to regression
7 dilution bias. However, some reports found that the baseline BP was a better predictor of
8 cardiovascular diseases than the current BP.³⁵ Finally, despite millions of patient-years of
9 observation, there were a total of 266 AD events to analyze in our cohorts, suggesting that clinical
10 action may be challenging, given the colossal numbers needed to be treated in order to prevent an
11 AD event; however, the benefits of reducing the BP may extend to other cardiovascular diseases as
12 well³⁶.

13 The main limitation of the current meta-analysis is the low number of published studies that
14 were included in the analyses. There were also few published studies on the relationship between
15 the SBP or DBP and AD, likely due to the relative rarity of the disease, which limited the possibility
16 of conducting subgroup and sensitivity analyses and testing for funnel plot asymmetry in the
17 analyses of SBP and DBP. The study outcome was AD mortality in the two studies (Whitehall Study
18 and J-SHC study) while the outcome was AD incidence in the other six studies, and we found no

1 significant heterogeneity between these subgroups in the meta-analysis. This is not surprising
2 given the relatively high fatality rate in AD. The number of cases in the studies included in the
3 meta-analysis ranged from 23 to 188 cases, with one particularly large population-wide Swedish
4 study enrolling 2,219 cases.⁸ Both the heterogeneity and funnel plot asymmetry observed in the
5 meta-analysis appeared to be explained by this Swedish study, which had the smallest effect size
6 but the highest weight among the studies. The weak associations observed in this study may have
7 been due to the crude nature of the registry-based data, e.g. hypertensive medication use was
8 used as a proxy for hypertension status and may have led to misclassification and likely attenuation
9 of the observed risk estimates; unadjusted or residual negative confounding due to a lack of data
10 on lifestyle factors; or the inclusion of several highly correlated and potentially intermediate
11 cardiovascular conditions in the multivariable model.

12 Our analyses are important for public health as they provide the first summary of the evidence
13 from prospective cohort studies on the association of BP and hypertension with the risk of AD, this
14 improving the evidence base from being based on reports of case series to an actual estimate of
15 the relative risk. This study also provides estimates of attributable risk, which were consistent with
16 a previous Swedish study.⁵ Although further studies are needed, the current results suggest that
17 reducing BP, either through healthy lifestyle or medications, may consequently reduce the
18 incidence of AD, and furthermore, the optimal target BP may be even lower than the current

1 cut-off for “normal” BP.

2 In conclusion, the analyses of the J-SHC study and UK Biobank as well as the meta-analysis of
3 eight cohort studies showed a roughly 3-fold higher risk of AD in hypertensive individuals than in
4 individuals without hypertension. The risk of AD was positively dose-dependent even within the
5 normal BP range in the J-SHC study, UK Biobank study and meta-analysis. In the nonlinear
6 dose-response meta-analysis, a high vs. low SBP and DBP was associated with an approximately 3-
7 and 20-fold higher risk of AD than the reference group, respectively. These results confirm previous
8 observations that a high BP is an important risk factor for AD and provide precise estimates of the
9 associated risks.

10

11

12

13

14

15 **Contribution**

16 Study concept and design: DA.

17 Acquisition, analysis or interpretation of data: MH, YO, HH, KA, KY, SF, KT, IN, MasatoK, YS, KI, TM,

18 MasahideK, TsuyoshiW, TK, TetsuW, DA.

1 Drafting of manuscript: MH.

2 Critical revision of the manuscript for important intellectual content: MH, YO, EK, HP, HH, HT, AM,

3 SV, KA, KY, SF, KT, IN, MasatoK, YS, KI, TM, MasahideK, TsuyoshiW, TK, TetsuW, MW, DA.

4 Statistical analysis: MH, YO.

5 Study supervision: DA.

6

7

8 **Acknowledgements**

9 The UK Biobank analysis was conducted under application number 41617. The authors thank the

10 participants of the UK Biobank and those building the resource. The views expressed in this

11 publication are those of the authors and not necessarily those of the NHS, NIHR or the Department

12 of Health and Social Care.

13

14 **Funding Sources**

15 We are grateful for support from the National Institute for Health (NIHR) Research Applied

16 Research Collaboration (ARC) Northwest London (AM). The J-SHC study was supported by a Health

17 and Labor Sciences Research Grant for Study on the design of the comprehensive health care

18 system for chronic kidney disease (CKD) based on the individual risk assessment by Specific Health

Checkup from the Ministry of Health, Labour and Welfare of Japan and a Grant-in-Aid for Research on Advanced Chronic Kidney Disease (REACH-J), Practical Research Project for Renal Disease from the Japan Agency for Medical Research and Development, AMED. DA has received funding from the Regional Health Authority of Norway (2017076).

Conflict of Interest Disclosures

SV holds a Tier 1 Canada Research Chair in Cardiovascular Surgery, University of Toronto; and has received research grants and/or speaking honoraria from Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, EOCI Pharmacomm Ltd., Janssen, Merck, Novartis, Novo Nordisk, Sanofi, Sun Pharmaceuticals, and the Toronto Knowledge Translation Working Group; and is the President of the Canadian Medical and Surgical Knowledge Translation Research Group, a federally incorporated not-for-profit physician organization. TK received honoraria from Fuji Yakuhin, Pfizer, Teijin and Sanwa Kagaku. MW received research grant and/or speaking honoraria from Ono Pharmaceutical, Chugai Pharmaceutical, Bayer, Medtronic, Astellas Pharma, Biotronik Japan, Abbott Vascular Japan, Cardinal Health Japan, Otsuka Pharmaceutical, Nippon Boehringer Ingelheim and Daiichi Sankyo. All the other authors state that they have no conflict of interest.

Supplemental Materials

1 *Supplementary Methods*

2 *Supplemental Tables I - VII*

3 *Supplemental Figures I - IV*

4

5

6 **References**

7

- 8 1. Mussa FF, Horton JD, Moridzadeh R, Nicholson J, Trimarchi S, Eagle KA. Acute
9 Aortic Dissection and Intramural Hematoma: A Systematic Review. *JAMA*.
10 2016;316:754–763.
- 11 2. Nienaber CA, Clough RE. Management of acute aortic dissection. *The Lancet*.
12 2015;385:800–811.
- 13 3. Howard DP, Banerjee A, Fairhead JF, Perkins J, Silver LE, Rothwell PM.
14 Population-based study of incidence and outcome of acute aortic dissection and
15 premorbid risk factor control: 10-year results from the Oxford Vascular Study.
16 *Circulation*. 2013;127:2031–2037.
- 17 4. Pape LA, Awais M, Woznicki EM, Suzuki T, Trimarchi S, Evangelista A, Myrmet
18 T, Larsen M, Harris KM, Greason K, et al. Presentation, Diagnosis, and Outcomes
19 of Acute Aortic Dissection: 17-Year Trends From the International Registry of
20 Acute Aortic Dissection. *J Am Coll Cardiol*. 2015;66:350–358.
- 21 5. Landenhed M, Engstrom G, Gottsater A, Caulfield MP, Hedblad B, Newton-Cheh C,
22 Melander O, Smith JG. Risk profiles for aortic dissection and ruptured or

- surgically treated aneurysms: a prospective cohort study. *J Am Heart Assoc.* 2015;4:e001513.
6. Strachan DP. Predictors of death from aortic aneurysm among middle-aged men: the Whitehall study. *BrJ Surg.* 1991;78:401–404.
7. Teng HI, Huang CC, Chiang CH, Huang PH, Chung CM, Lin SJ, Chen JW, Leu HB, Chan WL, Lee CY. Sleep apnea and risk of aortic dissection: A nonrandomized, pair-matched cohort study. *J Chin Med Assoc.* 2016;79:422–427.
8. Avdic T, Franzén S, Zarrouk M, Acosta S, Nilsson P, Gottsäter A, Svensson A-M, Gudbjörnsdottir S, Eliasson B. Reduced Long-Term Risk of Aortic Aneurysm and Aortic Dissection Among Individuals With Type 2 Diabetes Mellitus: A Nationwide Observational Study. *Journal of the American Heart Association.* 2018;7:e007618.
9. Murray CJL, Aravkin AY, Zheng P, Abbafati C, Abbas KM, Abbasi-Kangevari M, Abd-Allah F, Abdelalim A, Abdollahi M, Abdollahpour I, et al. Global burden of 87 risk factors in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *The Lancet.* 2020;396:1223–1249.
10. Otaki Y, Watanabe T, Konta T, Watanabe M, Fujimoto S, Sato Y, Asahi K, Yamagata K, Tsuruya K, Narita I, et al. Effect of Hypertension on Aortic Artery Disease-Related Mortality – 3.8-Year Nationwide Community-Based Prospective Cohort Study. *Circ J.* 2018;82:2776–2782.
11. Sudlow C, Gallacher J, Allen N, Beral V, Burton P, Danesh J, Downey P, Elliott P, Green J, Landray M, et al. UK Biobank: An Open Access Resource for Identifying the Causes of a Wide Range of Complex Diseases of Middle and Old Age. *PLoS Med.*

2015;12:e1001779.

12. Townsend P. Deprivation. *J Soc Policy*. 1987;16:125–146.

13. Newson RB. Attributable and unattributable risks and fractions and other scenario comparisons. *The Stata Journal*. 2013;13:672–698.

14. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7:177–188.

15. Bagnardi V, Zambon A, Quatto P, Corrao G. Flexible meta-regression functions for modeling aggregate dose-response data, with an application to alcohol and mortality. *Am J Epidemiol*. 2004;159:1077–1086.

16. Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Accessed 2021 Oct 22.

17. Reed D, Reed C, Stemmermann G, Hayashi T. Are aortic aneurysms caused by atherosclerosis? *Circulation*. 1992;85:205–211.

18. Raunso J, Song RJ, Vasan RS, Bourdillon MT, Norager B, Torp-Pedersen C, Gislason GH, Xanthakis V, Andersson C. Familial Clustering of Aortic Size, Aneurysms, and Dissections in the Community. *Circulation*. 2020:920–928.

19. Roberts WC, Vowels TJ, Kitchens BL, Ko JM, Filardo G, Henry AC, Hamman BL, Matter GJ, Hebeler RF, Jr. Aortic medial elastic fiber loss in acute ascending aortic dissection. *Am J Cardiol*. 2011;108:1639–1644.

20. Achneck H, Modi B, Shaw C, Rizzo J, Albornoz G, Fusco D, Elefteriades J. Ascending thoracic aneurysms are associated with decreased systemic atherosclerosis. *Chest*. 2005;128:1580–1586.

21. Nakashima Y, Sueishi K. Alteration of elastic architecture in the lathyrotic

rat aorta implies the pathogenesis of aortic dissecting aneurysm. *Am J Pathol.* 1992;140:959–969.

22. Nakashima Y. Pathogenesis of Aortic Dissection: Elastic Fiber Abnormalities and Aortic Medial Weakness. *Annals of Vascular Diseases.* 2010;3:28–36.

23. Mule G, Nardi E, Morreale M, Castiglia A, Geraci G, Altieri D, Cacciatore V, Schillaci M, Vaccaro F, Cottone S. The relationship between aortic root size and hypertension: An unsolved conundrum. *Adv Exp Med Biol.* 2017;956:427–445.

24. Milan A, Avenatti E, Tosello F, Iannaccone A, Leone D, Magnino C, Veglio F. Aortic root dilatation in essential hypertension: prevalence according to new reference values. *J Hypertens.* 2013;31:1189–1195.

25. Agmon Y, Khandheria BK, Meissner I, Schwartz GL, Sicks JD, Fought AJ, O’Fallon WM, Wiebers DO, Tajik AJ. Is aortic dilatation an atherosclerosis-related process?: Clinical, laboratory, and transesophageal echocardiographic correlates of thoracic aortic dimensions in the population with implications for thoracic aortic aneurysm formation. *J Am Coll Cardiol.* 2003;42:1076–1083.

26. Koullias G, Modak R, Tranquilli M, Korkolis DP, Barash P, Elefteriades JA. Mechanical deterioration underlies malignant behavior of aneurysmal human ascending aorta. *The Journal of Thoracic and Cardiovascular Surgery.* 2005;130:677–683.

27. Davies RR, Goldstein LJ, Coady MA, Tittle SL, Rizzo JA, Kopf GS, Elefteriades JA. Yearly rupture or dissection rates for thoracic aortic aneurysms: simple prediction based on size. *Ann Thorac Surg.* 2002;73:17–27.

28. Barbetseas J, Alexopoulos N, Brili S, Aggeli C, Chrysohoou C, Frogoudaki A,

- 1 Vyssoulis G, Pitsavos C, Stefanadis C. Atherosclerosis of the aorta in patients
2 with acute thoracic aortic dissection. *Circ J*. 2008;72:1773–1776.
- 3 29. Vapnik JS, Kim JB, Isselbacher EM, Ghoshhajra BB, Cheng Y, Sundt TM, III,
4 MacGillivray TE, Cambria RP, Lindsay ME. Characteristics and Outcomes of
5 Ascending Versus Descending Thoracic Aortic Aneurysms. *Am J Cardiol*.
6 2016;117:1683–1690.
- 7 30. Libby P, Ridker PM, Hansson GK. Progress and challenges in translating the
8 biology of atherosclerosis. *Nature*. 2011;473:317–325.
- 9 31. Prospective Studies Collaboration. Age-specific relevance of usual blood
10 pressure to vascular mortality: a meta-analysis of individual data for one
11 million adults in 61 prospective studies. *The Lancet*. 2002;360:1903–1913.
- 12 32. Kobeissi E, Hibino M, Pan H, Aune D. Blood pressure, hypertension and the risk
13 of abdominal aortic aneurysms: a systematic review and meta-analysis of cohort
14 studies. *Eur J Epidemiol*. 2019;34:547–555.
- 15 33. Fry A, Littlejohns TJ, Sudlow C, Doherty N, Adamska L, Sprosen T, Collins R,
16 Allen NE. Comparison of Sociodemographic and Health-Related Characteristics
17 of UK Biobank Participants With Those of the General Population. *Am J Epidemiol*.
18 2017;186:1026–1034.
- 19 34. Jurek AM, Greenland S, Maldonado G. How far from non-differential does exposure
20 or disease misclassification have to be to bias measures of association away
21 from the null? *Int J Epidemiol*. 2008;37:382–385.
- 22 35. Vasan RS, Massaro JM, Wilson PW, Seshadri S, Wolf PA, Levy D, D'Agostino RB.
23 Antecedent blood pressure and risk of cardiovascular disease: the Framingham
24 Heart Study. *Circulation*. 2002;105:48–53.

1 36. Higgins H, Mason AM, Larsson SC, Gill D, Langenberg C, Burgess S. Estimating
2 the Population Benefits of Blood Pressure Lowering: A Wide-Angled Mendelian
3 Randomization Study in UK Biobank. *Journal of the American Heart Association*.
4 2021;10:e021098.

5
6
7
8
9

Disclaimer: The manuscript and its contents are
confidential, intended for journal review purposes
only, and not to be further disclosed.

1 **Legends**

2

3 Figure 1. The flow of the literature screening process.

4 Figure 2. A meta-analysis of cohort studies on hypertension, systolic blood pressure (per 20 mmHg)
5 and diastolic blood pressure (per 10 mmHg) and the risk of aortic dissection

6 CI, confidence interval.

7

8 Figure 3. A nonlinear dose-response meta-analysis of cohort studies on systolic and diastolic blood
9 pressure and the risk of aortic dissection

Disclaimer: The manuscript and its contents are
confidential, intended for journal review purposes
only, and not to be further disclosed.

Table 1: Baseline characteristics of Entire J-SHC Study Cohort and Cases

	J-SHC Study (n=534,378)	AD death (n=84)	p values
Age, years	62.7 (8.8)	66.2 (6.5)	0.0004
Male	229,912 (43%)	48 (57%)	0.0090
Smoking (current smoker)	82,386 (15.4%)	17 (20.2%)	0.24
missing	0	0	
Alcohol (current drinker)	229,204 (42.9%)	37 (44.0%)	0.72
missing	0	0	
Region			0.54
Eastern Japan	146,410 (27.4%)	19 (22.6%)	
Western Japan	387,968 (72.6%)	65 (77.4%)	
Physical measurement			
SBP, mmHg	128.9 (17.6)	135 (18.3)	<0.0001
<120mmHg	145,521 (27.2%)	11 (13.1%)	0.0014
120-129mmHg	126,734 (23.7%)	19 (22.6%)	
130-139mmHg	122,226 (22.9%)	23 (27.4%)	
≥140mmHg	139,897 (26.2%)	31 (36.9%)	
missing	0	0	
DBP, mmHg	76.4 (10.9)	83.4 (11.7)	<0.0001
<80mmHg)	309,181 (57.9%)	19 (22.6%)	<0.0001
80-89mmHg	158,523 (29.7%)	38 (45.2%)	
≥90mmHg	66,674 (12.5%)	27 (32.1%)	
missing	0	0	
Hypertension (≥140/90mmHg or use of antihypertensive medication)	231,106 (43.3%)	64 (76.2%)	<0.0001
Anti-hypertensive drug use	159,123 (29.8%)	43 (51.2%)	<0.0001
BMI >25, kg/m ²	157,936 (29.6%)	34 (40.5%)	0.033
Past medical history			
Hyperlipidaemia	298,929 (55.9%)	44 (52.4%)	0.51
Diabetes mellitus	62,185 (11.6%)	7 (8.3%)	0.32
Coronary artery disease	27,717 (5.2%)	7 (8.3%)	0.43

mean (standard deviation) or count (percentage). AD, aortic dissection; BMI, body mass index; DBP, diastolic blood pressure; SBP, systolic blood pressure.

Table 2: Hazard ratios for the association between systolic blood pressure, diastolic blood pressure and hypertension and the risk of aortic dissection in J-SHC Study

	Systolic blood pressure (mmHg)					
	<120	120-129	130-139	≥140	P _{trend}	Per 20 mmHg
AD deaths	11	19	23	31		
Person-years	559,358	478,811	457,761	514,744		
Model 1	1.00	1.80 (0.87-3.92)	2.14 (1.06-4.57)	2.23 (1.14-4.67)	0.010	1.34 (1.07-1.70)
Model 2	1.00	1.80 (0.87-3.92)	2.11 (1.04-4.55)	2.38 (1.21-5.03)	0.016	1.33 (1.05-1.68)
Model 3	1.00	1.79 (0.86-3.92)	2.11 (1.04-4.54)	2.37 (1.21-5.03)	0.016	1.33 (1.05-1.68)
	Diastolic blood pressure (mmHg)					
	<80	80-89	≥90		P _{trend}	Per 10 mmHg
AD deaths	31	26	27			
Person-years	1,163,029	598,913	248,795			
Model 1	1.00	1.55 (0.92-2.62)	4.00 (2.36-6.75)		<0.0001	1.70 (1.43-2.03)
Model 2	1.00	1.52 (0.89-2.57)	3.80 (2.23-6.46)		<0.0001	1.67 (1.40-2.00)
Model 3	1.00	1.52 (0.89-2.57)	3.80 (2.25-6.45)		<0.0001	1.67 (1.40-2.00)
	Hypertension					
	No	Yes		P value		
AD deaths	20	64				
Person-years	1,169,882	840,212				
Model 1	1.00	3.58 (2.19-6.11)		<0.0001		
Model 2	1.00	3.57 (2.17-6.11)		<0.0001		
Model 3	1.00	3.57 (2.17-6.11)		<0.0001		

Model 1: Age, sex

Model 2: Age, sex, BMI, smoking, region, dyslipidemia, diabetes mellitus

Model 3: Age, sex, BMI, smoking, region, dyslipidemia, diabetes mellitus, coronary artery disease

AD, aortic dissection; BMI, body mass index; P_{trend}, P-value for linear trend

Table 3: Baseline characteristics of Entire UK Biobank Cohort and Cases

	UK Biobank Study Cohort (n=502,424)	AD death or hospitalization (n=182)	p values
Age, years	56.5 (8.1)	61.1 (6.9)	<0.0001
Male	229,068 (45.6%)	116 (63.7%)	<0.001
Townsend deprivation index	-1.3(3.1)	-1.1 (3.3)	0.46
1st quantile	100,643 (20.0%)	40 (21.2%)	0.82
2nd quantile	100,075 (19.9%)	31 (17.0%)	
3rd quantile	100,377 (20.0%)	35 (19.2%)	
4th quantile	100,352 (20.0%)	37 (20.3%)	
5th quantile	100,354 (20.0%)	39 (21.4%)	
missing	623	0	
Smoking			
never smoker	273,489 (54.8%)	79 (43.7%)	0.0001
past smoker	173,019 (34.6%)	66 (36.5%)	
current smoker	52,968 (10.6%)	36 (19.9%)	
missing	2948	1	
Physical measurement			
SBP, mmHg	139.8 (19.7)	148.8 (21.2)	<0.0001
<120mmHg	73,796 (14.7%)	7 (3.9%)	<0.0001
120-129mmHg	87,753 (17.5%)	29 (15.9%)	
130-139mmHg	102,363 (20.4%)	32 (17.6%)	
140-159mmHg	158,852 (31.7%)	57 (31.3%)	
160-179mmHg	61,751 (12.3%)	42 (23.1%)	
≥180mmHg	16,584 (3.3%)	15 (8.2%)	
Missing	1325	0	
DBP, mmHg	82.2 (10.7)	89.1 (13.5)	<0.0001
<80mmHg	207,118 (41.3%)	45 (24.7%)	<0.0001
80-84mmHg	92,777 (18.5%)	23 (12.6%)	
85-89mmHg	80,240 (16.0%)	28 (15.4%)	
90-99mmHg	91,618 (18.3%)	52 (28.6%)	
100-109mmHg	24,498 (4.9%)	20 (11.0%)	
≥110mmHg	4,850 (1.0%)	14 (7.7%)	
Missing	1323	0	
Hypertension (≥140/90mmHg or diagnosis in PMH)	289,874 (57.7%)	153 (84.1%)	<0.001
Heart Rate, bpm	69.7 (11.7)	70.4 (13.2)	0.37
missing	1323	0	
BMI >30, kg/m ²	125,324 (24.9%)	56 (30.1%)	0.069
Past medical history			
Dyslipidaemia	61,611 (12.3%)	33 (18.1%)	0.016
Diabetes mellitus	25,490 (5.1%)	8 (4.4%)	0.86
Coronary artery disease	22,715 (4.5%)	14 (7.7%)	0.039
Connective tissue disease	195 (0.04%)	2 (1.1%)	0.002
Chronic lung disease	59,278 (11.8%)	23 (12.6%)	0.72

mean (standard deviation) or count (percentage). AD, aortic dissection; BMI, body mass index; DBP, diastolic blood pressure; PMH. Past medical history; SBP, systolic blood pressure.

Table 4: Hazard ratios for the association between systolic blood pressure, diastolic blood pressure and hypertension and the risk of aortic dissection incidence in UK Biobank

	Systolic blood pressure (mmHg)							
	<120	120-129	130-139	140-159	160-179	≥180	P _{trend}	Per 20mmHg
AD cases	7	29	32	57	42	15		
Person-years	657,819	780,436	908,582	1,404,404	542,992	144,506		
Model 1	1.00	2.82 (1.24, 6.46)	2.31 (1.01, 5.24)	2.26 (1.02, 4.99)	3.79 (1.68, 8.53)	4.77 (1.92, 11.87)	0.0023	1.28 (1.11, 1.48)
Model 2	1.00	2.88 (1.26, 6.58)	2.38 (1.05, 5.41)	2.30 (1.04, 5.10)	3.95 (1.75, 8.90)	4.96 (1.99, 12.33)	0.0015	1.29 (1.12, 1.50)
Model 3	1.00	2.83 (1.24, 6.47)	2.31 (1.02, 5.27)	2.21 (0.99, 4.91)	3.78 (1.67, 8.52)	4.69 (1.88, 11.68)	0.0024	1.27 (1.11, 1.48)
	Diastolic blood pressure (mmHg)							
	<80	80-84	85-89	90-99	100-109	≥110	P _{trend}	Per 10mmHg
AD cases	45	23	28	52	20	14		
Person-years	1,832,119	822,617	711,004	813,003	217,243	42,771		
Model 1	1.00	1.05 (0.64, 1.74)	1.44 (0.90, 2.31)	2.30 (1.54, 3.44)	3.30 (1.95, 5.61)	12.43 (6.80, 22.72)	<0.0001	1.68 (1.48, 1.91)
Model 2	1.00	1.07 (0.65, 1.77)	1.48 (0.92, 2.37)	2.38 (1.59, 3.56)	3.24 (1.89, 5.55)	12.47 (6.82, 22.79)	<0.0001	1.68 (1.48, 1.91)
Model 3	1.00	1.05 (0.64, 1.74)	1.44 (0.90, 2.31)	2.30 (1.53, 3.45)	3.10 (1.80, 5.33)	11.82 (6.43, 21.72)	<0.0001	1.66 (1.46, 1.89)
	Hypertension							
	No	Yes	P value					
AD cases	29	153						
Person-years	1,893,314	2,553,821						
Model 1	1.00	2.70 (1.80, 4.05)	<0.001					
Model 2	1.00	2.71 (1.81, 4.08)	<0.001					
Model 3	1.00	2.68 (1.78, 4.04)	<0.001					

Model 1: Age, sex

Model 2: Age, sex, smoking, connective tissue disease

Model 3: Age, sex, BMI, smoking, connective tissue disease, diabetes mellitus

AD, aortic dissection; BMI, body mass index; P_{trend}, P-value for linear trend

Table 5: Selected studies on hypertension or blood pressure and the incidence of aortic dissection in meta-analysis

First author, publication year, region	Study name or description	Inclusion period (entry begin-entry end-study end, follow-up)	Number of participants, number of cases	AD definition	Type of exposure (definition)	Comparison	Adjusted relative risk (95% confidence interval)	Adjustment for confounders
Strachan DP et al, 1991, UK ⁶	Whitehall study	1967-1969-1987, mean 16.6 years follow-up	18,403 men, age 40-64 years (99 case and 990 age-matched nested control): 38 AD death cases	Death	DBP HTN (DBP≥90)*	per 10mmHg increase Yes vs. No*	OR2.4(1.7-3.2) RR3.39(1.77-6.49)*	Age, Smoking
Reed D et al, 1992, Hawaii ¹⁷	Honolulu Heart Program	1965-1968-1988, approximately 20 years follow-up	7,682 men, age 46-65 years with Japanese ancestry without clinical aortic aneurysm and CAD: 23 AD cases	Hospitalization and death	SBP	per 50mmHg increase	HR4.30(1.97-9.43)	Age, Serum cholesterol, Serum triglyceride, Smoking, Height
Landenhed M et al, 2015, Sweden ⁵	Malmö Diet and Cancer Study	1991-1996-2011, median 16 years follow-up	30,412 men and women, age 41-73 years without aortic diseases: 70 AD cases	Hospitalization and death	HTN (SBP/DBP≥140/90 or use of antihypertensive medication)	Yes vs. No	HR3.37(1.51-7.55)	Age, Sex, Smoking, apoA1
Teng H et al, 2015, Taiwan ⁷	The National Health Insurance Research Database	1995-2000-2007, mean 3.6 years follow-up	55,641 men and women, mean age 44.8 years without prior AD (15,837 sleep apnea patients, 39,804 age, sex and comorbidities matched population): 37 AD cases	Include hospitalization and death	HTN (ICD coding)	Yes vs. No	HR6.28(2.36-16.67)	Age, Sex, COPD, CAD, CCB, Sleep apnea
Avdic T et al, 2018, Sweden ⁸	Swedish National Diabetes Register combined with other national databases and registries	1998-2012-2015, mean 7.2 years follow-up	2,699,334 men and women, age 65.0 years (subjects with previous aortic aneurysm and AD were excluded from analysis) (448,319 T2DM patients, 2,251,015 age, sex and birth country matched population): 2,219 AD cases	Hospitalization and death	HTN (use of antihypertensive medication)	Yes vs. No	HR1.77(1.51–2.07)	Age, Sex, Stroke, Cardiovascular disease, CAD, Acute myocardial infarction, Atrial fibrillation, Renal complications, Mental disorders, T2DM, DM complications, Dementia, Cancers, Gastric bypass, Anticoagulation, Lipid-lowering drugs, ASA, Birth country, Marital status, Educational level
Raunso J et al, 2020, Denmark ¹⁸	Danish Registries	1997-2017-2017/12, median 7.1 years follow-up	722,909 men and women, mean age 39.2 (7,209 first-degree relatives to AD patients, 715,700 age and sex matched population): 188 AD cases	Diagnosis in any setting	HTN (use of at least 2 antihypertensive medications or ICD coding)	Yes vs. No	HR3.72(2.52-5.49)	Age, Sex, CAD, Marfan syndrome, Bicuspid aortic valve, First-degree family member of AD

J-SHC study, 2021, Japan	Japan Specific Health Checkups Study	2008-2015-2015, 534,378 men and women, age median 4.0 years	40-74 years: 84 AD deaths follow-up	Death	SBP DBP HTN (SBP/DBP≥140/90 or use of antihypertensive medication)	per 20mmHg increase HR1.33(1.05-1.68) per 10mmHg increase HR1.67(1.40-2.00) Yes vs. No HR3.57(2.17-6.11)	Age, Sex, BMI, Smoking, CAD, Region, Dyslipidaemia, DM
UK Biobank, 2021, UK	UK Biobank	2006-2010-2017/8, median 9.0 years follow-up	502,424 men and women, age 40-69: 182 AD cases	Hospitalization and death	SBP DBP HTN(SBP/DBP≥140/90 or diagnosis in PMH)	per 20mmHg increase HR1.27(1.11-1.48) per 10mmHg increase HR1.66(1.46-1.89) Yes vs. No HR2.68(1.78-4.04)	Age, Sex, BMI, Smoking, Connective tissue disease, DM

* calculated based on a stratified sheet in the article.

AD, aortic dissection; ASA, acetylsalicylic acid; BMI, body mass index; CAD, coronary artery disease; CCB, calcium channel blocker; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; DM, diabetes mellitus; HR, hazard ratio; HTN, hypertension; ICD, International Classification Diseases; OR, odds ratio; PMH, past medical history; RR, risk ratio; SBP, systolic blood pressure; T2DM, type 2 diabetes mellitus





