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ORIGINAL ARTICLE

Risk of subarachnoid haemorrhage reduces with blood pressure values below hypertensive thresholds

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Abstract

Background: Hypertension is a known risk factor for subarachnoid haemorrhage (SAH). The aim of this study was to describe the relationship between blood pressure and SAH using a large cohort study and perform a meta-analysis of the published literature.

Methods: Participants in the UK Biobank were followed up via electronic records until 31 March 2017. Cox proportional hazards models were used to analyse the association between baseline blood pressure (systolic blood pressure [SBP], diastolic blood pressure [DBP] and MABP [mean arterial blood pressure]) and subsequent aneurysmal SAH. Linearity was assessed by comparing models including and excluding cubic splines. Electronic databases were searched from inception until 11 February 2022 for studies reporting on blood pressure and SAH.

Results: A total of 500,598 individuals were included with 539 (0.001%) suffering from aneurysmal SAH. Nonlinear models including cubic splines visually appeared linear between SBP of 110 and 180 mmHg and there was minimal difference in fit between linear and nonlinear models. When values were stratified, those with SBP 120–130 mmHg were at higher risk compared to those with SBP <120 mmHg (hazard ratio [HR] 1.41 [1.02, 1.95]). The meta-analysis demonstrated a similar increased risk of SAH in individuals with SBP 120–130 mmHg relative to those with <120 mmHg (HR 1.41 [1.17, 1.72]). A stepwise increase in risk was also seen at each subsequent threshold (130–140 mmHg: HR 1.85 [1.53, 2.24], 140–160 mmHg: HR 2.16 [1.57, 2.98], 160–180 mmHg: HR 2.81 [1.85, 4.29], >180 mmHg: HR 5.84 [1.94, 17.54]).

Conclusions: The rate of SAH increases linearly with higher SBP in the general population and specifically appears lower in those with SBP <120 mmHg.

KEYWORDS
blood pressure, hypertension, stroke, subarachnoid haemorrhage

INTRODUCTION

Subarachnoid haemorrhage (SAH) is a rare form of stroke, associated with substantial morbidity and mortality [1]. Rupture of intracranial aneurysms accounts for the majority of spontaneous SAH cases. SAH is known to be more common in patients with hypertension [2, 3]. However, it is unclear whether the relationship between blood pressure and SAH is linear and whether there are thresholds above or below which the relationship no longer holds.

This question is mirrored for cardiovascular disease in general, where it is well established that elevated blood pressure, especially systolic blood pressure (SBP), is associated with an increased risk

of cardiovascular events, including many other types of intracranial haemorrhage [4–6]. Classically, patients have been deemed hypertensive if blood pressure values are >140/90 mmHg [6]. However, recent studies have suggested that lower blood pressure values for high-risk patients could be beneficial [7]. A recent randomised controlled trial found that intensive blood pressure management (SBP <120 mmHg) was associated with a reduced risk of all cause cardiovascular mortality, including stroke [7].

Consequently, the main aim of this study was to assess whether the relationship between blood pressure and SAH is linear and identify any threshold value over which the rate of SAH increases. Additionally, we aimed to compare the relative importance of SBP and diastolic blood pressure (DBP), and any differences between male and female subjects, given reports of differing relationships in these groups [8, 9].

METHODS

UK Biobank cohort

The UK Biobank is a population-based cohort study of 502,489 participants from England, Scotland and Wales. Participants aged 40–69 years were initially recruited between 2006 and 2010. Participants were followed up from baseline assessment until 31 March 2017 through follow-up assessment centre visits and electronic medical records in this study. Participants were censored at death. This study was conducted as part of UK Biobank application ID 49305. UK Biobank has National Research Ethics Committee approval (16/NW/0274) and this study had institutional approval (ERGO 45963, University of Southampton). All data are available from the UK Biobank. Written informed consent was obtained from all participants. Participants were kept blinded to their blood pressure measurements and were not given any advice about blood pressure treatment.

Subarachnoid haemorrhage

SAH cases were identified through linked hospital admission data, including Hospital Episode Statistics—Admitted Patient Care (England) (HES APC), Scottish Morbidity Records—General/Acute Inpatient and Day Case Admissions (Scotland) (SMR01) or Patient Episode Database for Wales (PEDW), and death registry data. This included participants with one (or more) International Classification of Diseases 10th Revision (ICD-10) codes associated with SAH (Table S1). Participants with a SAH code date prior to baseline assessment were excluded from this analysis (Figure S1). ICD-10 codes from linked hospital admissions data or death registry data were used to further categorise SAH cases. Cases associated with traumatic brain injury prior to or within 28 days of the SAH were excluded on the basis that they may have been incorrectly coded (Table S1). Cases associated with non-aneurysmal SAH codes were excluded.

Blood pressure

Automated blood pressure readings were recorded at the baseline assessment centre visit. Age, sex, smoking status, alcohol use, prior stroke, hypertension, ischaemic heart disease, anticoagulant use and antiplatelet use were ascertained from participants at assessment centre visits.

Statistical analysis

Cox proportional hazards models were used to analyse the association between blood pressure (SBP, DBP, mean arterial blood pressure [MABP]) and SAH. Prior to imputation, hazard ratios (HRs) were plotted as a function of blood pressure values (SBP and DBP) using models including natural cubic splines. Cubic spline interpolation fits cubic polynomials at specific intervals to create a curve fitting nonlinear data. A reference value of 110 mmHg was used for SBP and 75 mmHg was used for DBP. Knots were included at thresholds defined by the European Society of Cardiology (ESC)/European Society of Hypertension (ESH) guideline. To assess linearity, the Akaike Information Criterion (AIC) was used to compare the goodness of fit of models including and excluding splines. A delta-AIC >2 was used to define a difference between models. Multiple imputation, using classification and regression trees, was used to account for missing variables. Table 1 shows the level of missingness. Five separate datasets were generated, and results pooled by averaging the estimates of the complete data model and computing the total variance over the repeated analyses by Rubin's rules. A stepwise variable selection procedure, with iterations between the 'forward' and 'backward' steps, was used to obtain the best candidate final regression model for the multivariable regression analysis. The significance levels for entry (SLE) and for stay (SLS) used equalled 0.15. Covariates that were removed from the model included ischaemic heart disease, antiplatelet use and anticoagulant use and those used in the final multivariable model were age, sex, smoking, alcohol, and stroke history. Analyses were performed including SBP, DBP and MABP as continuous variables. Subsequent analyses were performed using ESC/ESH guidelines to stratify SBP and DBP values. Subgroup analyses were performed for male and female cohorts separately. Analysis was conducted in the statistical software package R (R Core Team, 2020. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria; https://www.R-project.org/).

Systematic review

We followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement for reporting of this systematic review. Electronic databases including Medline, Embase and Google Scholar were searched from inception to 11 February 2022.

TABLE 1 UK Biobank cohort characteristics.

Variable	Overall ($n = 500,598$)	Missing data
Aneurysmal subarachnoid haemorrhage	539 (0.001%)	0 (0%)
Sex (male)	228,346 (46%)	0 (0%)
Age (years)	60.77 (±6.74)	0 (0%)
Smoking		
Current smoking	52,716 (11%)	2578 (0.005%)
Previous smoking	172,512 (34%)	
Alcohol		
Current alcohol	459,086 (92%)	1279 (0.003%)
Previous alcohol	17,987 (4%)	
Antiplatelet use	4156 (0.008%)	0 (0%)
Anticoagulant use	5331 (0.01%)	0 (0%)
Hypertension	135,141 (27%)	1812 (0.004%)
Antihypertensive use	101,225 (20%)	0 (0%)
Ischaemic heart disease	22,858 (5%)	1812 (0.004%)
Stroke	7518 (2%)	1812 (0.004%)

Search terms for blood pressure ("blood pressure", "systolic blood pressure", "diastolic pressure", "mean arterial pressure" and "mean arterial blood pressure") were combined with search terms for SAH ("subarachnoid bleed", "subarachnoid h(a)emorrhage", "cerebral aneurysm" and "intracranial aneurysm").

Study selection

Following removal of duplicates, the titles and abstracts of each study were reviewed by one of the authors (F.E.). Full texts were reviewed for all studies reporting on blood pressure and SAH. Abstracts, case reports, conference presentations, editorials, reviews and expert opinions were excluded. Publications were limited to those involving human subjects written in English. When multiple papers reported on the same cohort of participants, the most recent or the most relevant study was included for analysis.

Data extraction

All data including reported HRs, odds ratios (ORs), rate ratios (RRs) and confidence intervals (CIs) were extracted from the text and figures presented in the published articles. Adjusted values were used wherever possible.

Statistical analysis

Analysis was conducted using Review Manager (RevMan version 5.3.5; The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen). The Newcastle-Ottawa Scale was used to assess the quality of included studies (Table 2). Studies stratifying results by ESC/ESH guidelines thresholds were compared. The overall effect of each analysis is presented in a forest plot. HR, OR and RR were analysed separately. For each analysis, the heterogeneity of the included studies was analysed using standard χ^2 tests. The percentage of variation across the studies was quantified using the I^2 statistic. I^2 values of 25%, 50% and 75% corresponded to low, moderate and high degrees of heterogeneity, respectively. A p value was considered significant at <0.05. Subgroup analyses were performed for male and female participants.

RESULTS

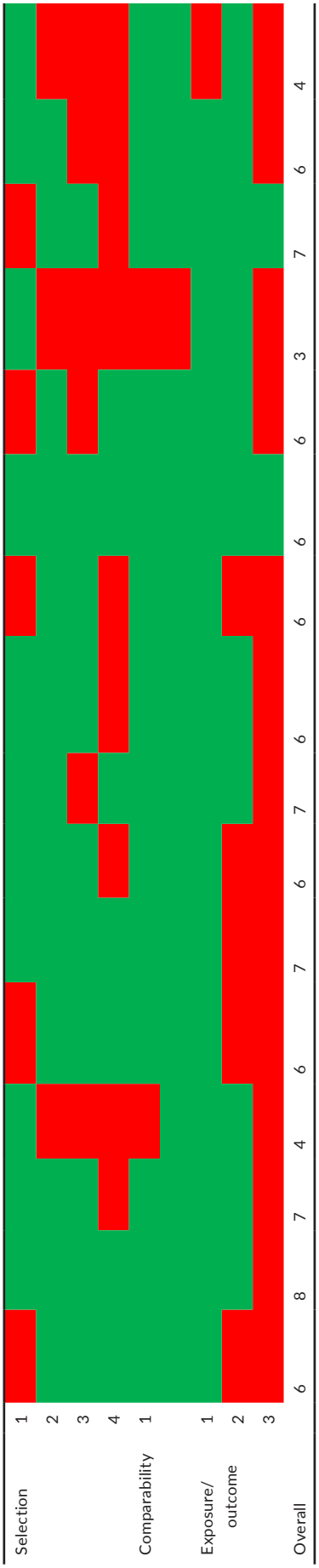
UK Biobank

Of a total of 502,489 participants in the UK Biobank, 500,598 participants were eligible for inclusion. There were a total of 539 SAH cases on follow-up. The mean time from baseline assessment to SAH was 4.45 years. Table 1 describes the cohort characteristics.

Blood pressure as a continuous variable

A history of hypertension was significantly associated with SAH (HR 1.25 [1.04–1.51]). A significant association was found between aneurysmal SAH and higher SBP (HR 1.10 [1.05, 1.15], /10 mmHg), DBP (HR 1.17 [1.07, 1.27], /10 mmHg) and MABP (HR 1.16 [1.08, 1.24], /10 mmHg). This association was seen in participants without

TABLE 2 Quality of included studies using the Newcastle-Ottawa Scale.



Note: Green- positive, Red- negative.

a history of hypertension (SBP: HR 1.15 [1.08–1.21], DBP: HR 1.22 [1.10–1.36], MABP: HR 1.23 [1.14–1.34]) and in participants not taking antihypertensive medication (SBP: HR 1.14 [1.08–1.20], DBP: HR 1.25 [1.14–1.38], MABP: HR 1.23 [1.12–1.34]). However, no association was seen in participants with a history of hypertension (SBP: HR 0.99 [0.91–1.08], DBP: HR 1.00 [0.86–1.16], MABP: HR 0.99 [0.87–1.13]) or in participants already taking antihypertensive medication (SBP: HR 0.97 [0.88–1.07], DBP: HR 0.92 [0.77–1.10], MABP: HR 0.93 [0.80–1.09]).

Figure 1 shows HR as a function of blood pressure for the nonlinear models with natural cubic splines at each of the ESC/ESH thresholds. For SBP, visually there is a broadly linear increase in HR between 100 and 180 mmHg beyond which CIs were wide due to low case numbers. Furthermore, there was a minimal difference between the nonlinear (AIC = 13712.28) and linear models (AIC = 13709.43). A similar relationship was found for DBP between 60 and 100 mmHg (Figure 1). The linear model (AIC = 13712.80) resulted in a better overall fit compared to the nonlinear model (AIC = 13716.72). The models of SBP provided a better fit than those of DBP (delta-AIC >2).

Blood pressure stratified

The HR associated with SAH stratified by SBP ESC/ESH guideline thresholds is shown in Table 3. Notably participants with SBP 120–130 mmHg were more likely to suffer a SAH than those with SBP <120 mmHg (HR 1.41 [1.02, 1.95]) (Table 3). Participants with blood pressures >130 mmHg were also more likely to suffer aSAH with greater HR noted (130–139 mmHg: HR 1.74 [1.28–2.38], 140–159 mmHg: HR 1.60 [1.18–2.16], 160–179 mmHg: HR 1.99 [1.39–2.84], >180 mmHg: HR 1.81 [1.02–3.21]). Compared to DBP <80 mmHg participants with a blood pressure of 80–84 mmHg were more likely to suffer a SAH (HR 1.26 [1.00–1.58]) (Table 3). There was no significant association for values 85–89 mmHg (HR 1.07 [0.83–1.39]). Subsequent thresholds showed a significant association (90–99 mmHg: HR 1.31 [1.03–1.66], 100–109 mmHg: HR 1.61 [1.09–2.40], >110 mmHg: 3.23 [1.66–6.31]). There was no difference in sensitivity analyses including non-aneurysmal SAH cases (data not presented).

Meta-analysis

A total of 4051 studies were identified from the initial database search (Figure S2). Overall, 16 studies fulfilled the relevant inclusion and exclusion criteria [8–23]. Table 4 summarises the characteristics of the included studies. Overall, these studies included 3,578,979 participants and 10,797 SAH cases. Eleven included studies were cohort studies, two studies were meta-analyses of multiple cohort studies, and the remaining three studies were case–control studies. The meta-analyses included several other studies included in this analysis [8, 12, 13, 20]. Only three studies reported on the

TABLE 3 Hazard ratio associated with subarachnoid haemorrhage stratified by systolic blood pressure thresholds.

SBP (mmHg)	SAH	HR	*P* value	DBP (mmHg)	SAH	HR	*P* value
<120	61	Ref.	Ref.	<80	219	Ref.	Ref.
120–129	96	1.41 (1.02–1.95)	0.04	80–84	120	1.26 (1.00–1.58)	0.05
130–139	129	1.74 (1.28–2.38)	<0.01	85–89	90	1.07 (0.83–1.39)	0.60
140–159	167	1.60 (1.18–2.16)	<0.01	90–99	109	1.31 (1.03–1.66)	0.03
160–179	71	1.99 (1.39–2.84)	<0.01	100–109	30	1.61 (1.09–2.40)	0.02
>180	15	1.81 (1.02–3.21)	0.04	>110	9	3.23 (1.66–6.31)	<0.01

Abbreviations: DBP, diastolic blood pressure; HR, hazard ratio; Ref., reference; SAH, subarachnoid haemorrhage; SBP, systolic blood pressure.

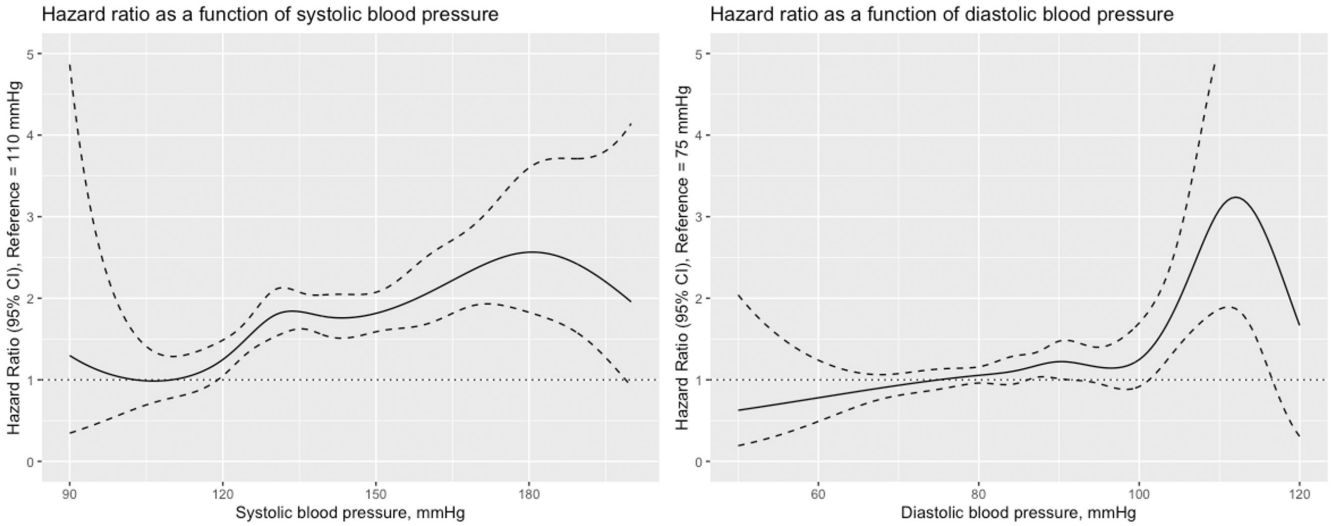


FIGURE 1 Nonlinear models including natural cubic splines at European Society of Cardiology/European Society of Hypertension (ESC/ESH) guideline thresholds. Solid line represents the hazard ratio and dotted line the 95% confidence interval. Reference for systolic blood pressure was 110 mmHg and for diastolic blood pressure 75 mmHg.

association between blood pressure and SAH in patients with known unruptured aneurysms [17, 19, 21]. None of these three studies provided stratified data or assessed linearity. Five studies reliably reported on the association between blood pressure and aneurysmal SAH [11, 17, 19, 21, 22]. Of these five studies, one provided stratified data, and none assessed linearity. Five studies did not include SAH cases identified from death records [13, 17, 19, 21, 22]. Nine studies reported HR, six studies reported OR and a single study reported risk ratio (RR).

Continuous blood pressure

Seven studies reported linearly fitted models between blood pressure as a continuous variable and SAH [11, 13, 16, 18–20, 23]. No study assessed linearity. All seven studies reported associations for SBP, and three studies reported associations for DBP. Three studies reported HR, a further three studies reported OR and a single study reported RR. In all studies higher SBP and DBP were found to be a significant predictor of SAH (Table S2).

Stratified blood pressure

Nine studies reported on stratified SBP ranges and SAH risk (and none on stratified DBP). Six studies reported HR and three studies reported OR [8–10, 12, 14, 15, 17, 21, 22]. Kim et al. and Arima et al. provided separate analyses in female and male participants only which were therefore included as separate studies in the meta-analysis [8, 9]. Korja et al. and Pierot et al. were the only studies to perform analyses on patients with known intracranial aneurysms [17, 21]. Korja et al. (2014), Pierot et al. and Muller et al. were also the only studies to include confirmed aneurysmal SAH cases [17, 21, 22].

Five studies compared blood pressure values <120 mmHg with those between 120 and 130 mmHg [8, 9, 14, 15, 22]. Suzuki et al. was the only study reporting OR and found a significant association (OR 2.8 [1.5, 5.4]) [14]. Only a single subgroup in a single study (Kim et al. [Female]) reporting HR found a significant association (HR 1.77 [1.04, 3.01]) [8]. However, meta-analysis including data from the UK Biobank showed an increased risk of SAH in patients with an SBP between 120 and 130 mmHg relative to <120 mmHg (HR 1.41

TABLE 4 Characteristics of included studies.

Study	Study design	Population	Study size	Events	Study period (years)	Age (years)	Sex (% male)	Outcome	Outcome measurement	Exposure	Exposure measurement	Statistic	Evidence for blood pressure target (mmHg)
Leppälä et al., 1999 [10]	Cohort	General population (smokers)	28,519	85	8	58 (median)	100	SAH	Hospital and death records	SBP and DBP	Baseline assessment	HR	<140/90
Isaksen et al., 2002 [11]	Case control	General population	130	26	15	53 (mean)	52	Aneurysmal SAH (imaging confirmed)	Hospital and death records including autopsy reports	SBP	Baseline and 5-yearly repeat assessments	OR	No
Kim et al., 2005 [8]	Cohort	General population	159,705	308	10s	44 (mean)	63	SAH	Hospital and death records	SBP and DBP combined	Baseline assessment	HR	<130/85
Feigin et al., 2005 [12]	Meta-analysis of cohort studies	General population	306,620	236	>33	48 (mean)	55	SAH	Hospital and death records	SBP	Baseline assessment	HR	<140
Lund Håheim et al., 2006 [13]	Cohort	General population	14,403	35	21	40–49 (range)	100	SAH	Hospital records	SBP	Baseline assessment	HR	No
Arima et al., 2009 [9]	Cohort	General population	1621	32	32	56.5 (mean)	44	SAH	Hospital and death records including autopsy reports	SBP and DBP combined	Baseline and 5-yearly repeat assessments	HR	No
Suzuki et al., 2011 [14]	Cohort	General population	156,892	89	10	54 (mean)	49	SAH	Hospital and death records	SBP and DBP combined	Baseline assessment within 3 years of event	OR	<120/80
Korja et al., 2013 [15]	Cohort	General population	64,349	437	37	45 (mean)	48	SAH	Hospital and death records	SBP and DBP	Baseline and 5-yearly repeat assessments	HR	<135/90

TABLE 1 (Continued)

Study	Study design	Population	Study size	Events	Study period (years)	Age (years)	Sex (% male)	Outcome	Outcome measurement	Exposure	Exposure measurement	Statistic	Evidence for blood pressure target (mmHg)
Rapsomaniki et al., 2014 [16]	Cohort	General population	1,258,006	830	13	NA	42	SAH	Hospital and death records	SBP and DBP	GP records during follow-up	HR	No
Korja et al., 2014 [17]	Cohort	Unruptured intracranial aneurysms	118	34	56	43.5 (median)	48	Aneurysmal SAH	Hospital records	SBP	Medical records within 5 years of event	OR	No
McGurgan et al., 2018 [18]	Cohort	General population	489,613	553	8	51 (mean)	41	SAH	Hospital and death records	SBP and DBP	Baseline assessment	HR	No
Huang et al., 2018 [19]	Case control	Unruptured intracranial aneurysms	581	355	7	54 (mean)	40	Aneurysmal SAH	Hospital records	SBP	At time of event	OR	No
Sundström et al., 2019 [20]	Meta-analysis of cohort studies	General population	949,683	2659	>50	44 (mean)	65	SAH	Hospital and death records	SBP and DBP	NA	RR	No
Pierot et al., 2020 [21]	Cohort	Unruptured intracranial aneurysms	1289	811	1.5	54 (mean)	33	Aneurysmal SAH	Hospital records	SBP	At time of event	OR	<140
Müller et al., 2020 [22]	Cohort	General population	83,710	111	15	NA	47	Aneurysmal SAH (imaging confirmed)	Hospital records	SBP and DBP	Baseline assessment	HR	<140/80
Karhunen et al., 2021 [23]	Mendelian randomisation study	General population	63,740	4196	NA	NA	NA	SAH	NA	SBP and DBP	NA	OR	No
Ewbank et al., 2023 (present study)	Cohort	General population	500,598	577	11 years	61 (mean)	46	SAH	Hospital and death records	SBP and DBP	Baseline assessment	HR	<120/90

Abbreviations: DBP, diastolic blood pressure; HR, hazard ratio; NA, not available; OR, odds ratio; RR, Risk ratio; SAH, subarachnoid haemorrhage; SBP, systolic blood pressure.

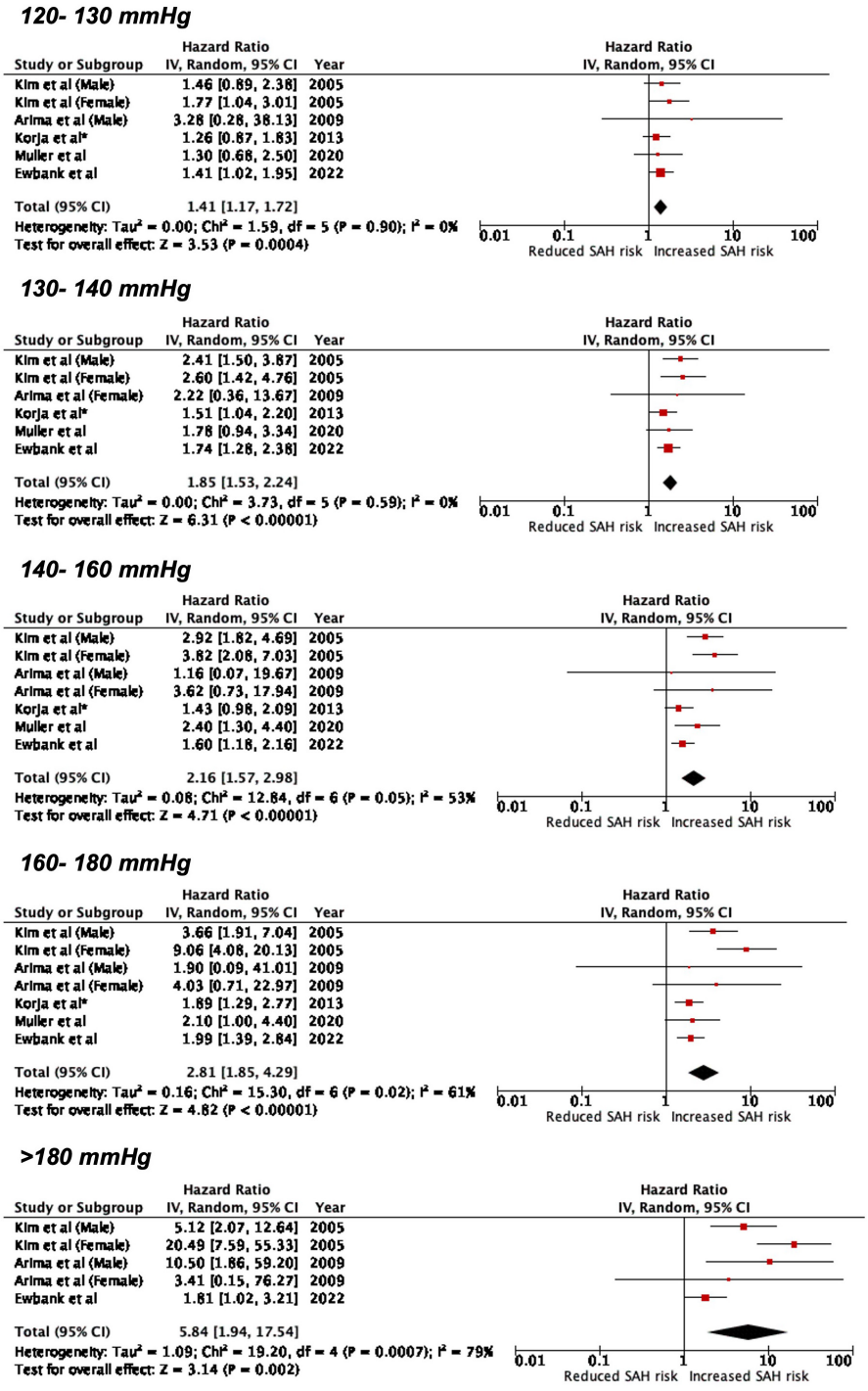


FIGURE 2 Forest plots of studies investigating blood pressure and subarachnoid haemorrhage (SAH) stratified by European Society of Cardiology/European Society of Hypertension (ESC/ESH) thresholds. *Korja et al. used blood pressure thresholds similar to ESC/ESH guidelines.

[1.17, 1.72]) (Figure 2). No significant heterogeneity was observed between these studies ($p = 0.90$). There were further stepwise increases for each group 130–140 mmHg (HR 1.85 [1.53, 2.24]), 140–160 mmHg (HR 2.16 [1.57, 2.98]), 160–180 mmHg (HR 2.81 [1.85, 4.29]), >180 mmHg (HR 5.84 [1.94, 17.54]).

Male and female subgroups

Subgroup analysis of males and females was performed in the UK Biobank dataset. In males, Cox proportional hazards models showed there was no association between SAH and SBP (HR 1.01 [0.92, 1.10], /10 mmHg), DBP (HR 1.05 [0.90, 1.21], /10 mmHg) and MABP (HR 1.03 [0.90, 1.17], /10 mmHg). In females, there was an association between SAH and SBP (HR 1.14 [1.08, 1.20], /10 mmHg), DBP (HR 1.22 [1.11, 1.35], /10 mmHg) and MABP (HR 1.22 [1.12, 1.33], /10 mmHg).

A forest plot of a meta-analysis of studies is shown in Figure 3. In females, all blood pressure thresholds show an increased risk of SAH relative to those with SBP <120 mmHg, including the 120–130 mmHg group, and each successive group shows a stepwise increase in HR. In males, while all HRs are greater than one, all are

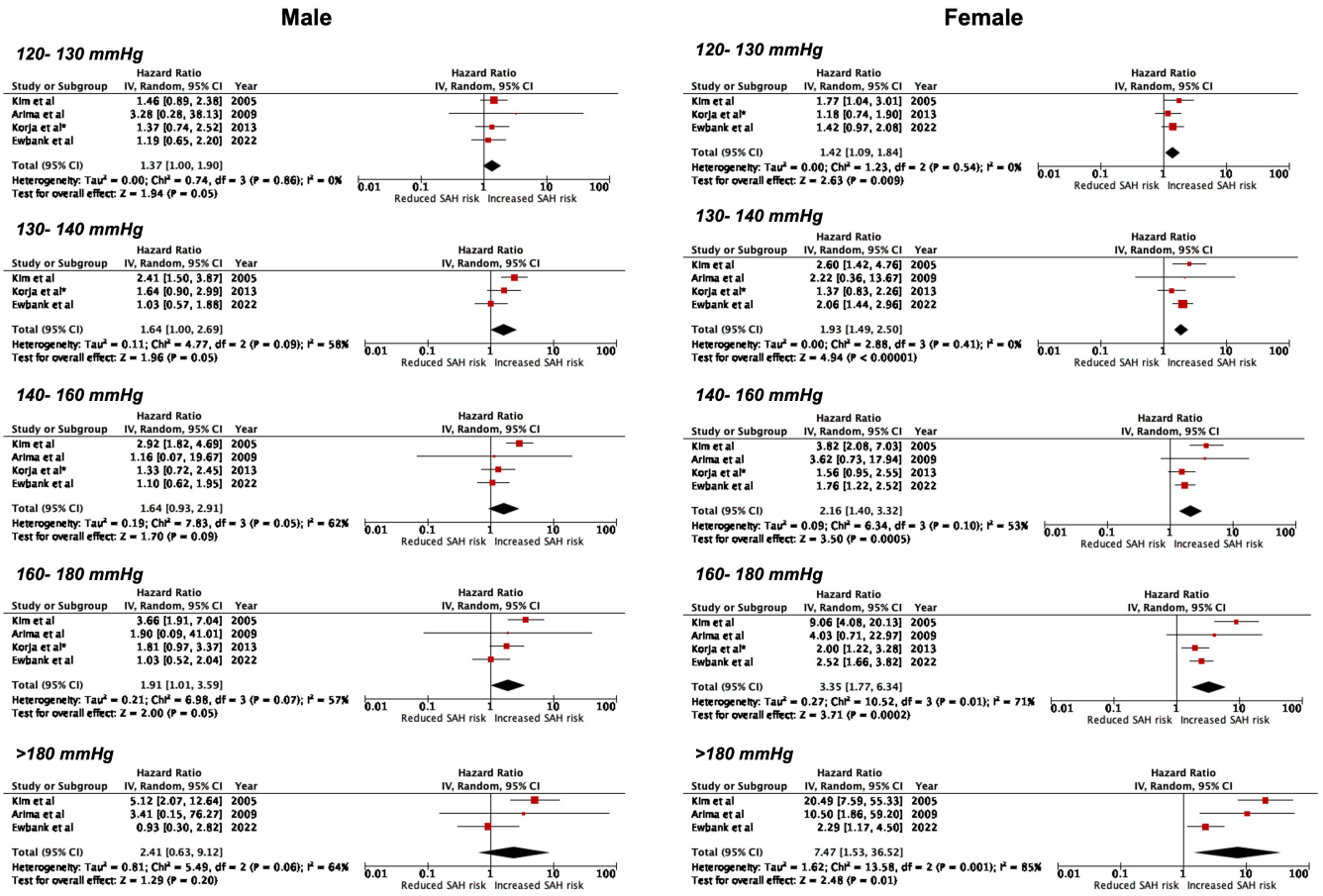


FIGURE 3 Forest plots of studies investigating blood pressure and subarachnoid haemorrhage (SAH) stratified by European Society of Cardiology/European Society of Hypertension (ESC/ESH) thresholds in male and female participants. *Korja et al. used blood pressure thresholds similar to ESC/ESH guidelines.

smaller than in females and only some reach significance. Consistent with this, there was a significant interaction between SBP and sex in the UK Biobank ($p = 0.01$).

DISCUSSION

In this study, we have shown that the relationship between blood pressure and SAH is linear with no clear floor or ceiling of effect. Additionally, patients with a SBP >120 mmHg more frequently suffer SAH than those with SBP <120 mmHg. Similar patterns are observed for SBP and DBP with similar effect sizes, although SBP models display a better fit. This relationship was more clearly seen in females, and less marked in males.

These findings are important and add to previous studies which did not assess linearity and were unclear if risk of SAH was reduced in the lower SBP subgroups of 130–140, 120–130 and <120 mmHg. This meta-analysis provides convincing evidence that there are stepwise reductions in risk in each of these categories.

Differences between SBP and DBP models were small although SBP generated the best fitting models. Hence, SBP appears most closely related to SAH and the best candidate for titrating any interventions to prevent SAH. Surprisingly, while hypertensive participants were more likely to suffer SAH, no relationship was seen between their actual blood pressure and occurrence of SAH. There are multiple possible explanations for this which require further research. While participants were not informed of their blood pressure results, it is possible that the experience of having it taken led to the hypertensive participants re-measuring in the community and ensuring subsequent tighter blood pressure control. It could also be due to the long-lasting effects of hypertension such that normalising participants' blood pressures after years of hypertension does little to influence their risk of SAH. Finally, it could be due to off-target effects of antihypertensives that reduce rupture risk via a mechanism not mediated by blood pressure.

The difference between males and females is also convincing and important. The reasons for the difference are not clear. It is possible that the underlying risk posed by blood pressure is not from its absolute value but from the magnitude of its rise. Healthy young women are known to have lower blood pressure than men and are known to experience larger increases in blood pressure over the course of adulthood [24]. Given measurements in the UK Biobank were made in middle age, it is therefore possible that for any given hypertensive threshold, women had experienced a larger increase in

blood pressure than equivalent males, explaining why they demonstrate a stronger association with SBP. Similar sensitivity to different blood pressure thresholds has been shown in other cardiovascular conditions [25, 26]. Alternatively, it could relate to a different pathophysiology of aneurysms in men and women. It is well known that females are more likely to develop aneurysms, and recent data suggest that aneurysms in women are more likely to rupture than in men [27, 28]. This implies that there is a higher sensitivity in females to both aneurysm formation and rupture. Since hypertension is a risk factor for rupture, it is possible that the higher female sensitivity extends to aneurysmal rupture related to increases in blood pressure. The cause of the disparity in aneurysm formation and rupture between men and women is not known. One long-standing but unproven hypothesis is that it is related to the menopause or hormone exposure [29]. This is based on the observation that the disparity increases with age. Our data did not support any such mechanism being aggravated by hypertension and showed no evidence of a change around the age of 50 years (data not presented).

These results are drawn mostly from volunteers not previously known to have an aneurysm. Therefore, they apply to spontaneous SAH of all causes; however, where analyses were available, similar results were seen for aneurysmal SAH. Given SAH rates are low in the general population, the results are of limited utility to this group whose blood pressure targets are likely to be dictated by the risk of more common cardiovascular conditions, such as ischaemic heart disease and stroke. The real question is therefore how these data apply to patients with an unruptured intracranial aneurysm (UIA).

Hypertension is already an established risk factor for the stratification of UIA rupture [2, 30], and it is well known that hypertension has an important role in the formation and growth of aneurysms [31]. Elevated blood pressure is also thought to trigger rupture of UIA [32]. However, there are no evidence-based specific blood pressure targets for patients with UIA. We had hoped to perform a subgroup analysis of patients with UIA, but unfortunately no studies reported risk of SAH by SBP strata for this patient group. Therefore, there are little or no data on which to base any clinical management. All that is available are recent guidelines published by the European Stroke Organisation which have suggested maintaining blood pressure <130/80 mmHg. However, the quality of available evidence supporting this recommendation is very low. One study has shown that intensive blood pressure management is likely to be well tolerated in patients with UIA [33] and going forwards there is a randomised trial currently examining the effects of intensive blood pressure management (SBP <120 mmHg) and aspirin on the risk of rupture (PROTECT-U) [34]. However, this trial will not be able to disentangle the contributions of aspirin and aggressive blood pressure lowering since both will be employed in combination.

Although our main study findings are based on a different population, given there are no other available data, it is currently the only evidence suggesting that aggressive blood pressure lowering to below 120 mmHg in patients with UIA may be desirable.

This study of the UK Biobank is the largest single cohort to examine the relationship between blood pressure and SAH and the first to assess linearity of this relationship. The meta-analysis is also the largest to date. However, both the UK Biobank and the meta-analysis have limitations.

The greatest difficulty in studying the influence of blood pressure on risk is that it is a non-stationary variable that fluctuates over time. However, its assessment in the UK Biobank (and all studies in the meta-analysis) is at a single timepoint. It is unclear how well this will represent an individual's blood pressure immediately prior to SAH.

Another limitation of the studies in the meta-analysis is that they considered all SAH events grouped together and did not confirm aneurysmal SAH. Given the causes of non-aneurysmal SAH are varied, it is possible that the risk associated with increases in blood pressure could also vary. While the analysis of the UK Biobank showed a similar relationship, and the coding of SAH in the cohort has been well validated, when comparing aneurysmal and non-aneurysmal events, the sensitivity and specificity of these coded records has not been determined [35].

Relatively few studies provided stratified blood pressure values, meaning that only a minority of studies could be included in the meta-analysis. However, it was reassuring that heterogeneity was low in these analyses.

Several studies were conducted in the same country, and some patients may have been included in more than one study. We also included two meta-analyses which included cohorts examined in this study [12, 20]. However, as far as we can assess, we did not include any overlapping patients in the meta-analysis.

Unfortunately, a few studies in the meta-analysis did not examine death records or autopsy reports for their identification of SAH cases. This is an important form of selection bias and benefit of the UK Biobank data which included death records.

The results of this study show that risk of SAH increases linearly with SBP >120 mmHg, with the effect of blood pressure being greater in female patients compared to male patients. Despite this study's limitations, in the absence of any other data, aggressive blood pressure lowering to a target SBP <120 mmHg should be considered in patients with UIA.

AUTHOR CONTRIBUTIONS

Frederick Ewbank: Conceptualization (lead); methodology (lead); formal analysis (lead); writing—original draft (lead); writing—review and editing (equal). Benjamin Gaastra: Writing—review and editing (equal). Samuel Hall: Writing—review and editing (equal). Ian Galea: Writing—review and editing (equal). Diederik Bulters: Conceptualization (supporting); writing—review and editing (equal).

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CONFLICT OF INTEREST STATEMENT

The authors declare no competing interests.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available in UK Biobank at https://www.ukbiobank.ac.uk.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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