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Associations of blood pressure with cardiovascular and mortality outcomes in over 2 million older persons with or without diabetes mellitus: A systematic review and meta-analysis of 45 cohort studies☆

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ABSTRACT

Background: The impact of blood pressure on cardiovascular disease (CVD) and mortality outcomes in older people with diabetes mellitus (DM) is not well quantified. Using a systematic review and meta-analysis of observational cohort studies, we aimed to compare the associations of blood pressure levels with cardiovascular and mortality outcomes in older people aged ≥ 65 years with or without DM.

Methods: Studies were identified from MEDLINE, Embase, Web of Science, and search of bibliographies to July 2022. Study-specific risk ratios (RRs) with 95% confidence intervals (CIs) were pooled.

Results: Forty-five unique observational cohort studies (n = 2305,189 participants) assessing the associations of systolic blood pressure (SBP) and/or diastolic blood pressure (DBP) levels with adverse cardiovascular outcomes were included. In the general population, the pooled RRs (95% CIs) of SBP ≥ 140 vs < 140 mmHg and per 10 mmHg increase for composite CVD/MACE were 1.26 (0.96–1.64) and 1.15 (1.08–1.23), respectively. The respective estimates were 1.56 (1.04–2.34) and 1.10 (1.04–1.18) for patients with DM. SBP ≥ 130 vs < 130 mmHg was not associated with an increased risk of adverse cardiovascular outcomes in both populations. SBP < 120 vs ≥ 120 mmHg was associated with an increased risk of all cause-mortality in the general population (n = 10 studies). DBP ≥ 90 mmHg was associated with an increased risk of some adverse cardiovascular outcomes in both populations. Interaction analyses suggested similar risk of outcomes in both populations.

Conclusions: Observational evidence suggests SBP and DBP confer similar cardiovascular and mortality risk in older adults in the general population and those with DM. A blood pressure target range of > 130/80 to < 140/90 mmHg may be optimal for patients ≥ 65 years with DM, but specific targets may need to be individualised based on patients' unique circumstances. Furthermore, findings do not support stringent blood pressure control in this population group. Definitive RCTs are needed to support these observational findings.

1. Introduction

Cardiovascular disease (CVD) complications are the leading cause of morbidity and death in individuals with type 2 diabetes (T2D),[1] the most common form of diabetes (DM). The management of T2D and its complications also places substantial financial pressures on healthcare systems and global economies;[2,3] in 2021, T2D was responsible for an estimated USD 966 billion in global health expenditure.[4] Though a wealth of epidemiological and clinical studies have improved our understanding of T2D in addition to effective treatment and preventive strategies, its prevalence is still on the rise mainly due to the obesity epidemic.[5] Current global estimates suggest that 422 million people have diabetes (DM)[6] and it has been projected that the number will reach 642 million by 2040.[7] People with DM need intensive control of

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glucose and risk factors such as lipids and blood pressure to reduce the risk of disease progression and complications.[8].

Among risk factors for CVD, the leading cause of mortality, high blood pressure or hypertension is the one with the strongest evidence for causation.[9] Age is also a major risk factor for hypertension; the prevalence of hypertension increases with age.[10] Several high quality observational cohort studies and randomised controlled trials (RCTs) have demonstrated the effectiveness of blood pressure lowering for CVD and mortality prevention.[11–13] Management of blood pressure in older people is challenging and the optimal blood pressure target for cardiovascular and mortality benefit is uncertain in this population group,[14] largely due to contrasting findings from both observational studies and RCTs.[15–20] Furthermore, most guidelines on blood pressure targets have been based on evidence from RCTs, which rarely recruit older people.[21] Hypertension and DM are common conditions that co-exist. Guidelines have differed in their recommendations on blood pressure targets in patients with DM and the class of drug treatment most appropriate for the treatment of patients with hypertension and DM is controversial.[22] Achieving blood pressure control in older people with DM is even more problematic compared with the general population. This is because of the limited data available on target blood pressure levels in this population group and the challenges associated with extrapolating data from the general population to these frail individuals.[23] By how much blood pressure should be lowered in older individuals with DM is controversial and guidelines are also not clear on this.[23] A number of studies have reported on the impact of blood pressure on CVD and mortality outcomes in older populations, with inconsistent results. Furthermore, the evidence is also not certain in older people with DM. It will be clinically useful to summarise the existing evidence on the impact of blood pressure on CVD and all-cause mortality in older people and how this compares in those with and without DM. We therefore conducted a systematic review and meta-analysis to compare the associations of blood pressure with cardiovascular and mortality outcomes in older people with or without DM.

2. Methods

2.1. Data sources and search strategy

The predefined protocol for this systematic review and meta-analysis was prospectively registered in the PROSPERO prospective register of systematic reviews (CRD42022324546). The methodology and reporting followed PRISMA and MOOSE guidelines (**Appendices 1 and 2**). We searched MEDLINE and Embase from inception till 05 July 2022 without restrictions on language. The searches combined free texts and MeSH terms related to older people, blood pressure, diabetes, cardiovascular disease, and mortality. A MEDLINE search strategy was initially employed (**Appendix 3**), which was then adapted for Embase. One author (SKK) screened the titles and abstracts of the retrieved citations using Rayyan (http://rayyan.qcri.org), a free online bibliographic tool that helps to expedite the initial screening using a process of semi-automation.[24] This was followed by full-text evaluation, which was independently conducted by two authors (SS and SKK). To identify potential studies missed by the search strategy, we searched the reference lists of relevant studies and reviews and the "Cited Reference Search" function in Web of Science was also used.

2.2. Study selection and eligibility criteria

Our eligibility criteria included the following studies: (i) population-based cohort studies with at least one year follow-up; (ii) recruited older adults ($\geq$ 65 years) with or without DM; (iii) had blood pressure assessed at baseline with or without treatment; and (iv) reported associations of blood pressure or hypertension with cardiovascular and/or mortality outcomes.

2.3. Data extraction

A predesigned standardised data extraction form was used to extract information on first author, publication year, baseline year of recruitment, location of study, specific study design, participant characteristics (including average age, sex, percentage of males), number of participants included in study, follow-up duration, type and number of outcome events, risk ratios (relative risks, odds ratios or hazard ratios), and covariates adjusted for. One author (SKK) initially extracted the data from eligible studies and a second author (SS) independently checked the data with that in original articles.

2.4. Outcomes

Outcomes prespecified to be evaluated included (i) composite cardiovascular events or major adverse cardiovascular events (henceforth referred to as "composite CVD/MACE") (ii) other cardiovascular outcomes (CV mortality, fatal or non-fatal myocardial infarction (MI), coronary heart disease (CHD), stroke, arrhythmias, and heart failure) and (iii) all-cause mortality.

2.5. Risk of bias and certainty of evidence

The Cochrane Risk of Bias in Non-randomised Studies – of Interventions (ROBINS-I) tool was used to evaluate the risk of bias for each individual observational cohort study.[25] This tool assesses risk of bias for the following domains: confounding, participant selection, classification of interventions, deviations from intended interventions, missing data, outcome measurements, and selective reporting. The risk is quantified in each domain as low risk, moderate risk, serious risk, or critical risk, followed by an overall judgement of the risk of bias for each study. The quality of the body of evidence on each outcome was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADEpro) tool (https://gdt.gradepro.org), based on study limitations, inconsistency of effect, imprecision, indirectness and publication bias.[26] The quality was rated as four levels: high, moderate, low and very low.

2.6. Statistical analysis

Summary measures of association were reported as risk ratios (RRs) with 95% confidence intervals (CIs). Given that studies reported risk estimates by different blood pressure categories, we re-categorised the estimates comparing groups based on the data available and according to treatment thresholds by various guidelines.[27–29] Where there was more than one category on either side of the threshold, risk estimates from directly neighbouring categories were extracted and pooled using fixed effect meta-analysis. This was done to ensure a consistent approach to the meta-analysis and enhance comparison and interpretation of the findings. We employed the following risk comparisons for SBP: $\geq$ 140 versus $<$ 140 mmHg; $\geq$ 130 versus $<$ 130 mmHg; $<$ 120 versus $\geq$ 120 mmHg; and per 10 mmHg increase and for DBP: $\geq$ 90 versus $<$ 90 mmHg; $\geq$ 80 versus $<$ 80 mmHg; $<$ 70 versus $\geq$ 70 mmHg; and per 10 mmHg increase. When studies published more than one estimate of the association according to subgroups (e.g., by sex, frailty status, ability to perform activities of daily living, etc), we obtained a within-study summary estimate using a fixed effect meta-analysis. To minimize the effect of between-study heterogeneity, RRs were pooled using a random effects model.[30] Quantification of the extent of statistical heterogeneity across studies employed standard chi-square tests and the I^2 statistic.[31,32] For outcomes with $\geq$ 10 studies, we assessed for small study effects (e.g., publication bias) using formal tests such as Begg's funnel plots[33] and Egger's regression symmetry test.[34] To compare the BP-outcome associations between DM and no DM populations when there was enough data, we employed meta-regression analyses to assess for interactions between the population and the effect of BP on the

outcome.[35,36] A narrative synthesis was performed for a few studies that could not be pooled. The findings of such studies were summarised in tables that included the main characteristics of the study and the results in natural units as reported by the investigators. All tests were two-tailed and p-values of 0.05 or less were considered significant. All analyses were conducted using Stata version MP 17 (Stata Corp, College Station, Texas).

3. Results

3.1. Study identification and selection

Fig. 1 shows the flow diagram of the study selection process. We identified 2289 potentially relevant citations following a search of relevant databases, citation checking, and manual scanning of reference lists of relevant articles and reviews. After the initial screening of titles and abstracts, 184 articles remained for full text evaluation. Following detailed evaluation, 140 articles were excluded because (i) study population was not relevant (n = 86); (ii) exposure was not relevant (n = 29); (iii) they were duplicate studies (n = 9); (iv) outcome was not relevant (n = 8); (v) study design was not relevant (n = 7); and (vi) article was retracted ((n = 1). The remaining 44 articles met the inclusion criteria and were included in the review.[17,37–79].

3.2. Study characteristics and risk of bias

The 44 eligible articles comprised 45 observational cohort studies (41 prospective and 4 retrospective designs) published between 2006 and 2023; 32 studies were based in general population participants (n = 1586,752) and 13 studies based in patients with DM (n = 718,437) (Table 1). Twenty studies were based in Europe (Belgium, Finland, France, Germany, Italy, The Netherlands, Spain, Sweden, and the UK), 15 in Asia (China, Japan, Republic of Korea, and Taiwan), and 10 in North America (Canada and USA). For the general population studies, the average age of participants at baseline ranged from 66 to 92 years, with a weighted mean of 71.1 years. The average duration of follow-up ranged from 2 to 23.8 years, with a weighted mean of 7.9 years. For the population with DM, the corresponding values for average age were 67–81 years and 71.4 years and that for the follow-up duration were 2–10 years and 8.6 years. Systolic and diastolic blood pressure were reported as an average of between one and five readings. Some studies analysed blood pressure as a continuous variable (per 10 mmHg

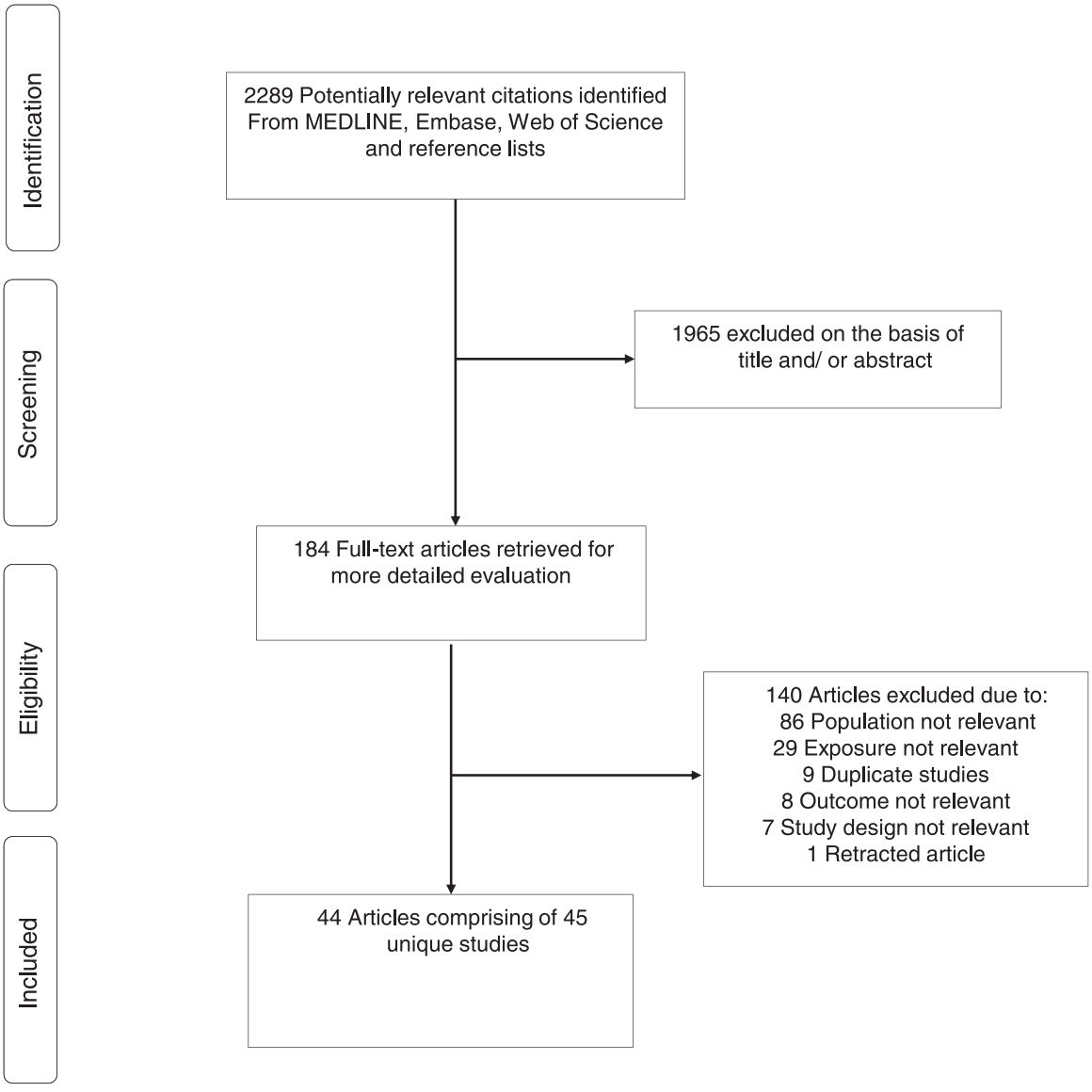

Fig. 1. Selection of studies included in the meta-analysis.

Table 1
Baseline characteristics of included studies.

Author, year of publication	Study	Country	Baseline year	Population	Average age/ range, yrs	Male, %	Follow-up, yrs	No. of participants	Adjustment factors
Ronnback, 2006	Botnia Study	Finland	1990–1997	Diabetes	69.1	46	9.5	1294	Age, gender, smoking, DM duration, and previous CVD
Protogerou, 2007	PROTEGER	France	2000–2001	General population	85.1	26	2.0	331	Age, sex, center effect, stroke, CHD, DM, smoking
Eguchi, 2008	Jichi Medical School- JMS ABPM Study Wave 1/Kar-atsu-Nishiarita Study	Japan	1990–1998/ 1996–2002	General population	71.1	34.7	4.2	967	Age, sex, BMI, antihypertensive drugs, serum creatinine, and site
Eguchi, 2008	Jichi Medical School- JMS ABPM Study Wave 1/Kar-atsu-Nishiarita Study	Japan	1990–1998/ 1996–2002	Diabetes	67.8	48.2	4.2	301	Age, sex, BMI, antihypertensive drugs, serum creatinine, and site
van Hateren, 2010	ZODIAC	The Netherlands	1998–1999	Diabetes	80.0	36	9.8	326	Gender, smoking, BMI, duration of DM, serum creatinine level, cholesterol-HDL ratio, macrovascular complications, albuminuria, the use of lipid lowering and antihypertensive medications and age
Odden, 2012	NHANES	USA	1999–2000/ 2001–2002	General population	74.2	42	6.0	2340	Survey year, age, gender, black race, education, smoking status, cholesterol, CHD, HF, and stroke
Sabayan, 2013	The Leiden 85-Plus Study	Netherlands	1997–1999	General population	85.0	32.9	5.0	513	Sex, cardiovascular diseases, diabetes mellitus, antihypertensive medication, and smoking
Peralta, 2014	Cardiovascular Health Study	USA	1989–1993	General population	78.0	39	8.5	2358	Age, gender, race, education, smoking, physical activity, BMI, DM, total cholesterol, cystatin C and hypertension meds and SBP or DBP, respectively
Iritani, 2014	Ishikawa	Japan	2008	General population	74.2	39.5	4.0	570	Age, female sex, past history of stroke, past history of heart disease, CKD, DM, hyperuricemia, and hypoalbuminemia
Gutiérrez-Misis, 2015	Peñagrande cohort	Spain	2008	General population	77.0	48.5	6.0	649	Age, sex, BMI, TC, depression, cognitive decline, HF and stroke
Hospers, 2015	LASA	The Netherlands	1995–1996	General population	75.8	49	10.6	1466	Age, sex, level of education, BMI, smoking, alcohol consumption, total cholesterol level, CVD, DM and antihypertensive drug use
Afghahi, 2015	Swedish National Diabetes Register	Sweden	2005–2007	Diabetes	75.0	42.8	5.3	33356	Age, diabetes duration, sex, HbA1c, BMI, presence/ absence of albuminuria, smoking, LDL-cholesterol, triacylglycerol/HDL, history of CVD, previous history of CHF, and antihypertensive and lipid-lowering treatment
Ogliari, 2015	Milan Geriatrics 75 + Cohort Study	Italy	2000–2004	General population	82.0	29.8	10.0	1587	Age, sex, education, smoke, hypertension, DM, atrial fibrillation, CHD, claudication, history of TIA or stroke, depression/anxiety, cancer, number of medications, alpha-anti-adrenergics, diuretics, β-blockers, CCBs, angiotensin-converting enzyme inhibitors/angiotensin II antagonists
Yi, 2015	Kangwha Cohort Study	Korea	1985	General population	≥ 65	NR	23.8	3309	Age, sex, hypertension, smoking status, drinking

(*continued on next page*)

Table 1 (*continued*)

Author, year of publication	Study	Country	Baseline year	Population	Average age/ range, yrs	Male, %	Follow-up, yrs	No. of participants	Adjustment factors
									status, occupation, education, marital status, self-reported health, and BMI
Hamada, 2016	UK CPRD	UK	2011	Diabetes	≥ 80	47	2.0	25966	Age, sex, duration of DM, HbA1c, BP, TC, prescription of antidiabetic and cardiovascular drugs, smoking status, BMI, previous diagnoses of CVD, frequency of physician visits, and clustering according to general practice
Tessier, 2016	Sherbrooke	Canada	2002	Diabetes	75.3	50	8.0	198	Unadjusted
Weber, 2016	ACCOMPLISH Substudy	USA	2003	General population	69.7	66.3	3.0	4246	Unadjusted
Weber, 2016	ACCOMPLISH Substudy	USA	2003	Diabetes	67.4	57.5	3.0	6459	Unadjusted
Hartog, 2016	Hengelo	The Netherlands	2010–2011	General population	80.8	29	2.7	290	Age, sex, smoking, DM, history of CVD, hypertension, BMI, number of medication, Barthel index
Hartog, 2016	Hengelo	The Netherlands	2010–2011	Diabetes	80.8	29	2.7	104	Age, sex, smoking, DM, history of CVD, hypertension, BMI, number of medication, Barthel index
Hornsten, 2016; Weidung, 2015	GERDA	Sweden	2000/2002/ 2005/ 2007/ 2010/2012	General population	89.3	34.1	2.9	955	Atrial fibrillation, previous stroke, and congestive heart failure, mini–mental state examination, mini-nutritional Assessment score, Geriatric Depression Scale score, and usual gait speed
Odden, 2016	Health ABC	USA	1997–1998	General population	73.6	48.9	10.0	2669	Age, gender, race, education, smoking status, BMI, fasting glucose, HDL-C, LDL-C, triglycerides, CHD, cerebrovascular disease (not for stroke model), HF, and antihypertensive medications
Shih, 2016	Taipei City Elderly Health Examination Database	Taiwan	2001–2010	General population	72.5	52.1	5.8	128765	Age, sex, BMI, smoking, alcohol intake, DBP, pulse rate, eGFR, diabetes mellitus, CAD, cerebrovascular disease, serum total cholesterol, triglycerides, HDL-C, hemoglobin, fasting glucose, albumin, and uric acid
Vaes, 2017	BELFRAIL	Belgium	2008–2009	General population	84.7	37.3	5.0	566	Gender, age and level of education
Wu, 2017	Health and Retirement Study	USA	2006–2008	General population	74.4	43.7	6.0	7492	Age, sex, race (white, non-white), years of education, smoking status (current, former, never), body mass index, antihypertensive medication, stroke, cardiac disease, cancer, diabetes, high-density lipoprotein cholesterol, total cholesterol, cystatin C, glycosylated hemoglobin, and C reactive protein
Windham, 2017	ARIC	USA	1987–1989	General population	68.9	46.5	12.9	3915	Race, sex, BMI, smoking, DM, heart disease, heart failure, statin use, antihypertensive medications, and clustering by site
Lv, 2018	CLHLS	China	2011	General population	92.1	42.6	3.0	4658	Sex, age (as linear term), marital status, educational background (as linear term), residence, economic income, current smoking, current alcohol consumption, cognitive impairment,

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Table 1 (*continued*)

Author, year of publication	Study	Country	Baseline year	Population	Average age/ range, yrs	Male, %	Follow-up, yrs	No. of participants	Adjustment factors
									restriction on activities of daily living, poor visual function, body mass index (as linear term), central obesity, diabetes mellitus, cardiovascular disease, stroke and other cerebrovascular diseases, respiratory disease, cancer, and frailty
Streit, 2018	The Leiden 85-Plus Study	Netherlands	1997–1999	General population	85.0	33.3	5.0	570	Sex and CVD
Kawauchi, 2018	J-HOP	Japan	2005–2012	General population	82.8	40	3.0	349	Age, sex, BMI, smoking status, DM, pre-existing angina pectoris, myocardial infarction, or stroke, TC, HDL-C, and statin or antihypertensive medication use
Wijsman, 2018	PROSPER	Ireland, Scotland and the Netherlands	1998–1999	General population	75.0	48.3	3.2	5804	Sex, age, country, treatment during follow-up of the study, SBP, histories of hypertension, DM, smoking, BMI, eGFR, NT-proBNP, cardiac troponin T, HDL, LDL, and triglycerides
Douros, 2019	Berlin Initiative Study	Germany	2009–2011	General population	81.0	47.7	6.1	1628	Age, sex, BMI, smoking, alcohol consumption, physical exercise, duration of treated hypertension, GFR, albuminuria, previous MI, previous stroke, diabetes, and number of classes of antihypertensive drugs
Uijl, 2019	CALIBER	UK	2000–2010	General population	65-> 75	NR	5.8	146947	Age, haemoglobin, platelets, total WBC count, total cholesterol, triglycerides, albumin, creatinine, ethnicity, smoking habits, index of multiple deprivation, blood pressure-lowering medication and lipid-lowering drugs
Kim, 2020	NIHS-HEALS	Korea	2002–2011	Diabetes	≥ 70	NR	10.0	241148	Age, income level, history of smoking, physical activity, alcohol consumption, body mass index, fasting glucose, total cholesterol, and use of aspirin or statin
Wan, 2020; Wan, 2018	Hong Kong Hospital Authority	China	2008–2011	Diabetes	70–79	NR	9.3	180492	age, sex, smoking status, BMI; LDL-C, HbA1c, eGFR, use of ACEIs/ARBs), β-blockers, CCBs, diuretics, other antihypertensive drugs, oral antidiabetic drugs, insulin, or lipid-lowering agents, Charlson index, and age-specific regression dilatation ratio
Masoli, 2020	UK CPRD	UK	2000–2014	General population	79.5	41	10.0	415980	IMD, age at index date, sex, blood pressure decline and cardiovascular risk
Hong, 2021	NHID	Republic of Korea	2009–2017	Diabetes	71.0	NR	7.8	225563	Age, sex, smoking, alcohol consumption, regular exercise, BMI, dyslipidemia, CKD, Charlson Comorbidity Index, insulin treatment, number of oral diabetes medications, fasting plasma glucose, hypertension medication, and systolic or diastolic blood pressure
Bragg, 2021	China Kadoorie Biobank	China	2004–2008	Diabetes	70–89	NR	9.0	2873	Educational attainment, smoking, alcohol consumption, physical activity and BMI

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Table 1 (*continued*)

Author, year of publication	Study	Country	Baseline year	Population	Average age/ range, yrs	Male, %	Follow-up, yrs	No. of participants	Adjustment factors
Chun, 2022	Korean NHIS-NSPTA	Korea	2009–2012	General population	66.0	45.7	6.8	708964	Sex, BMI, smoking, hemoglobin level, alcohol drinking, regular exercise, income, antihypertensive drug use, DM, CKD, and COPD
Gabriel, 2022	EPICARDIAN study	Spain	1995	General population	≥ 65	42.1	10.0	3729	Age, DM, smoking, TC, and antihypertensive treatment
Haring, 2022	WHI-LLS	USA	1993–1998	General population	79.0	0	5.3	7354	History of stroke or CHD, age, race/ethnicity, antihypertensive medications, SBP and SBP2, smoking, DM, and BMI
Inoue, 2022	Nambu Cohort Study	Japan	2017	General population	78.0	51	3.4	535	Age and Sex
Kremer, 2022	ActiFE Ulm study	Germany	2009–2010	General population	73.9	58.4	8.1	1170	Age, sex, education, alcohol consumption, smoking, sleep disturbance, DBP, antihypertensive medication
Tian, 2022	Kailuan study	China	2006	General population	66.4	89.6	13.0	97841	Gender, educational level, and family income
Fukunaga, 2023	3 Medical Institutions	Japan	2004	Diabetes	74.9	49.0	7.7	357	Age, gender, HbA1c, total cholesterol, and HDL-C
Howard, 2023	REGARDS	USA	2003–2007	General population	73.0	47.0	11.3	28235	DM, smoking, AF, LVH, and heart disease

ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BMI, body mass index; CAD, coronary artery disease; CCB, calcium channel blocker; CHD, coronary heart disease; CI, confidence interval; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; DBP, diastolic blood pressure; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; HDL-C, high density lipoprotein cholesterol; HF, heart failure; LDL-C, low density lipoprotein cholesterol; LVH, left ventricular hypertrophy; NR, not reported; SBP, systolic blood pressure; TC, total cholesterol; TIA, transient ischemic attack; WBC, white blood cell

Study Abbreviations: ACCOMPLISH, Avoiding Cardiovascular Events in Combination Therapy in Patients Living With Systolic Hypertension; ARIC, Atherosclerosis Risk in Communities; CALIBER, CArdiovascular research using LInked Bespoke studies and Electronic health Records; CLHLS, Chinese Longitudinal Healthy Longevity Survey; GERDA, Gerontological Regional Database; Health ABC, Health, Aging, and Body Composition; J-HOP, Japan Morning Surge-Home Blood Pressure; LASA, Longitudinal Ageing Study Amsterdam; NHID, National Health Information Database; NHANES, National Health and Nutrition Examination Survey; NHIS-NSPTA, National Health Insurance Service- National Health Screening Program for Transitional Ages; NIHS-HEALS, National Health Insurance Services-Health Screening; PROSPER, PROspective Study of Pravastatin in the Elderly at Risk; PROTEGER, PRonostic cardiovasculaire Optimisation Therapeutique En GERiatric Study; REGARDS, REasons for Geographic And Racial Differences in Stroke; UK CPRD, United Kingdom Clinical Practice Research Datalink; WHI-LLS, Women's Health Initiative Long Life Study; ZODIAC, Zwolle Outpatient Diabetes project Integrating Available Care

increase), others as a categorical variable, and others as both. The degree of covariate adjustment varied across studies, but the majority of studies adjusted for established cardiovascular risk factors such as age, sex, body mass index, lipids, smoking, and comorbidities. Using the ROBINS-I risk of bias tool, 40 studies were at moderate risk of bias (i.e., at low or moderate risk of bias for all domains) and 5 studies were at serious risk of bias (i.e., were judged to be at serious risk of bias in at least one domain, but not at critical risk of bias in any domain) (**Appendix 4**).

3.3. Associations of systolic blood pressure with adverse cardiovascular outcomes by diabetes status

3.3.1. Composite CVD/MACE

3.3.1.1. Systolic blood pressure ≥ 140 versus < 140 mmHg –. In the general population, SBP ≥ 140 versus < 140 mmHg was not significantly associated with the risk of composite CVD/MACE (n = 3 studies): RR (95% CIs) of 1.26 (0.96–1.64) (Fig. 2A).

In patients with DM, SBP ≥ 140 versus < 140 mmHg was associated with an increased risk of composite CVD/MACE (n = 3 studies): RR (95% CIs) of 1.56 (1.04–2.34) (Fig. 2**B**). There was no significant evidence of an interaction between DM status and the effect of SBP ≥ 140 versus < 140 mmHg on composite CVD/MACE (*p*-value for meta-regression=.48).

3.3.1.2. Systolic blood pressure ≥ 130 versus < 130 mmHg –. No study evaluated the association between SBP ≥ 130 versus < 130 mmHg and the risk of composite CVD/MACE in the general population.

In patients with DM, SBP ≥ 130 versus < 130 mmHg was not significantly associated with the risk of risk of composite CVD/MACE (n = 2 studies): RR (95% CIs) of 0.79 (0.47–1.33) (Appendix 5B).

3.3.1.3. Systolic blood pressure < 120 versus ≥ 120 mmHg –. In the general population, results of a single study showed that SBP < 120 versus ≥ 120 mmHg was associated with a decreased risk of composite CVD/MACE (Appendix 6). No study evaluated the association in patients with DM.

3.3.1.4. Per 10 mmHg increase in SBP –. In the general population, a 10 mmHg increase in SBP was associated with an increased risk of composite CVD/MACE (n = 4 studies): RR (95% CIs) of 1.15 (1.08–1.23) (Fig. 3A).

In patients with DM, a 10 mmHg increase in SBP was also associated with an increased risk of composite CVD/MACE (n = 2 studies): RR (95% CIs) of 1.10 (1.04–1.18) (Fig. 3B). The associations were not significantly modified by diabetes status (*p*-value for meta-regression=.60).

3.3.2. All-cause mortality

3.3.2.1. Systolic blood pressure ≥ 140 versus < 140 mmHg –. In the general population, SBP ≥ 140 versus < 140 mmHg was not significantly associated with the risk of all-cause mortality (n = 16 studies): RR

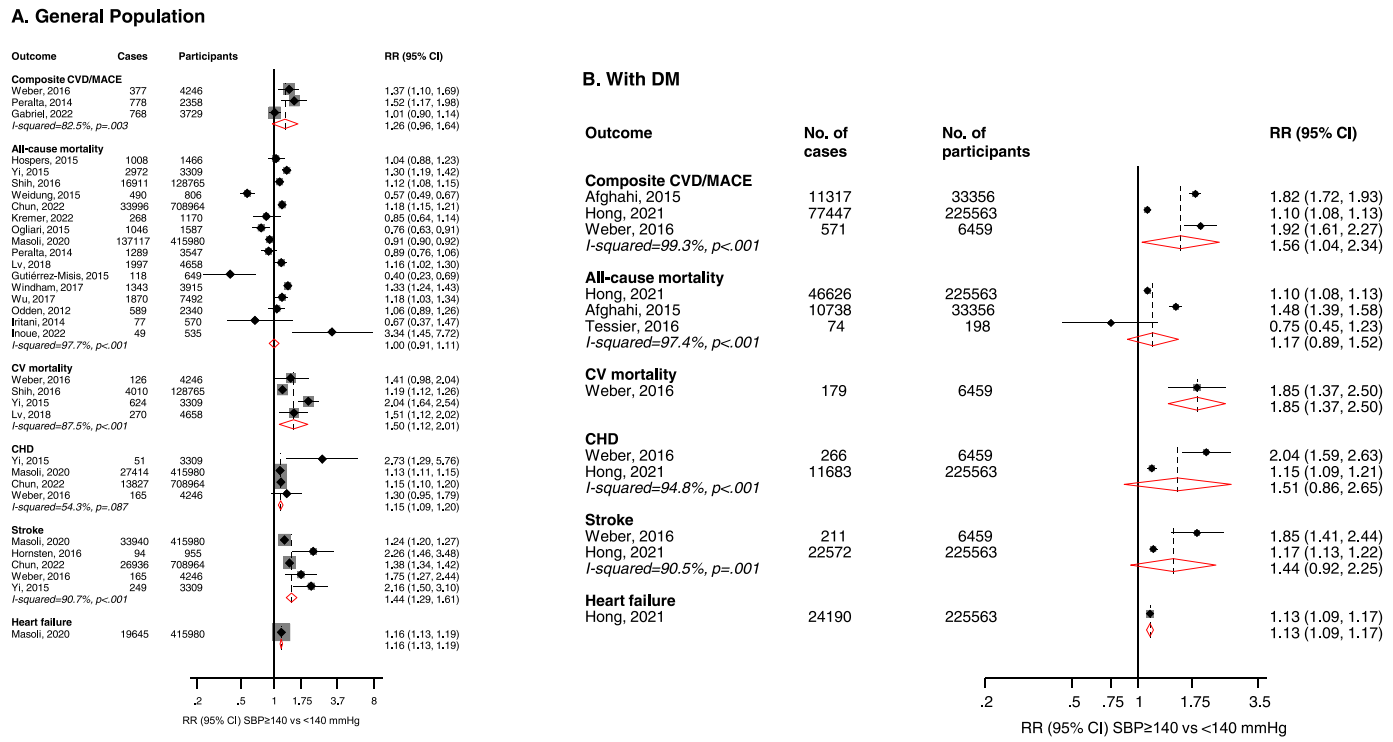

Fig. 2. Risk for adverse cardiovascular outcomes in older people with or without diabetes mellitus for systolic blood pressure threshold ≥ 140 vs < 140 mmHg. CI, confidence interval (bars); CHD, coronary heart disease; CVD, cardiovascular disease; MACE, major adverse cardiovascular events; RR, risk ratio.

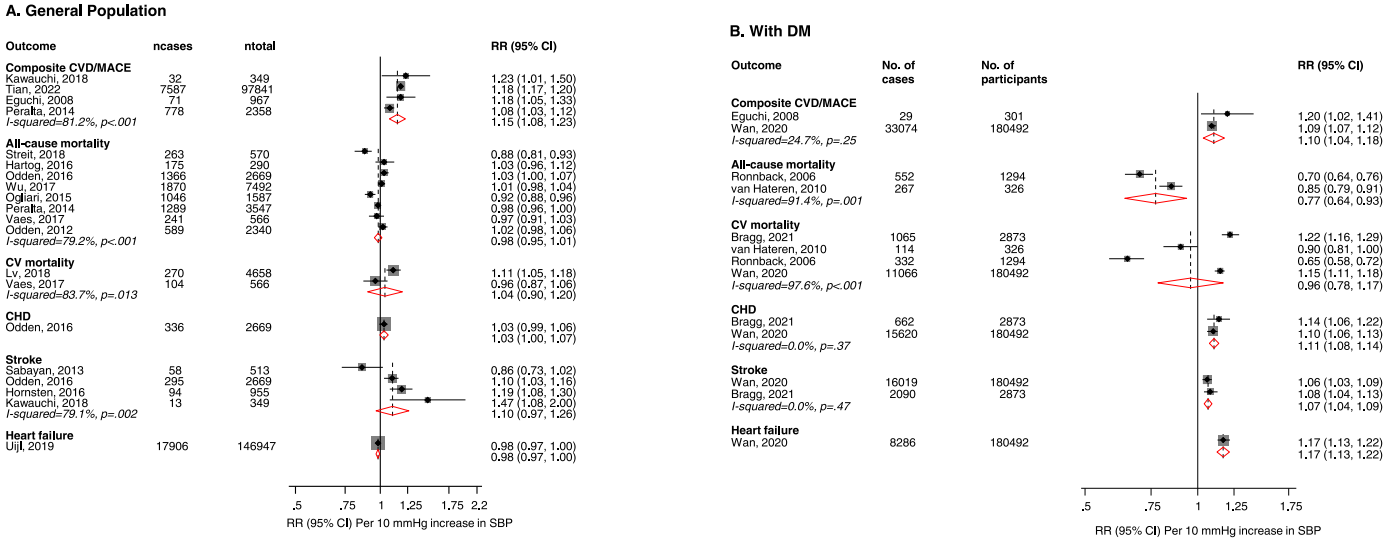

Fig. 3. Risk for adverse cardiovascular outcomes in older people with or without diabetes mellitus per 10 mmHg increase in systolic blood pressure. CI, confidence interval (bars); CHD, coronary heart disease; CVD, cardiovascular disease; MACE, major adverse cardiovascular events; RR, risk ratio.

(95% CIs) of 1.00 (0.91–1.11) (Fig. 2A).

In patients with DM, SBP ≥ 140 versus < 140 mmHg was not significantly associated with the risk of all-cause mortality (n = 3 studies): RR (95% CIs) of 1.17 (0.89–1.52) (Fig. 2B).

3.3.2.2. Systolic blood pressure ≥ 130 versus < 130 mmHg –. In the general population, SBP ≥ 130 versus < 130 mmHg was not significantly associated with the risk of all-cause mortality (n = 4 studies): RR (95% CIs) of 0.95 (0.84–1.06) (Appendix 5A).

In patients with DM, SBP ≥ 130 versus < 130 mmHg was not significantly associated with the risk of risk of all-cause mortality (n = 4 studies): RR (95% CIs) of 0.78 (0.53–1.15) (Appendix 5B).

3.3.2.3. Systolic blood pressure < 120 versus ≥ 120 mmHg –. In the general population, SBP < 120 versus ≥ 120 mmHg was significantly associated with an increased risk of all-cause mortality (n = 10 studies): RR (95% CIs) of 1.22 (1.07–1.38) (Appendix 6). No study evaluated the association in patients with DM.

3.3.2.4. Per 10 mmHg increase in SBP –. In the general population, a 10 mmHg increase in SBP was not significantly associated with all-cause mortality (n = 8 studies): RR (95% CIs) of 0.98 (0.95–1.01) (Fig. 3A).

In patients with DM, a 10 mmHg increase in SBP was associated with a decreased risk of all-cause mortality (n = 2 studies): RR (95% CIs) of 0.77 (0.64–0.93) (Fig. 3B).

3.3.3. CV mortality

3.3.3.1. Systolic blood pressure ≥ 140 versus < 140 mmHg –. In the general population, SBP ≥ 140 versus < 140 mmHg was significantly associated with the risk of CV mortality (n = 4 studies): RR (95% CIs) of 1.50 (1.12–2.01) (Fig. 2A).

A single study in patients with DM showed that SBP ≥ 140 versus < 140 mmHg was significantly associated with an increased risk of CV mortality (Fig. 2B).

3.3.3.2. Systolic blood pressure ≥ 130 versus < 130 mmHg –. Single study results showed that SBP ≥ 130 versus < 130 mmHg was not significantly associated with the risk of CV mortality in the general population (**Appendix 5 A**), but significantly associated with a decreased risk in patients with DM (**Appendix 5B**).

3.3.3.3. Systolic blood pressure < 120 versus ≥ 120 mmHg –. In the general population, SBP < 120 versus ≥ 120 mmHg was not significantly associated with CV mortality (n = 2 studies): RR (95% CIs) of 0.93 (0.74–1.16) (Appendix 6). No study evaluated the association in patients with DM.

3.3.3.4. Per 10 mmHg increase in SBP –. A 10 mmHg increase in SBP was not significantly associated with the risk of CV mortality in the general population (n = 2 studies) or patients with DM (n = 4 studies): RRs (95% CIs) of 1.04 (0.90–1.20) and 0.96 (0.78–1.17), respectively (Fig. 3).

3.3.4. Other cardiovascular outcomes

3.3.4.1. Systolic blood pressure ≥ 140 versus < 140 mmHg –. SBP ≥ 140 versus < 140 mmHg was significantly associated with an increased risk of CHD (n = 4 studies) and stroke (n = 5 studies) in the general population: RRs (95% CIs) of 1.15 (1.09–1.20) and 1.44 (1.29–1.61), respectively (Fig. 2A).

In patients with DM, SBP ≥ 140 versus < 140 mmHg was not significantly associated with the risk of CHD (n = 2 studies) or stroke (n = 2 studies): RRs (95% CIs) of 1.51 (0.86–2.65) and 1.44 (0.92–2.25), respectively (Fig. 2B). The associations were not significantly modified by DM status (*p*-values for meta-regression for all>.10).

Single study results showed that SBP ≥ 140 versus < 140 mmHg was significantly associated with an increased risk of heart failure in the general population and in patients with DM (Fig. 2).

3.3.4.2. Systolic blood pressure ≥ 130 versus < 130 mmHg –. In the general population, SBP ≥ 130 versus < 130 mmHg was not significantly associated with the risk of CHD (n = 2 studies) and stroke (n = 2 studies): RRs (95% CIs) of 1.03 (0.95–1.11) and 1.07 (0.96–1.20), respectively (Appendix 5A). Single study results showed that SBP ≥ 130 versus < 130 mmHg was significantly associated with a decreased risk of heart failure (Appendix 5A).

In patients with DM, results of single studies showed no significant associations with the risk of CHD or heart failure, but an increased risk of stroke (Appendix 5B).

3.3.4.3. Systolic blood pressure < 120 versus ≥ 120 mmHg –. In the general population, SBP < 120 versus ≥ 120 mmHg was not significantly associated with the risk of CHD (n = 3 studies) and stroke (n = 3 studies): RRs (95% CIs) of 1.02 (0.97–1.08) and 0.94 (0.87–1.01), respectively (Appendix 6). Single study results showed that SBP < 120 versus ≥ 120 mmHg was significantly associated with an increased risk of heart failure (Appendix 6). No study evaluated these associations in patients with DM.

3.3.4.4. Per 10 mmHg increase in SBP –. A 10 mmHg increase in SBP was not significantly associated with the risk of stroke in the general population (n = 4 studies): RR (95% CIs) of 1.10 (0.97–1.26) (Fig. 3A).

Pooled analysis of two studies showed that a 10 mmHg increase in SBP was associated with an increased risk of stroke in patients with DM: RR (95% CIs) of 1.07 (1.04–1.09) (Fig. 3b). The associations were not significantly modified by DM status (*p*-value for meta-regression=.58).

Single study results showed that a 10 mmHg increase in SBP was not significantly associated with the risk of CHD or HF in the general population (Fig. 3A). In patients with DM, a 10 mmHg increase in SBP was associated with an increased risk of CHD (n = 2 studies) and heart failure (n = 1 study) (Fig. 3B).

3.4. Associations of diastolic blood pressure with adverse cardiovascular outcomes by diabetes status

3.4.1. Composite CVD/MACE

3.4.1.1. Diastolic blood pressure ≥ 90 versus < 90 mmHg –. In the general population, DBP ≥ 90 versus < 90 mmHg was not significantly associated with the risk of composite CVD/MACE (n = 2 studies) RR (95% CIs) of 1.06 (0.80–1.40) (Fig. 4A).

In patients with DM, single study results showed that DBP ≥ 90 versus < 90 mmHg was associated with an increased risk of composite CVD/MACE (Fig. 4B).

3.4.1.2. Diastolic blood pressure ≥ 80 versus < 80 mmHg –. In the general population, DBP ≥ 80 versus < 80 mmHg was not significantly associated with the risk of composite CVD/MACE (n = 2 studies) RR (95% CIs) of 1.03 (0.95–1.13) (Appendix 7A).

In patients with DM, DBP ≥ 80 versus < 80 mmHg was not significantly associated with the risk of composite CVD/MACE (n = 2 studies): RR (95% CIs) of 1.45 (0.89–2.38) (Appendix 7B).

3.4.1.3. Diastolic blood pressure < 70 versus ≥ 70 mmHg –. In the general population, DBP < 70 versus ≥ 70 mmHg was not significantly associated with the risk of composite CVD/MACE (n = 3 studies): RR (95% CIs) of 1.09 (0.98–1.22) (Appendix 8A).

In patients with DM, DBP < 70 versus ≥ 70 mmHg was not significantly associated with the risk of composite CVD/MACE (n = 2 studies): RR (95% CIs) of 1.20 (0.71–2.01) (Appendix 8B).

3.4.1.4. Per 10 mmHg increase in DBP –. A 10 mmHg increase in DBP was not significantly associated with the risk of composite CVD/MACE in the general population (n = 2 studies): RR (95% CIs) of 1.02 (0.86–1.21) (Fig. 5A). No study evaluated these associations in patients with DM.

3.4.2. All-cause mortality

3.4.2.1. Diastolic blood pressure ≥ 90 versus < 90 mmHg –. In the general population, DBP ≥ 90 versus < 90 mmHg was significantly associated with an increased risk of all-cause mortality (n = 10 studies): RR (95% CIs) of 1.14 (1.07–1.22) (Fig. 4A).

In patients with DM, single study results showed that DBP ≥ 90 versus < 90 mmHg was associated with an increased risk of all-cause mortality (Fig. 4B).

3.4.2.2. Diastolic blood pressure ≥ 80 versus < 80 mmHg –. In the general population, DBP ≥ 80 versus < 80 mmHg was not significantly associated with the risk of all-cause mortality (n = 7 studies): RR (95% CIs) of 1.01 (0.90–1.12) (Appendix 7A).

In patients with DM, DBP ≥ 80 versus < 80 mmHg was not significantly associated with the risk of all-cause mortality (n = 3 studies): RR (95% CIs) of 1.35 (0.87–2.08) (Appendix 7B).

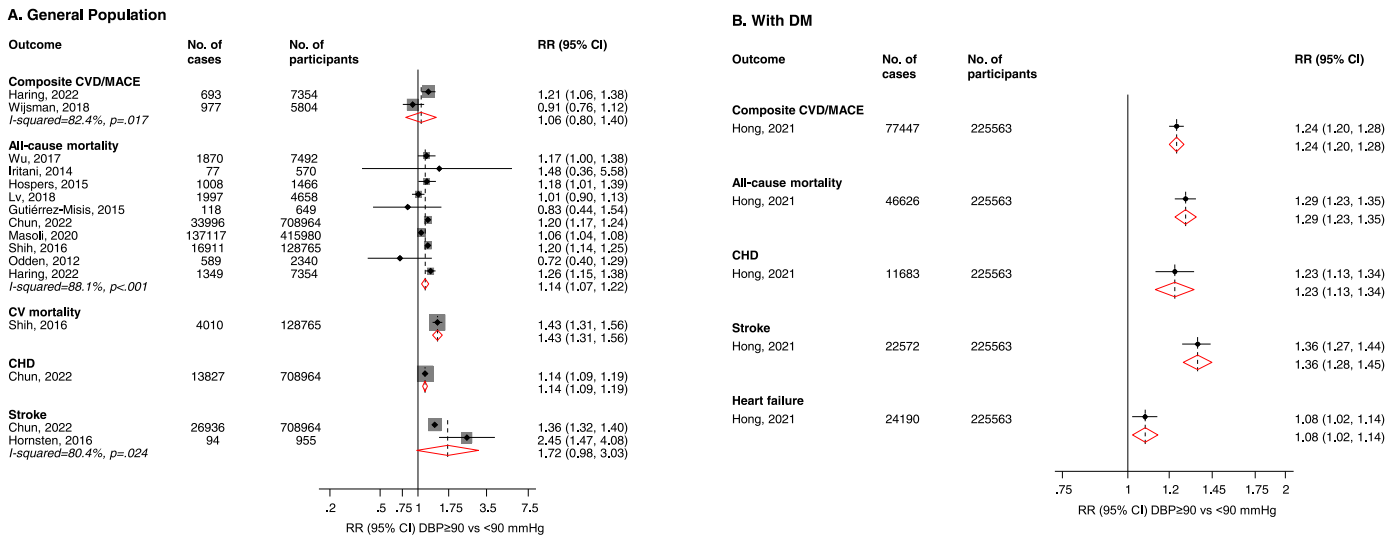

Fig. 4. Risk for adverse cardiovascular outcomes in older people with or without diabetes mellitus for diastolic blood pressure threshold ≥ 90 vs < 90 mmHg. CI, confidence interval (bars); CHD, coronary heart disease; CVD, cardiovascular disease; MACE, major adverse cardiovascular events; RR, risk ratio.

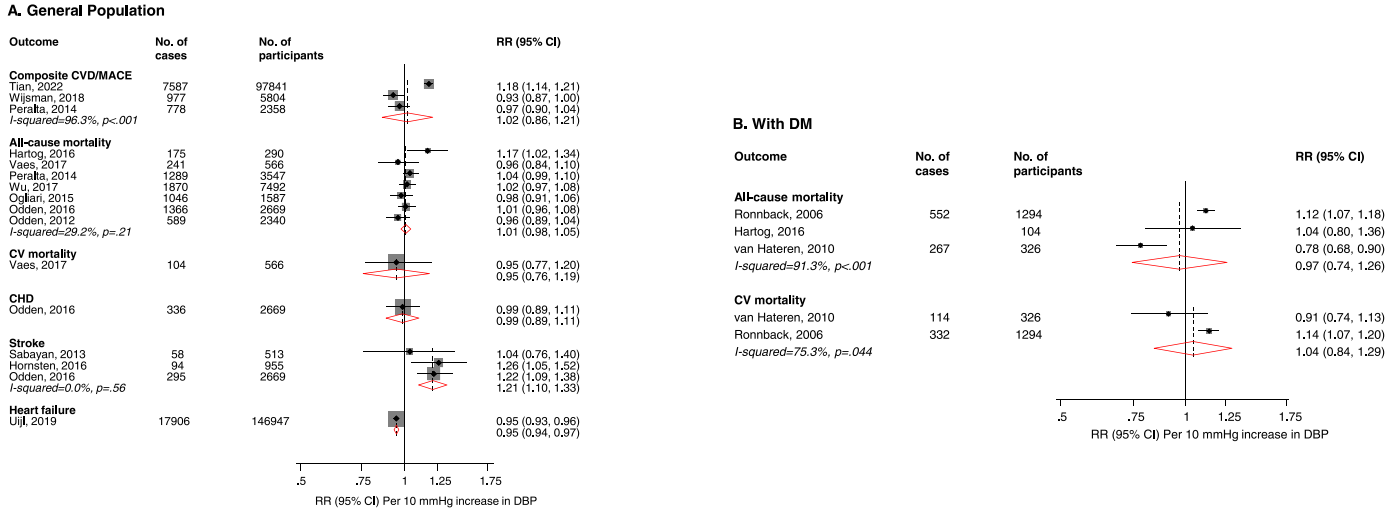

Fig. 5. Risk for adverse cardiovascular outcomes in older people with or without diabetes mellitus per 10 mmHg increase in diastolic blood pressure. CI, confidence interval (bars); CHD, coronary heart disease; CVD, cardiovascular disease; MACE, major adverse cardiovascular events; RR, risk ratio.

3.4.2.3. Diastolic blood pressure < 70 versus ≥ 70 mmHg –. In the general population, DBP < 70 versus ≥ 70 mmHg was not significantly associated with the risk of all-cause mortality (n = 8 studies): RR (95% CIs) of 1.04 (0.98–1.11) (Appendix 8A).

In patients with DM, DBP < 70 versus ≥ 70 mmHg was not significantly associated with the risk of all-cause mortality (n = 3 studies): RR (95% CIs) of 1.40 (0.89–2.22) (Appendix 8B).

3.4.2.4. Per 10 mmHg increase in DBP –. In the general population, a 10 mmHg increase in DBP was not significantly associated with the risk of all-cause mortality (n = 7 studies): RR (95% CIs) of 1.01 (0.98–1.05) (Fig. 5A).

In patients with DM, a 10 mmHg increase in DBP was not significantly associated with the risk of all-cause mortality (n = 3 studies): RR (95% CIs) of 0.97 (0.74–1.26) (Fig. 5B).

3.4.3. CV mortality

3.4.3.1. Diastolic blood pressure ≥ 90 versus < 90 mmHg –. In the general population, a single study showed that DBP ≥ 90 versus < 90 mmHg was significantly associated with an increased risk of CV mortality (Fig. 4A). No study evaluated this association in patients with DM.

3.4.3.2. Diastolic blood pressure ≥ 80 versus < 80 mmHg –. In the general population, a single study showed that DBP ≥ 80 versus < 80 mmHg was significantly associated with an increased risk of CV mortality (**Appendix 7 A**). No study evaluated this association in patients with DM.

3.4.3.3. Diastolic blood pressure < 70 versus ≥ 70 mmHg –. Single study results showed DBP < 70 versus ≥ 70 mmHg was not significantly associated with the risk of CV mortality in the general population, with evidence of an association in patients with DM (Appendix 8).

3.4.3.4. Per 10 mmHg increase in DBP –. In the general population, a single study showed that a 10 mmHg increase in DBP was not significantly associated with the risk of CV mortality (Fig. 5A).

In patients with DM, a 10 mmHg increase in DBP was not significantly associated with the risk of CV mortality (n = 2 studies): RR (95%

CIs) of 1.04 (0.84–1.29) (Fig. 5B).

3.4.4. Other cardiovascular outcomes

3.4.4.1. Diastolic blood pressure ≥ 90 versus < 90 mmHg –. In the general population, DBP ≥ 90 versus < 90 mmHg showed weak evidence of an association with increased risk of stroke (n = 2 studies): RR (95% CIs) of 1.72 (0.98–3.03), with single study results showing an increased risk of CHD (Fig. 4A).

In patients with DM, single study results showed that DBP ≥ 90 versus < 90 mmHg was significantly associated with an increased risk of CHD, stroke and heart failure (Fig. 4B).

3.4.4.2. Diastolic blood pressure ≥ 80 versus < 80 mmHg –. In the general population, single study results showed no associations of DBP ≥ 80 versus < 80 mmHg with the risk of CHD or stroke (Appendix 7A).

In patients with DM, DBP ≥ 80 versus < 80 mmHg was associated with an increased risk of CHD and stroke, but not heart failure in single studies (Appendix 7B).

3.4.4.3. Diastolic blood pressure < 70 versus ≥ 70 mmHg –. Single study results showed that DBP < 70 versus ≥ 70 mmHg was not significantly associated with the risk of CHD or stroke in the general population (Appendix 8 A).

In patients with DM, single study results showed that DBP < 70 versus ≥ 70 mmHg was not significantly associated with the risk of CHD, stroke, or HF (Appendix 8B).

3.4.4.4. Per 10 mmHg increase in DBP –. In the general population, single studies showed that a 10 mmHg increase in DBP was not significantly associated with the risk of CHD but associated with a decreased risk of heart failure (Fig. 5A). Pooled analysis of 3 studies showed that a 10 mmHg increase in DBP was significantly associated with an increased risk of stroke: RR (95% CIs) of 1.21 (1.10–1.33) (Fig. 5A). No study evaluated these associations in patients with DM.

3.5. Qualitative synthesis

A number of studies reported results that could not be pooled because they presented risk estimates for combined thresholds of SBP and DBP.[44,52,77–79] The results were inconsistent, however, SBP cutoffs of ≥ 140 and DBP cutoffs of ≥ 90 mmHg were associated with increased risk of adverse cardiovascular outcomes (Appendix 9).

3.6. Publication bias

We assessed for evidence of small study effects (publication bias) among studies of outcomes that were based on a pooled analysis of ≥ 10 studies. Funnel plots of the associations between (i) SBP ≥ 140 versus < 140 mmHg and the risk of all-cause mortality in the general population (n = 16 studies); (ii) SBP < 120 versus ≥ 120 mmHg and the risk of all-cause mortality in the general population (n = 10 studies); and (iii) DBP ≥ 90 versus < 90 mmHg and the risk of all-cause mortality in the general population (n = 10 studies), all showed visual evidence of symmetry (**Appendix 10**). These were consistent with Egger's regression symmetry tests ($p = .32$), ($p = .92$) and ($p = .62$), respectively.

3.7. GRADE summary of findings

The GRADE working group recommends up to 7 patient-important outcomes to be listed in the "summary of findings" tables in systematic reviews.[26] We selected the most relevant outcomes of composite CVD/MACE and all-cause mortality, and the blood pressure comparisons were chosen based on how frequently they were reported. GRADE ratings for the relevant outcomes are reported in a summary of findings table in Appendix 11. GRADE quality of the evidence ranged from low to very low.

4. Discussion

In an aggregate synthesis of 45 unique observational cohort studies aimed at comparing the relationship between blood pressure and the risk of adverse cardiovascular outcomes in older individuals with and without DM, the overall findings suggested that SBP and DBP conferred similar risk in both populations. Systolic blood pressure at a threshold of ≥ 140 mmHg was associated with an increased risk of CV mortality and heart failure in both populations, as well as an increased risk of composite CVD/MACE in patients with DM. Pooled analysis demonstrated that SBP at a threshold of ≥ 130 mmHg was not associated with an increased risk of any of the assessed outcomes in either population, whereas a threshold of < 120 mmHg was associated with an increased risk of all-cause mortality in the general population. No study was identified that assessed associations between SBP at a threshold of < 120 mmHg and adverse outcomes in patients with DM. In studies that modelled SBP as a continuous variable, a 10 mmHg increase in SBP was associated with an increase in the risk of composite CVD/MACE. A DBP ≥ 90 mmHg was associated with an increased risk of certain adverse cardiovascular outcomes in both populations, such as stroke, CHD, and all-cause mortality. There was no significant evidence of associations between DBP at a threshold of ≥ 80 or < 70 mmHg with most outcomes, except for an increased risk of CV mortality based on a single study. The certainty of the evidence, as assessed by the GRADE framework, ranged from low to very low.

There has been no previous synthesis comparing adverse cardiovascular outcomes of different blood pressure thresholds in older individuals with and without diabetes mellitus (DM). Therefore, direct comparisons and discussions of these findings in the context of previous work are not possible. A recent systematic meta-analysis of 9 observational cohort studies explored the association between blood pressure and clinical outcomes in older adults, but the comparison focused on individuals with and without frailty.[20] Among their several pre-specified outcomes, only mortality outcomes were evaluated. Furthermore, the study reported risk estimates per 10 mmHg difference in SBP or DBP, and only one risk category for SBP or DBP was utilized (<140 vs >140 and <90 vs >90 mmHg).

Most guidelines for hypertension recommend a blood pressure goal of < 140/90 mmHg at all ages;[27–29] the threshold is lower for those with co-existing hypertension and DM at < 130/80 mmHg given their substantially higher risk of developing CVD.[28,29] Given that older patients are often frail, have multiple comorbidities, and are more vulnerable to the complications of intensive blood pressure control, by how much blood pressure should be lowered in older patients with DM is a very controversial topic. There is limited data on target blood pressure levels in these patients because most landmark hypertension trials did not report age-specific results or excluded older patients with DM.[23] Recommended blood pressure targets for older adults with DM have been mostly extrapolated from data in the general population and have not been consistent. It appears some previous guidelines have not been very clear on blood pressure targets specifically for older people with DM; most have specifically focused on the general population, patients with DM, and older patients. For instance, the UK National Institute for Health and Care Excellence guideline for hypertension in adults recommends that clinic blood pressure should be reduced to below 150/90 mmHg for adults with hypertension aged 80 years and over and that clinical judgement should be used for people with frailty or multimorbidity.[27] On the contrary, a number of guideline bodies have recently specified targets for older patients with DM. The U.S. Department of Veteran Affairs and Department of Defence 2020 guidelines for primary care providers recommend a SBP goal of < 150 mmHg for patients with DM aged 60 years and over.[80] The 2018 European Society of Cardiology (ESC)/European Society of Hypertension (ESH) guidelines

recommend a target of 130–140/< 80 mmHg for patients ≥ 65 years with DM.[29] The International Diabetes Federation suggests target values of < 140/90 mmHg for patients 70–80 years old and < 150/90 mmHg for patients over 80 years old.[81].

Our study findings do not support stringent blood pressure control for older patients with DM (e.g., <120/70 mmHg). The evidence suggests a target range of > 130/80 to < 140/90 mmHg would be most appropriate for patients ≥ 65 years with DM. In an elegant study by Grossman and Grossman that comprehensively reviewed the evidence supporting different blood pressure targets in patients with DM and various guideline recommendations, the authors proposed that blood pressure target levels should be < 140–150/90 mmHg in older patients (>80 years) with DM.[22] These targets reflect the current study findings. The 2018 ESC/ESH guidelines also recommend that SBP should not be lowered to < 120 mmHg, which also reflect our study findings showing an increased risk of all-cause mortality for a SBP threshold of < 120 mmHg. Whether to choose 130/80 or 140/90 mmHg as the goal for these patients may depend on the presence of kidney disease and other comorbidities. Trial evidence does suggest that blood pressure targets may differ according to the stage of kidney disease.[82] Though tighter blood pressure control may be associated with better kidney outcomes, people with diabetic kidney disease are older, frail and have multiple morbidities, hence, lower blood pressure targets are likely to be associated with increased adverse events including postural hypotension, falls, fractures, acute kidney injury and hyperkalaemia. Blood pressure treatment of older patients with hypertension and DM is a complex process and specific blood pressure targets may need to be individualised and tailored to each patient's health status. Grossman and Grossman[22] propose that blood pressure levels in this population should be monitored in the sitting and standing position. There is a paucity of prospective trials on clinical outcomes of blood pressure regulation in older patients with DM; this is a topic that warrants further investigation.

4.1. Strengths and limitations

We have conducted the first systematic meta-analysis to estimate the risk of adverse cardiovascular outcomes associated with different blood pressure thresholds in older adults with DM compared to the risk in participants from the general population. This review has several strengths. Firstly, we were able to harmonize various blood pressure categories into consistent accepted thresholds, which improved the pooling approach. Secondly, we evaluated a comprehensive range of adverse cardiovascular outcomes, including all-cause mortality. Thirdly, we assessed the risk of bias in individual studies and used validated tools to rate the certainty of the evidence. Although the limitations of this review are inherent to the included studies rather than the adopted methodology, they should still be taken into consideration. One important limitation was the inability to make direct head-to-head comparisons of the associations between blood pressure and outcomes in individuals with and without DM, as these associations were predominantly evaluated in different cohorts. However, we drew appropriate inferences using meta-regression techniques. It would have been valuable to assess the impact of SBP at a threshold of ≥ 150 mmHg on adverse outcomes, as some guideline bodies recommend SBP target levels of < 150 mmHg for patients with DM who are over 80 years old. However, most eligible studies did not provide data on this aspect. Additionally, we were unable to evaluate the impact of blood pressure on outcomes at different age cutoffs (e.g., ≥65–80 vs >80 years) due to limited data availability. A concern arises from the fact that a number of studies included in our analysis relied on single readings of blood pressure for their analyses, which are considered unreliable. The pooled findings were based on studies that inconsistently adjusted for confounding factors. However, we extracted risk estimates that were maximally adjusted, and the majority of studies did account for established risk factors such as age, sex, body mass index, lipids, smoking, and comorbidities. An important limitation that emerged was our inability to evaluate the effect of blood pressure on adverse cardiovascular outcomes in participants with chronic kidney disease (CKD) or albuminuria. This is particularly significant given that interventional evidence differs in type 1 and type 2 diabetes populations and in different stages of CKD in terms of blood pressure target levels. For instance, guidelines of the Joint Association of British Clinical Diabetologists and UK Kidney Association recommend that in people with T2D, CKD and urine albumin to creatinine ratio (ACR) > 3 mg/mmol, one should aim for a target upright blood pressure that is consistently < 130/80 mmHg; however, a target blood pressure of < 140/90 mmHg is recommended for those with T2D, CKD stages G4 and G5, and ACR ≤ 3 mg/mmol.[82] Our inability to assess these specific subgroups due to the lack of data underscores the need for further research in this area.

5. Conclusions

Elevated SBP, defined as a threshold of ≥ 140 mmHg or per 10 mmHg increase, was associated with an increased risk of major adverse cardiovascular outcomes in older adults, both in the general population and in individuals with DM. No excess risk was observed in either population. There was no evidence of associations between SBP at a threshold of ≥ 130 mmHg and adverse cardiovascular outcomes in both populations. Systolic blood pressure below < 120 mmHg was linked to an increased risk of all-cause mortality. Diastolic blood pressure at a threshold of ≥ 90 mmHg was associated with an increased risk of adverse cardiovascular outcomes and all-cause mortality in individuals with DM. The current findings, albeit based on a relatively limited number of pooled studies and low to very low certainty of evidence, suggests that a blood pressure target range of > 130/80 to < 140/90 mmHg may be optimal for patients aged ≥ 65 years with DM, which aligns with recommendations from some guideline bodies. Specific blood targets may need to be individualised based on patients' unique circumstances. Moreover, these findings do not support the implementation of strict blood pressure control in this specific population group. However, it is important to note that definitive RCTs are needed to support these observational data. Large-scale studies are warranted to provide further clarity on the impact of higher SBP levels (e.g., a threshold of ≥150 mmHg) on adverse cardiovascular outcomes in these populations.

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Primary Care Diabetes Europe.

CRediT authorship contribution statement

Samuel Seidu: Conceptualization (lead); Data curation (equal); Formal analysis (equal); Funding acquisition (lead); Investigation (lead); Methodology (lead); Project administration (lead); Resources (lead); Software (equal); Supervision (equal); Validation (equal); Visualization (equal); Writing-original draft (equal); Writing-review & editing (equal). **Setor Kunutsor**: Conceptualization (supporting); Data curation (equal); Formal analysis (lead); Funding acquisition (supporting); Investigation (equal); Methodology (equal); Project administration (supporting); Resources (supporting); Software (equal); Supervision (supporting); Validation (equal); Visualization (equal); Writing-original draft (lead); Writing-review & editing (lead). **PINAR TOPSEVER:** Conceptualization (supporting); Data curation (supporting); Formal analysis (supporting); Funding acquisition (supporting); Investigation (supporting); Methodology (supporting); Project administration (supporting); Resources (lead); Software (supporting); Supervision (supporting); Validation (equal); Visualization (equal); Writing-original draft (supporting); Writing-review & editing (equal). **Clare Hambling:** Conceptualization (supporting); Data curation (supporting); Formal analysis (supporting); Funding acquisition (supporting); Investigation

(supporting); Methodology (equal); Project administration (supporting); Resources (supporting); Software (supporting); Supervision (supporting); Validation (equal); Visualization (supporting); Writing-original draft (supporting); Writing-review & editing (equal).

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Conflict of interest

SS reports personal fees from Amgen, AstraZeneca, NAPP, Lilly, Merck Sharp & Dohme, Novartis, Novo Nordisk, Roche, Sanofi-Aventis, and Boehringer Ingelheim. Additonally SS reports grants from AstraZeneca, Sanofi-Aventis, Servier, and Janssen.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.pcd.2023.09.007.

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