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Cohort study of preoperative blood pressure and risk of 30-day mortality after elective non-cardiac surgery

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Abstract

Background: Preoperative blood pressure (BP) thresholds associated with increased postoperative mortality remain unclear. We investigated the relationship between preoperative BP and 30-day mortality after elective non-cardiac surgery.
Methods: We performed a cohort study of primary care data from the UK Clinical Practice Research Datalink (2004–13). Parsimonious and fully adjusted multivariable logistic regression models, including restricted cubic splines for numerical systolic and diastolic BP, for 30-day mortality were constructed. The full model included 29 perioperative risk factors, including age, sex, comorbidities, medications, and surgical risk scale. Sensitivity analyses were conducted for age (>65 *vs* <65 years old) and the timing of BP measurement.
Results: A total of 251 567 adults were included, with 589 (0.23%) deaths within 30 days of surgery. After adjustment for all risk factors, preoperative low BP was consistently associated with statistically significant increases in the odds ratio (OR) of postoperative mortality. Statistically significant risk thresholds started at a preoperative systolic pressure of 119 mm Hg (adjusted OR 1.02 [95% confidence interval (CI) 1.01–1.02]) compared with the reference (120 mm Hg) and diastolic pressure of 63 mm Hg [OR 1.24 (95% CI 1.03–1.49)] compared with the reference (80 mm Hg). As BP decreased, the OR of mortality risk increased. Subgroup analysis demonstrated that the risk associated with low BP was confined to the elderly. Adjusted

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analyses identified that diastolic hypertension was associated with increased postoperative mortality in the whole cohort. **Conclusions:** In this large observational study we identified a significant dose-dependent association between low preoperative BP values and increased postoperative mortality in the elderly. In the whole population, elevated diastolic, not systolic, BP was associated with increased mortality.

Key words: blood pressure; mortality; surgery

Editor's key points

- There remains some uncertainty about the relationship between preoperative blood pressure and perioperative mortality, particularly for hypotension.
- In this large UK cohort study, blood pressure values <119 mm Hg systolic and 63 mm Hg diastolic were independently associated with a progressive increase in postoperative mortality.
- The increased risk with hypotension was confined to elderly patients.
- There was no independent relationship between systolic hypertension and mortality, but diastolic blood pressure >84 mm Hg was associated with an increased risk of death after adjustment for covariables.
- These data have implications for perioperative risk stratification.

Community control of blood pressure (BP) exerts profound effects on cardiovascular outcomes with J-shaped risk curves, indicating risks at either end of the BP spectrum.[1–3] The optimal BP remains unclear due to the complexity of the relationship between hypertension, cardiovascular disease, age, and other risk factors.[4 5] Excessive reduction of BP may increase cardiovascular risk, especially in the elderly or patients with diabetes or coronary artery disease,[2 4 6] perhaps due to impaired diastolic coronary perfusion.[2] Hence recent guidelines recommend relaxed BP targets in these populations. However, the recent SPRINT study challenged these recommendations: lowering systolic BP to a mean value of 121 mm Hg (*vs* 136 mm Hg) was associated with reduced cardiovascular events in the community.[7]

While there is strong evidence for the longitudinal control of BP to reduce incident vascular events,[7] guidance for the optimization of preoperative BP lacks a strong evidence base.[8–10] Recent guidelines sensibly emphasize the need to focus on primary care readings,[10] however, they acknowledge that 'whether or not these [community] thresholds and targets should be rigorously applied in the perioperative setting is not clear'. In the perioperative period, anaesthesia and surgery lead to hemodynamic changes, an exaggerated stress response, hypercoagulability, and inflammation. Hence the optimal preparation for the physiological strain of anaesthesia and surgery is unlikely to be the same as reducing long-term vascular risk in the community. Recent studies stress how perioperative hypotension leads to increased postoperative mortality.[11 12] In particular, the hypothesis that preoperative low BP may be a risk factor for postoperative mortality requires evaluation. Conceptually this hypothesis is supported by evidence that preoperative low BP is a predictor of intraoperative hypotension[13] and intraoperative hypotension is a predictor of postoperative mortality.[14 15] The recent guidelines do not mention the potential impact of preoperative low BP on postoperative outcomes.[10]

Similarly, the contribution of comorbid hypertension to postoperative mortality is unclear despite its prevalence in the community and the established effects on multiple vascular outcomes.[5] In 2004, a meta-analysis found an association between the diagnosis of preoperative hypertension and increased postoperative cardiac events; however, we were unable to identify numerical BP thresholds associated with increased risk.[16] Moreover, the diagnosis of preoperative hypertension (or elevated pulse pressure[17 18]) is not universally considered important in determining postoperative risk,[19 20] as suggested by its omission from the widely used revised cardiac risk index.[21] Despite the lack of clarity on this issue, in the UK ~1% (~100 patients per day) of elective surgical patients have surgery delayed for further primary care management of BP.[10]

To date, no large study has attempted to identify BP thresholds associated with increased postoperative mortality in elective non-cardiac surgery. Herein we analysed primary care data from an elective non-cardiac surgery cohort to identify preoperative numerical BP thresholds associated with increased postoperative mortality in all patients and in the elderly. Our aim was to identify preoperative BP thresholds beyond which the odds of postoperative mortality increase through analysis of BP as a continuous measure.

Methods

Data source and study design

This research study was approved by the Independent Scientific Advisory Committee for the Medicines and Healthcare Products Regulatory Agency, UK (number 11_034). We extracted longitudinal data from the Clinical Practice Research Datalink (CPRD), a primary care database including a representative sample of ~6% of the UK population. Patients who underwent specific non-cardiac surgical procedures between January 1, 2004 and December 31, 2013 were identified using medical codes (Appendix 1). We retained only adult patients (≥18 years of age) who had been registered with their general practitioner (GP) for at least 1 year prior to the date of elective non-cardiac surgery (see STROBE diagram, Supplementary Fig. 1). Our internal audit has identified a <1% discrepancy in the CPRD and HES coding of operations.

Patient involvement

Patients were not involved in the design of this study.

Exposure variables

The latest BP measurement recorded before surgery was the exposure variable.

Outcome variable

Postoperative mortality, defined as death occurring within 30 days following non-cardiac surgery, was the outcome variable. In the event of a death in the UK, a medical certificate is required from the deceased individual's GP or a hospital doctor within 5 days (8 days in Scotland). Death certificates issued by GPs are directly entered into the primary care database. Copies of medical certificates obtained from a hospital doctor are sent to the deceased individual's GP. The death also needs to be registered with the government (online facilities enable this to be done whether the death occurred in the UK or abroad: https://www.gov.uk/register-a-death) and these data go to the Office of National Statistics (ONS). Validation of death data using the ONS records is possible in a proportion of CPRD practices in England and Wales and these data can be used for a sensitivity analysis, especially since it is possible that delays in death notification could result in some deaths being missed if they occurred close to the data extraction date. However, even in such circumstances, any misclassification bias due to missing death records would be non-differential and at most, shift the relative risk towards unity. A sensitivity analysis in our validation sample showed that our findings and key message remained unchanged.

Covariates

Suitable comorbidity codes were identified by searching the CPRD medical code dictionary browser tool using a combination of search terms to ensure that all relevant codes were captured. The retrieved codes were then reviewed by at least two of the authors (S.V. and P.R.M.) to further refine the list of codes. The final code lists were approved by all authors and is available (see Supplementary Appendix). Study participant records were searched for all relevant codes, and for chronic comorbidities, the occurrence of a code at any point in the patient's history indicated the presence of the comorbidity. Chronic diseases are well recorded in UK primary care because of the Quality Outcomes Framework (QOF) and patients diagnosed with common chronic diseases are enrolled in a disease register with annual updating of their disease status. Of course, there is a possible limitation that undiagnosed cases are missed, but this would lead to a non-differential misclassification bias that at most would shift the relative risk estimates towards 1 (i.e. no association detected).

The following comorbidities were adjusted for: atrial fibrillation, unstable angina, valvular heart disease, myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, chronic obstructive pulmonary disease, liver disease, diabetes mellitus, renal disease, and cancer. Additionally, we also adjusted for Charlson's comorbidity score[22] as a weighted indicator of comorbidity burden. Medications adjusted for included statins, beta blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, alpha-2 agonists, loop diuretics, thiazide diuretics, aspirin, other antiplatelet drugs, and selective serotonin re-uptake inhibitors. When adjusted for as covariates, drugs were coded as binary variables. Body mass index (BMI) was adjusted for by being categorized as <18.5, 18.5–24.99, 25–29.99 and >30, reflecting the range from underweight to obese. Patients were also categorized as current smoker, ex-smoker or non-smoker, with alcohol consumption status above or below the recommended UK limits (21 units per week for men and 14 units per week for women). To account for variations in access to care, we adjusted for socioeconomic status [Index of Multiple Deprivation (IMD) 2010 quintiles] and number of BP measurements recorded in the dataset. The IMD 2010 is a composite measure of deprivation that assigns a deprivation score to a geographical area based on a number of factors, including employment, education, neighbourhood crime rates and access to health care facilities (https://www.gov.uk/government/statistics/english-indices-of-deprivation-2010). We used the IMD deprivation score assigned to individual subjects' postcode of residence. Finally, we adjusted for the variation in risk posed by the different types of non-cardiac surgical procedures using the operative procedure classes in the validated surgical risk scale.[23 24] Each surgical procedure included was given a score from 1 to 5, in increasing order of risk posed by the specific specialty and procedure. Emergency surgical codes were excluded from the analysis. All codes were reviewed by both surgeons and anaesthetists. Additionally, we performed a sensitivity analysis excluding operations occurring within 7 days of the most recent BP to reduce the risk of selection bias in the sample. Missing data were coded as a dummy variable category.

Statistical analysis

Our primary analysis investigated the association between systolic BP, diastolic BP, and pulse pressure with postoperative mortality. The reference systolic and diastolic BP and pulse pressure were the modes of the population. We identified statistical "cut-offs" where the odds of mortality increased relative to the reference, hence we empirically defined thresholds for an increase in mortality based on the restricted cubic splines analysis of BP as a continuous measure. To reduce any confounding that the BP reading was associated with the pathology driving the need for surgery, or not reflecting the preoperative period, we conducted additional sensitivity analyses based on the time of BP measurement by restricting analysis to BP values recorded between day 8 and 84 (1–12 weeks) or day 8 and 365 prior to surgery. For the overall analysis, systolic and diastolic BP measurements were separately modelled as continuous variables using unadjusted and adjusted restricted cubic spline regression analyses (with four knots: systolic 104, 124, 138, and 160 mm Hg and diastolic 60, 74, 80, and 94 mm Hg). The location of the knots was determined based on recommended percentiles at 5, 35, 65 and 95%.[25] Two sets of adjusted logistic regression models were constructed: a fully adjusted model where the entire covariate list of *a priori* confounders was adjusted for and a parsimonious model where only those covariates that were statistically significantly associated with the outcome (postoperative mortality) were entered into the model. For the systolic and diastolic BP analyses, 120 and 80 mm Hg, respectively, were chosen as reference values, as these were the population modes in the whole cohort. Pulse pressure was calculated as diastolic BP subtracted from systolic BP, with a reference value of 40 mm Hg. Model fit was assessed using the Hosemer–Lemeshow (HL) goodness of fit test. Thresholds for risk were set when the 95% confidence intervals (CIs) no longer overlapped with 1 ($P<0.05$). We used the *P*-value obtained from a likelihood ratio test to separately test for interaction between systolic and diastolic BP and patient age and heart failure. We also conducted a subgroup analysis ($\geq$65 years and $<$65 years[26]), as we hypothesized that the extremes of BP would be particularly associated with increased mortality in the elderly.[27] Analysis was conducted using Stata software (StataCorp, College Station, TX, USA).

Results

Our study cohort included 251 567 adult patients who underwent elective non-cardiac surgery (Fig. 1). Details of the

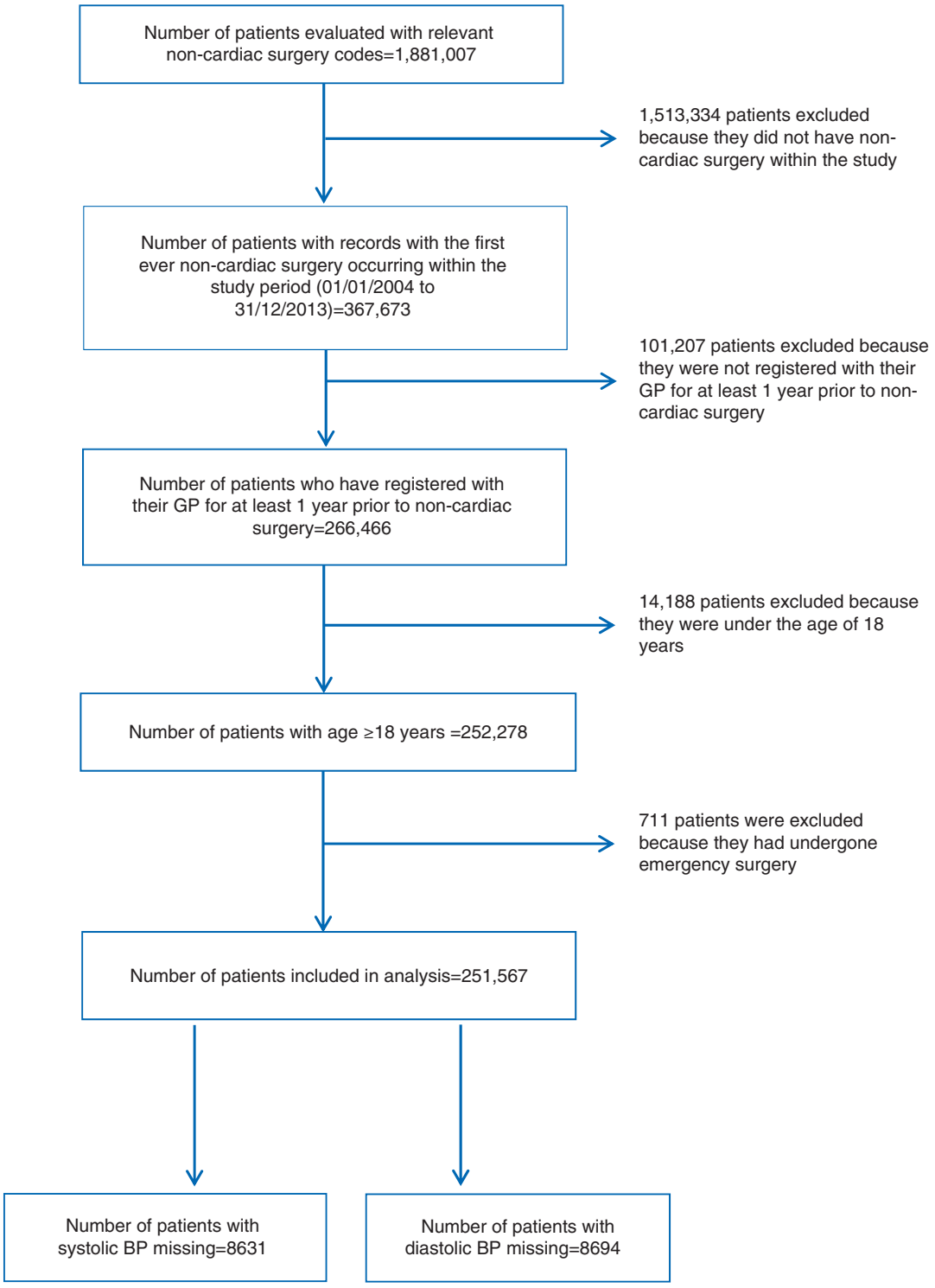

Fig 1 STROBE diagram.

operations included are described in Supplementary Table 1 (online only). In total, 52 241 had a systolic BP <120 mm Hg, 110 488 had a systolic BP of 120–139 mm Hg, and 80 207 had a systolic BP ≥140 mm Hg. Systolic and diastolic BP measurements were missing in 8631 and 8694 cases, respectively. A total of 589 deaths were observed (0.23%) within 30 days of surgery. Those who died within 30 days of surgery tended to have more comorbidities than those who survived (Table 1). Absolute risk values associated with different BP values are available in Supplementary Tables 2–4. For example, mortality was 0.28% in all patients with a preoperative systolic BP <100 mm Hg and 2.15% in elderly patients (>65 years old) with a systolic BP <100 mm Hg.

Primary analysis

For systolic BP, unadjusted restricted cubic spline analysis showed increased odds of postoperative mortality associated with hypertension (≥123 mm Hg). Due to the relationship between age and BP, we confirmed a significant interaction with age for both systolic ($P<0.001$) and diastolic ($P=0.011$) BP (likelihood ratio test). When adjusting for all covariates including age (full model), low systolic BP, starting at 119 mm Hg [adjusted odds ratio (OR) 1.02 (95% CI 1.01–1.02) for 119 mm Hg compared with the reference] was significantly associated with postoperative mortality, with the OR of death increasing with each unit decrease in systolic BP (Fig. 2). Systolic hypertension was not associated with increased mortality in adjusted analyses. Table 2 shows the point estimates for specific BP values separated by 20-mm Hg intervals derived from the cubic splines curve (comprehensive fully adjusted data in Supplementary Table 5). For the fully adjusted model, the HL goodness of fit test produced a X^2 value of 8.25 (P-value: 0.4091) suggesting a good fit. Results from the parsimonious model were similar to the full model (Supplementary Table 6, Supplementary Fig. 1, online only).

Similar to systolic BP, low diastolic BP (≤70mmHg) was associated with postoperative mortality in the unadjusted analysis. While this effect persisted in the fully adjusted model, the magnitude of effect observed was smaller and an increase in odds ratio of postoperative mortality was observed at 63mmHg (OR 1.24 [95% CI: 1.03 to 1.49]) which was dose-dependent (Fig. 2, Table 2, online Supplementary Table 7). Similar results were obtained from the parsimonious model (Supplementary Table 6, Supplementary Fig. 1, online-only). While unadjusted analysis of elevated diastolic BP suggested it was not associated with an increased odds of mortality, after adjustment, diastolic hypertension was associated with an increased risk in the overall population, with a threshold at >84 mm Hg [OR 1.07 (95% CI 1.01–1.13)] (Table 2).

Increased pulse pressure (≥50 mmHg) was seen to be associated with a statistically significant increase in postoperative mortality in the unadjusted analysis. However, after adjusting for all covariates this effect was attenuated. Rather, pulse pressures from 42 to 58mmHg were associated with a small reduction in OR of postoperative mortality. Furthermore pulse pressures <37mmHg were associated with increased risk (Fig. 2, Supplementary Tables 6 and 8). For the fully-adjusted model, the HL goodness of fit test produced a χ^2 value of 12.10 ($P=0.1466$), suggesting a good fit.

Sensitivity analyses

We performed a sensitivity analysis with exclusion of BP values <80/40 mm Hg that may be considered non-physiological, leaving 251 484 patients in the whole cohort and 84 601 in the elderly cohort, and found similar results (Supplementary Table 9 and Supplementary Figs 2 and 3). To identify if preoperative hypotension may reflect heart failure (despite adjusting for the diagnosis of heart failure and prescription of loop diuretics), we tested for an interaction between BP values and congestive heart failure. Indeed, heart failure occurred in 1.52% of patients with a systolic pressure <120 mm Hg and 1.29% of normotensive patients (Supplementary Table 10). However, we did not find evidence of an interaction using the likelihood ratio test (systolic BP $P=0.113$, diastolic BP $P=0.179$).

A histogram showing the timing of BP measurements is available in Supplementary Figure 4. A further sensitivity analysis was conducted based on the timing of BP measurement to exclude indication bias associated with low BP. For example, hypotension may be associated with emergency surgery, hence, in addition to restriction of our dataset to elective surgery, we excluded BP values obtained within a week of surgery (as longer time intervals between primary care measurement of low BP and surgical admission would appear imprudent). Furthermore, we restricted the dataset to within 12 weeks of surgery (day 8–84) to reflect preoperative rather than long-term measurement. Where BP measurements were made between 1 and 12 weeks preoperatively ($n=57\,084$), systolic BP ≤119 mm Hg and diastolic BP ≤64 mm Hg were associated with an increased OR of postoperative mortality (Fig. 3 and Table 2). The HL goodness of fit suggested a good fit (systolic BP: $\chi^2=4.67$, $P=0.7925$; diastolic BP: $\chi^2=10.53$, $P=0.2300$). Similar analysis of values from 1 to 52 weeks before surgery found a similar effect ($n=143\,462$) with systolic BP ≤119 mm Hg and diastolic BP ≤65 mm Hg associated with an increased OR of postoperative mortality. The HL goodness of fit χ^2 of 6.89 ($P=0.5481$) also suggested a good fit.

To address concerns that the lack of effect of systolic hypertension on postoperative mortality was due to a type II error, we categorized hypertension based on either BP 140–159 mm Hg (stage 1) or >160 mm Hg (stage 2). The reference was defined as 120–139 mm Hg. While unadjusted data suggested a modest increase in risk [140–159 mm Hg: OR 1.30 (95% CI 1.07–1.58) and ≥160 mm Hg: OR 2.26 (95% CI 1.73–2.97)], this disappeared in the fully adjusted model [140–159 mm Hg: OR 0.90 (95% CI 0.74–1.10) and ≥160 mm Hg: OR 1.16 (95% CI 0.88–1.53)]. As a comparison, we also confirmed our results from the cubic splines analysis that preoperative diastolic hypertension may influence postoperative mortality in the whole population. Diastolic BP values >100 mm Hg ($n=6229$) were associated with an increased odds of postoperative mortality in both unadjusted [OR 1.77 (95% CI 1.14–2.75)] and fully adjusted [OR 2.12 (95% CI 1.35–3.3)] analyses compared with diastolic BP 80–89 mm Hg. No effect was apparent with diastolic BP 90–99 mm Hg.

The impact of preoperative BP in the elderly

An *a priori* planned subgroup, supported by our interaction analysis for age, included patients ≥65 years of age ($n=84\,633$). Unadjusted and adjusted data (fully adjusted and parsimonious models) demonstrated a dose-dependent increased OR in postoperative mortality associated with systolic and diastolic hypotension (Table 2 and Fig. 4) supporting our hypothesis that elderly patients harbour the hypotension risk in the cohort. Adjusted associations (fully adjusted model) with increased mortality were first observed at 119 mm Hg systolic [OR 1.02 (95% CI 1.01–1.03)] and 63 mm Hg diastolic [OR 1.24 (95% CI 1.01–1.53)]. Results from parsimonious models are presented in Supplementary Table 4 and Supplementary Figure 2. A pulse

Table 1 Demographic and clinical characteristics. *P-values derived from χ^2 test for categorical values and independent samples t-test for continuous variables. ACE, angiotensin-converting enzyme

	All (n=251 567)	Survived (n=250 978)	30-day mortality (n=589)	P-value*
Age, years, mean (SD)	55.78 (16.95)	55.73 (16.93)	77.00 (13.22)	<0.001
Sex, n (%)				
Male	107 596 (42.77)	107 279 (42.74)	317 (53.82)	<0.001
Female	143 971 (57.23)	143 699 (57.26)	272 (46.18)	
Body mass index, n (%)				
Underweight (<18.5)	4955 (1.97)	4914 (1.96)	41 (6.96)	<0.001
Normal (18.5–24.99)	80 672 (32.07)	80 447 (32.05)	225 (38.20)	
Overweight (25–29.99)	78 667 (31.27)	78 513 (31.28)	154 (26.15)	
Obese (≥30)	56 830 (22.59)	56 753 (22.61)	77 (13.07)	
Missing	30 443 (12.10)	30 351 (12.09)	92 (15.62)	
Smoking status				
Non-smoker	133 398 (53.03)	133 149 (53.05)	249 (42.28)	<0.001
Current smoker	46 108 (18.33)	45 987 (18.32)	121 (20.54)	
Ex-smoker	66 430 (26.41)	66 223 (26.39)	207 (35.14)	
Missing	5631 (2.24)	5619 (2.24)	12 (2.04)	
Alcohol consumption status				
Below limit	115 920 (46.08)	115 704 (46.10)	216 (36.67)	<0.001
Above limit	19 878 (7.90)	19 841 (7.91)	37 (6.28)	
Missing	115 769 (46.02)	115 433 (45.99)	336 (57.05)	
Comorbidities, n (%)				
Atrial fibrillation	8233 (3.27)	8141 (3.24)	92 (15.62)	<0.001
Other arrhythmia	74 (0.03)	74 (0.03)	0 (0)	0.677
Unstable angina	1393 (0.55)	1381 (0.55)	12 (2.04)	<0.001
Valvular heart disease	38 (0.02)	38 (0.02)	0 (0)	0.765
Myocardial infarction	10 435 (4.15)	10 344 (4.12)	91 (15.45)	<0.001
Congestive heart failure	3525 (1.40)	3458 (1.38)	67 (11.38)	<0.001
Peripheral vascular disease	6999 (2.78)	6906 (2.75)	93 (15.79)	<0.001
Cerebrovascular disease	7831 (3.11)	7759 (3.09)	72 (12.22)	<0.001
Chronic pulmonary disease	45 601 (18.13)	45 463 (18.11)	138 (23.43)	0.001
Liver disease	1102 (0.44)	1094 (0.44)	8 (1.36)	0.001
Diabetes	17 485 (6.95)	17 399 (6.93)	86 (14.60)	<0.001
Renal disease	14 650 (5.82)	14 527 (5.79)	123 (20.88)	<0.001
Cancer	34 072 (13.54)	33 846 (13.49)	226 (38.37)	<0.001
Charlson comorbidity score, n (%)				
No comorbidity	143 263 (56.95)	143 171 (57.05)	92 (15.62)	<0.001
1–2	80 201 (31.88)	79 975 (31.87)	226 (38.37)	
3–5	24 477 (9.73)	24 279 (9.67)	198 (33.62)	
>5	3626 (1.44)	3553 (1.42)	73 (12.39)	
Statins, n (%)	55 052 (21.88)	54 812 (21.84)	240 (40.75)	<0.001
Beta blockers, n (%)	57 181 (22.73)	56 937 (22.69)	244 (41.43)	<0.001
ACE inhibitors, n (%)	50 110 (19.92)	49 886 (19.88)	224 (38.03)	<0.001
Calcium channel blockers, n (%)	41 716 (16.58)	41 524 (16.54)	192 (32.60)	<0.001
Alpha-2 agonists, n (%)	3588 (1.43)	3577 (1.43)	11 (1.87)	0.366
Thiazide diuretics, n (%)	47 688 (18.96)	47 490 (18.92)	198 (33.62)	<0.001
Loop diuretics, n (%)	24 179 (9.61)	23 977 (9.55)	202 (34.30)	<0.001
Aspirin, n (%)	48 294 (19.20)	47 988 (19.12)	306 (51.95)	<0.001
Other antiplatelet drugs, n (%)	9181 (3.65)	9115 (3.63)	66 (11.21)	<0.001
Surgical risk score, n (%)				
1	0 (0)	0 (0)	0 (0)	<0.001
2	69 783 (27.74)	69 745 (27.79)	38 (6.45)	
3	48 165 (19.15)	48 121 (19.17)	44 (7.47)	
4	43 714 (17.38)	43 657 (17.56)	57 (9.68)	
5	89 905 (35.74)	89 455 (35.64)	450 (76.40)	
Socio-economic status (IMD 2010 quintiles), n (%)				
1	39 078 (15.53)	39 019 (15.55)	59 (10.02)	<0.001
2	36 804 (14.63)	36 709 (14.63)	95 (16.13)	
3	28 494 (11.33)	28 401 (11.32)	93 (15.79)	
4	24 321 (9.67)	24 248 (9.66)	73 (12.39)	
5	18 014 (7.16)	17 963 (7.16)	51 (8.66)	
Missing	104 856 (41.68)	104 638 (41.69)	218 (37.01)	
Number of BP measurements, mean (SD)	15.68 (27.08)	15.67 (27.07)	22.45 (30.79)	<0.001

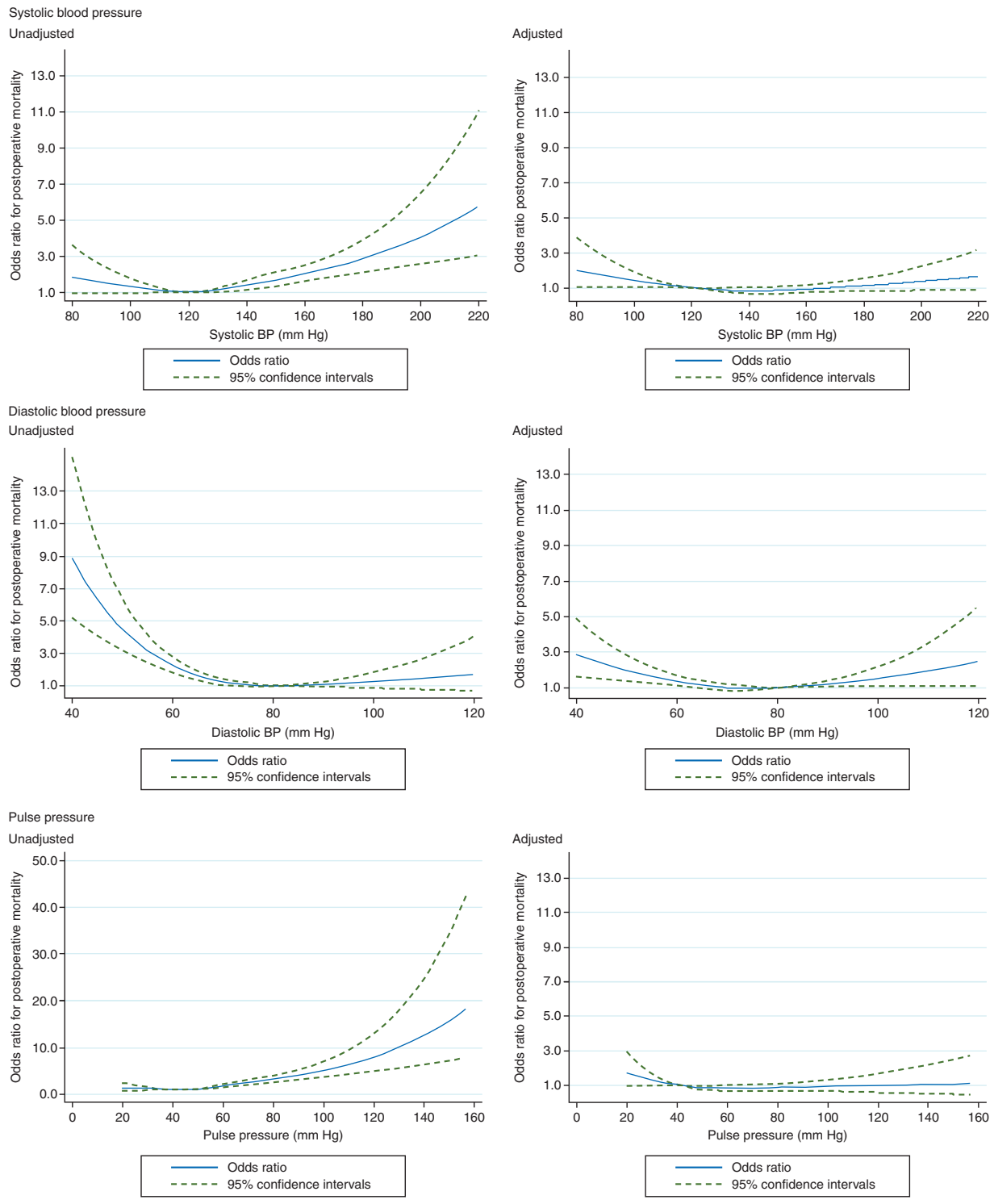

Fig 2 Unadjusted and fully adjusted spline graphs for the association between systolic BP, diastolic BP, and pulse pressure and perioperative mortality. Fully adjusted model adjusted for age, gender, atrial fibrillation, unstable angina, valvular heart disease, myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, chronic obstructive pulmonary disease, liver disease, diabetes mellitus, renal disease, cancer, Charlson's comorbidity score, smoking, alcohol, surgical risk scale, socioeconomic status (IMD 2010), number of BP measurements, statins, beta blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, alpha-2 agonists, loop diuretics, thiazide diuretics, aspirin, other antiplatelet drugs, and selective serotonin re-uptake inhibitors.

Table 2 Unadjusted and fully adjusted results for systolic, diastolic, and pulse pressure data (20-mm Hg intervals). Age ≥65 years and BP measurements recorded 8–84 days prior to surgery are post hoc outcomes. Data represent point estimates from restricted cubic spline curves. Data presented as OR (95% CI). *Statistically significant results (P<0.05)

	Study population (n=251 567)		Age ≥65 years (n=84 633)		BP measurements recorded 8–84 days prior to surgery (n=57 084)	
Systolic pressure (mm Hg)	**Unadjusted**	**Adjusted**	**Unadjusted**	**Adjusted**	**Unadjusted**	**Adjusted**
≤80	1.83 (0.93–3.60)	2.02 (1.06–3.85)*	5.29 (3.05–9.19)*	2.47 (1.40–4.37)*	3.63 (1.46–9.03)*	2.94 (1.20–7.21)*
100	1.30 (0.95–1.76)	1.41 (1.05–1.89)*	2.28 (1.74–2.98)*	1.56 (1.18–2.06)*	1.88 (1.21–2.92)*	1.71 (1.11–2.64)*
120	Reference	Reference	Reference	Reference	Reference	Reference
140	1.38 (1.13–1.68)*	0.82 (0.67–1.01)	0.71 (0.60–0.84)*	0.85 (0.71–1.01)	0.82 (0.60–1.13)	0.67 (0.48–0.92)
160	2.01 (1.61–2.51)*	0.93 (0.74–1.17)	0.86 (0.67–1.10)	0.93 (0.72–1.20)	0.98 (0.66–1.47)	0.62 (0.41–0.94)
180	2.86 (2.10–3.90)*	1.13 (0.82–1.55)	1.14 (0.82–1.59)	1.06 (0.75–1.49)	1.24 (0.69–2.22)	0.65 (0.36–1.19)
200	4.07 (2.55–6.50)*	1.36 (0.85–2.20)	1.53 (0.89–2.62)	1.20 (0.69–2.08)	1.57 (0.61–4.00)	0.68 (0.26–1.79)
≥220	5.79 (3.03–11.07)*	1.65 (0.86–3. 81)	2.05 (0.94–4.44)	1.36 (0.61–3.01)	1.98 (0.52–7.52)	0.72 (0.18–2.81)
Diastolic pressure (mm Hg)	**Unadjusted**	**Adjusted**	**Unadjusted**	**Adjusted**	**Unadjusted**	**Adjusted**
≤40	8.83 (5.15–15.15)*	2.84 (1.64–4.91)*	8.54 (4.93–14.80)*	2.78 (1.57–4.93)*	19.79 (9.19–42.60)*	6.11 (2.72–13.71)*
60	2.24 (1.84–2.73)*	1.37 (1.12–1.68)*	2.36 (1.90–2.92)*	1.37 (1.10–1.71)*	3.27 (2.36–4.52)*	1.82 (1.29–2.55)*
80	Reference	Reference	Reference	Reference	Reference	Reference
90	1.09 (0.95–1.25)	1.21 (1.06–1.39)*	1.13 (0.96–1.32)	1.20 (1.02–1.41)*	0.93 (0.71–1.22)	1.18 (0.90–1.55)
100	1.26 (0.87–1.83)	1.53 (1.08–2.19)*	1.42 (0.93–2.14)	1.49 (0.99–2.24)	0.89 (0.42–1.90)	1.40 (0.67–2.95)
≥120	1.71 (0.72–4.06)	2.46 (1.07–5.63)*	2. 23 (0.87–5.74)	2.29 (0.90–5.78)	0.82 (0.13–5.00)	1.98 (0.34–11.58)
Pulse pressure (mm Hg)	**Unadjusted**	**Adjusted**	**Unadjusted**	**Adjusted**	**Unadjusted**	**Adjusted**
≤20	1.45 (0.84–2.49)	1.71 (1.01–2.91)*	2.32 (1.56–3.44)*	1.70 (1.14–2.54)*	1.20 (0.80–1.81)	1.70 (0.76–3.82)
40	Reference	Reference	Reference	Reference	Reference	Reference
60	1.83 (1.51–2.22)*	0.83 (0.67–1.01)	0.66 (0.54–0.80)*	0.76 (0.62–0.92)*	0.90 (0.51–1.59)	0.65 (0.47–0.90)
80	3.24 (2.61–4.01)*	0.87 (0.69–1.09)	0.91 (0.72–1.15)	0.83 (0.65–1.06)	1.34 (0.77–2.32)	0.61 (0.41–0.90)
100	5.08 (3.71–6.96)*	0.93 (0.66–1.30)	1.18 (0.83–1.70)	0.84 (0.58–1.22)	1.98 (0.96–4.11)	0.65 (0.37–1.14)
120	7.98 (4.91–12.98)*	0.99 (0.59–1.66)	1.54 (0.84–2.83)	0.84 (0.45–1.58)	2.94 (1.05–8.27)*	0.69 (0.28–1.69)
140	12.54 (6.37–24.69)*	1.06 (0.52–2.16)	2.01 (0.84–4.84)	0.85 (0.34–2.09)	4.37 (1.10–17.40)*	0.74 (0.21–2.60)
160	19.69 (8.21–47.25)*	1.13 (0.45–2.84)	2.62 (0.82–8.34)	0.85 (0.26–2.81)	6.49 (1.13–37.32)*	0.78 (0.15–4.07)

pressure ≤39 mm Hg was associated with an increased OR of postoperative mortality (fully adjusted model), while measurements from 41 to 66 mm Hg were associated with a reduced OR of postoperative mortality (Fig. 2). HL goodness of fit tests showed good model fit (systolic pressure: χ^2=14.13, P=0.0785; diastolic pressure: χ^2=10.78, P=0.2144; pulse pressure: χ^2=14.06, P=0.0803). Restricted cubic splines analysis did not identify associations between elevated systolic or diastolic BP and increased mortality in the elderly. In patients <65 years old (n=166 934), no association was observed between preoperative BP and postoperative mortality in fully adjusted or parsimonious models (data not shown).

Discussion

This cohort study demonstrated a dose-dependent association between preoperative hypotension and postoperative mortality that was consistent across systolic and diastolic BP and sensitivity analyses including the timing of BP measurement. This effect was confined to the elderly, with no relationship between preoperative BP and postoperative mortality apparent in 18–65 year olds. It is important to note that risk thresholds were identified by statistical difference from the reference (P<0.05) at a systolic BP of ~119 mm Hg and a diastolic BP of ~63 mm Hg. At these thresholds the risk associated with the BP value was small, but there was a non-linear increase in the odds of mortality as preoperative BP decreased. Hence every 1-mm Hg drop in BP below these thresholds is associated with a larger increase in risk. To put this finding in context, following adjustment, a systolic BP of 100 mm Hg approximated a similar risk to a preoperative diagnosis of heart failure [adjusted OR 1.38 (95% CI 1.02–1.88)] in the main dataset. In contrast, elevated diastolic, not systolic BP, was associated with an increased odds of mortality in the whole cohort following adjustment. However, the effect of elevated diastolic BP was not evident in the elderly or when we restricted our analyses to the preoperative period (1–12 weeks prior to surgery). Additionally, we observed that low, not elevated, pulse pressure values were associated with an increased OR of postoperative mortality.

Overall, these data have important implications for perioperative risk stratification. The dose-dependent and consistent association in the elderly of preoperative hypotension and postoperative mortality reveals a novel, overlooked perioperative risk factor, with increased risk apparent with BP values <119/63 mm Hg. This represents a cheap and readily available preoperative marker of postoperative risk.

Preoperative hypotension

Prima facie, the emphasis of our results on hypotension seem to contrast with accumulating data on the community control of BP, and recent perioperative guidelines, that emphasize

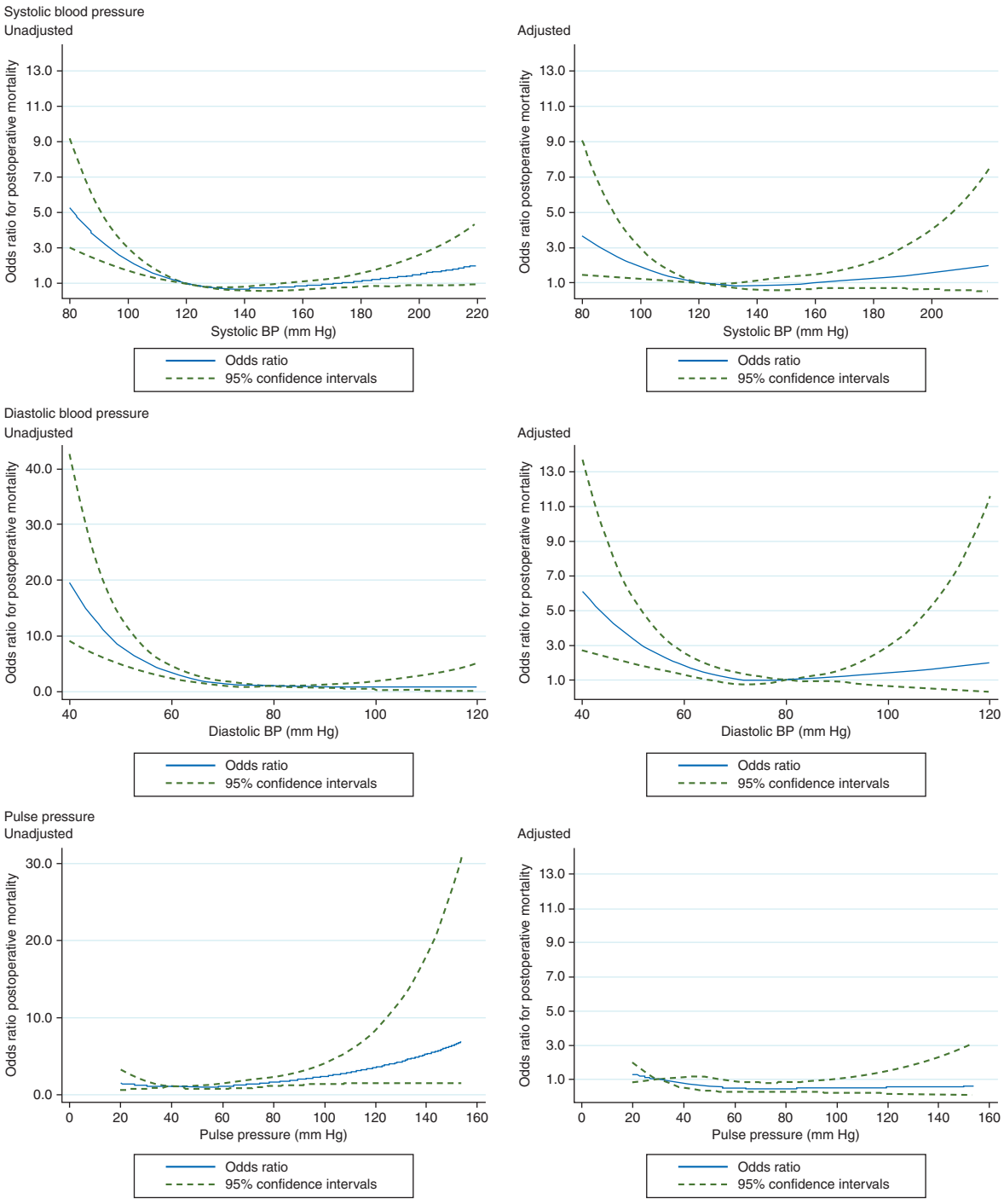

Fig 3 Unadjusted and fully adjusted spline graphs for the association between systolic BP, diastolic BP, and pulse pressure and postoperative mortality in patients in whom BP measurements were recorded between 8 and 84 days prior to surgery. Fully adjusted model adjusted for age, gender, atrial fibrillation, unstable angina, valvular heart disease, myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, chronic obstructive pulmonary disease, liver disease, diabetes mellitus, renal disease, cancer, Charlson's comorbidity score, smoking, alcohol, surgical risk scale, socioeconomic status (IMD 2010), number of BP measurements, statins, beta blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, alpha-2 agonists, loop diuretics, thiazide diuretics, aspirin, other antiplatelet drugs, and selective serotonin re-uptake inhibitors.

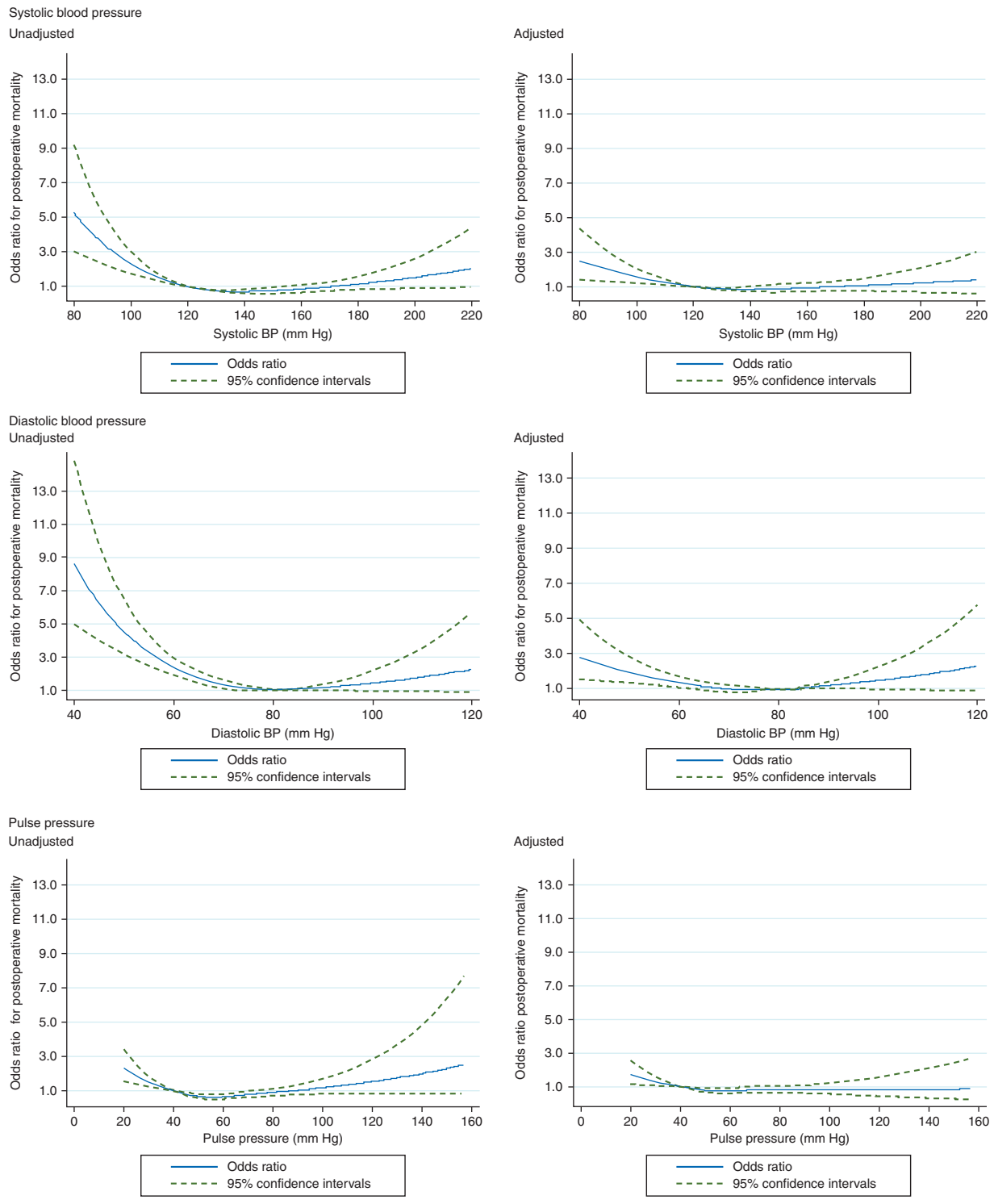

Fig 4 Unadjusted and fully adjusted spline graphs for the association between systolic BP, diastolic BP, and pulse pressure and postoperative mortality in patients ≥65 years of age. Fully adjusted model adjusted for age, gender, atrial fibrillation, unstable angina, valvular heart disease, myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, chronic obstructive pulmonary disease, liver disease, diabetes mellitus, renal disease, cancer, Charlson's comorbidity score, smoking, alcohol, surgical risk scale, socioeconomic status (IMD 2010), number of BP measurements, statins, beta blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, alpha-2 agonists, loop diuretics, thiazide diuretics, aspirin, other antiplatelet drugs, and selective serotonin re-uptake inhibitors.

hypertension.[5 10] However, in the perioperative period anaesthesia and surgery induce multiple physiological stresses, including hemodynamic variation, surgical bleeding, increased myocardial work, pain, alterations in coagulabilty, and inflammation that do not occur simultaneously or at a predictable time in the community.[14 15] As such, it seems plausible that preparation for elective surgery should require an alternate strategy compared to reducing long-term vascular risk.

The association of preoperative low BP with subsequent postoperative mortality was robust across sensitivity analyses, including when purely focused on the preoperative period (8–84 days prior to surgery). This links the events closely in time and increases the plausibility for the impact of preoperative hypotension on postoperative mortality. While the mechanisms of this effect remain unclear, the biological plausibility of a link to perioperative hypotension is strong. For example, in the perioperative period, low BP is associated with increased postoperative mortality.[11 12] We hypothesize that elderly patients with preoperative hypotension are operating at the lower limit of cerebral and other end-organ autoregulation[9] and that this predisposes them to harm from perioperative changes in hemodynamics, inflammation, and the stress response, leading to secondary organ injury and increased risk of death. Consistent with this, low preoperative BP is a predictor of intraoperative hypotension,[13] and intraoperative hypotension, like postoperative hypotension,[11 12] is a predictor of postoperative mortality.[14 15] Based on this interpretation, patients with low preoperative BP should have rigorous control of their BP in the perioperative period to maintain it at community levels.

In our sample, 9.4% (n=7924) of elderly subjects had a systolic BP <120 mm Hg, meaning that preoperative hypotension is a prevalent risk factor. One possibility is that low BP represents heart failure in our population. However, in the UK the prevalence of heart failure is ~1%, while in our dataset it was 1.4%, suggesting that there is not a deficit in coding of the diagnosis. Hence we consider that our adjustment for a heart failure diagnosis and exposure to loop diruretics would account for confounding from this variable. We also conducted an interaction analysis for BP and heart failure and did not find a significant effect. Overall, we do not consider that heart failure alone explains the association of low preoperative BP and postoperative mortality. An alternative explanation is the prescription of vasoactive medications; 2329 elderly patients with a systolic BP <120 mm Hg (29%) had a CPRD diagnosis of hypertension, hence overtreatment of BP is another possible explanation. Accumulating data suggest that some community vasoactive medications may cause harm when continued into the perioperative period.[11 28 29] Randomized trials are required to define the optimal management of community BP medications in the perioperative period.

Preoperative hypertension

Across the whole population and in the elderly, consistent associations of hypertensive BP values with postoperative mortality were lacking. However, in adjusted analysis of the whole cohort we identified through restricted cubic splines analysis that elevated diastolic BP was associated with increased mortality in a dose-dependent manner. We confirmed this by categorizing diastolic BP into strata, finding that diastolic BP >100 mm Hg was associated with increased mortality. Given the role of diastolic BP in coronary perfusion, the prognostic implications of elevated diastolic BP for cardiac events in the community in young to middle age[30], and the prevalence of cardiac events and myocardial injury in the perioperative period[31], future study of the impact of elevated diastolic BP on the risk of postoperative cardiac events appears warranted. It is possible that patients with diastolic hypertension may be vulnerable to myocardial injury through impaired coronary perfusion during episodes of perioperative hypotension. Indeed, myocardial injury is a major risk factor for postoperative mortality.[31] However, one small randomized controlled trial of low cardiovascular risk patients did not find a reduction in perioperative risk with acutely lowering diastolic BP to <110 mm Hg during a preoperative admission.[32] Randomized trials focussed on patients at increased cardiac risk seem indicated based on our findings. In particular, studies should investigate whether establishing a lower limit of or maximum decrease in perioperative diastolic BP would improve perioperative outcomes.

Interestingly, systolic BP was only associated with increased postoperative mortality in the unadjusted analyses of the whole cohort, suggesting that age and other comorbidities, including the secondary consequences of systolic hypertension, exert a greater impact on perioperative risk. Indeed, the increase in systolic BP with age leads to accumulation of end-organ vascular disease such as stroke and myocardial infarction that have important known effects on postoperative mortality. Hence, while we were unable to show that systolic BP itself is an independent risk factor for postoperative mortality, including through sensitivity analyses, we rationalize that our data suggest that any influence of systolic BP on postoperative mortality is due to the accumulation of related secondary vascular disease.

Overall, our data indicate that elevated diastolic, rather than systolic, BP may influence postoperative risk. It is important to note that recent guidelines[10] emphasize both systolic and diastolic hypertension. Our data directly inform these guidelines, as preoperative hypotension, rather than hypertension, is the major hemodynamic factor for postoperative mortality and diastolic hypertension exerts greater perioperative impact than systolic hypertension on postoperative mortality. Furthermore, our data do not indicate a clear preoperative hypertensive threshold, obtained within 12 weeks of surgery, at which elective surgery is associated with a large increase in mortality. Hence our data do not advocate for the cancellation or delaying of elective surgery for better preoperative control of hypertension as occurs in ~1% of elective surgical patients.[10] Nonetheless, our data do support the concept that normalization of BP is beneficial.

Strengths and weaknesses

It is important to recognize that any numerical threshold for BP may be confounded by age, exposure to antihypertensive medications, end-organ vascular disease and other comorbidities. Hence we adjusted for many confounders in fully adjusted and parsimonious models as well as conducting sensitivity analyses for the timing of BP measurement. Not only was the observed effect of preoperative hypotension consistent across models, it fulfils many of the Bradford–Hill criteria, including biological gradient (dose dependence), plausibility,[11 12 14 15] coherence,[1–4] strength, and temporality.

We concentrated on primary care readings of BP to provide information about perioperative risk prior to admission for an operation and limit the impact of perioperative anxiety. The available BP data were recorded between 1 and 12 weeks (and additionally 1 and 52 weeks) preoperatively in our sensitivity analyses. We focussed on mortality, as it is the most important

marker of severe postoperative complications and has strong clinical relevance; however, future studies should also include postoperative morbidity endpoints.

Our data are limited in other ways. The observational design of our study, like all large-scale epidemiology studies, is unable to prove causality and is vulnerable to unmeasured confounding. We did not account for perioperative factors other than surgical severity in our analyses, as we were interested in defining preoperative risk factors for postoperative mortality (enhancing preoperative risk stratification). Inclusion of factors that are not known preoperatively, such as intraoperative bleeding, cannot be used to enhance these estimates. Second, factors such as intraoperative BP management and bleeding risk may be related to preoperative BP values, perhaps mediating or limiting their effects. Adjusting confounders in the causal chain that follow chronologically would obviously reduce the impact of an earlier event, as they are causally related.

An important preoperative confounder is heart failure, which is not in the causal chain (does not follow chronologically and is known preoperatively), and we have explicitly attempted to address this variable through adjustment for loop diuretics and heart failure in our models and through an interaction analysis. Nonetheless, we cannot exclude unmeasured confounding from our results. Similarly, the impact of missing data on our results is hard to estimate. Missing data can introduce bias into the results, and there are flaws in each of the attempts to handle this issue.[33] Hence, while we addressed missing data using a validated method, we cannot exclude that this biased the results.

Future research will have to identify the mechanisms through which preoperative low BP may lead to postoperative mortality, as, while our findings have biological plausibility, they do not imply causality. This should include investigation of whether there is a dose-dependent effect of antihypertensive drugs on postoperative mortality in patients with preoperative hypotension. Establishing a link between preoperative BP values and intra- and postoperative values, as well as identifying preoperative BP risk thresholds that predispose to postoperative morbidity, would further enhance the biological plausibility of our findings. Likewise, studies should evaluate whether the risk associated with intra- and postoperative hypotension are causally driving mortality or are mediators related to baseline preoperative values. Future studies should address when is the optimal time to measure preoperative BP to predict postoperative risk. We showed that our thresholds are predictive when obtained within 3 months of surgery in our sensitivity analysis. However, it is unknown how these values relate to those taken closer to surgery or on the day of surgery. Perioperative datasets should be used to probe this association.

Conclusions

These data suggest that a previously unrecognized perioperative risk factor, preoperative hypotension, exerts significant effects on postoperative mortality in the elderly. As preoperative BP drops below 119/63 mm Hg in the elderly, the OR increases, mandating further study of how to optimize perioperative care of these vulnerable patients. While the SPRINT study demonstrated that targeting a mean systolic BP of 120 mm Hg leads to improvement in health over 5 years,[7] our data suggest that aggressive lowering of BP below this threshold may be harmful in the setting of surgery in the elderly.

Author's contribution

R.D.S. and P.M. designed the research question and study analysis plan with input from the co-authors. S.V. performed the analysis with input from P.M. and R.D.S. S.V. and P.M. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All co-authors advised on the analyses. R.D.S. and S.V. wrote the manuscript with significant input from P.M. All authors advised on the manuscript content and contributed to editing and scientific direction. All authors approved the final manuscript. S.V., P.M., and R.D.S. affirm that the manuscript is an honest, accurate, and transparent account of the study being reported and that no important aspects of the study have been omitted.

Supplementary material

Supplementary material is available at *British Journal of Anaesthesia* online.

Declaration of interest

All authors have completed the unified competing interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare no competing interests that may be relevant to the submitted work.

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References

1. Chockalingam A, Campbell NR, Fodor JG. Worldwide epidemic of hypertension. *Can J Cardiol* 2006; **22**: 553–5
2. D'Agostino RB, Belanger AJ, Kannel WB, Cruickshank JM. Relation of low diastolic blood pressure to coronary heart disease death in presence of myocardial infarction: the Framingham Study. *BMJ* 1991; **303**: 385–9
3. Kannel WB, D'Agostino RB, Silbershatz H. Blood pressure and cardiovascular morbidity and mortality rates in the elderly. *Am Heart J* 1997; **134**: 758–63
4. Bangalore S, Fayyad R, Laskey R, *et al*. Lipid lowering in patients with treatment-resistant hypertension: an analysis from the Treating to New Targets (TNT) trial. *Eur Heart J* 2014; **35**: 1801–8
5. Rapsomaniki E, Timmis A, George J, *et al*. Blood pressure and incidence of twelve cardiovascular diseases: lifetime risks, healthy life-years lost, and age-specific associations in 1.25 million people. *Lancet* 2014; **383**: 1899–911
6. Rosendorff C, Lackland DT, Allison M, *et al*. Treatment of hypertension in patients with coronary artery disease: a scientific statement from the American Heart Association, American College of Cardiology, and American Society of Hypertension. Journal of the American Society of Hypertension. *J Am Soc Hypertens* 2015; **9**: 453–98

7. SPRINT Research Group, Wright JT Jr, Williamson JD, *et al*. A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med* 2015; **373**: 2103–16
8. Fleisher LA, Fleischmann KE, Auerbach AD, *et al*. 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines. *J Am Coll Cardiol* 2014; **64**: e77–137
9. Sanders RD. How important is peri-operative hypertension? *Anaesthesia* 2014; **69**: 948–53
10. Hartle A, McCormack T, Carlisle J, *et al*. The measurement of adult blood pressure and management of hypertension before elective surgery: joint guidelines from the Association of Anaesthetists of Great Britain and Ireland and the British Hypertension Society. *Anaesthesia* 2016; **71**: 326–37
11. Devereaux PJ, Yang H, Yusuf S, *et al*. Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): a randomised controlled trial. *Lancet* 2008; **371**: 1839–47
12. Devereaux PJ, Sessler DI, Leslie K, *et al*. Clonidine in patients undergoing noncardiac surgery. *N Engl J Med* 2014; **370**: 1504–13
13. Cheung CC, Martyn A, Campbell N, *et al*. Predictors of intraoperative hypotension and bradycardia. *Am J Med* 2015; **128**: 532–8
14. Walsh M, Devereaux PJ, Garg AX, *et al*. Relationship between intraoperative mean arterial pressure and clinical outcomes after noncardiac surgery: toward an empirical definition of hypotension. *Anesthesiology* 2013; **119**: 507–15
15. Monk TG, Bronsert MR, Henderson WG, *et al*. Association between intraoperative hypotension and hypertension and 30-day postoperative mortality in noncardiac surgery. *Anesthesiology* 2015; **123**: 307–19
16. Howell SJ, Sear JW, Foex P. Hypertension, hypertensive heart disease and perioperative cardiac risk. *Br J Anaesth* 2004; **92**: 570–83
17. Asopa A, Jidge S, Schermerhorn ML, Hess PE, Matyal R, Subramaniam B. Preoperative pulse pressure and major perioperative adverse cardiovascular outcomes after lower extremity vascular bypass surgery. *Anesth Analg* 2012; **114**: 1177–81
18. Mazzeffi M, Flynn B, Bodian C, Bronheim D. Preoperative arterial pulse pressure has no apparent association with perioperative mortality after lower extremity arterial bypass. *Anesth Analg* 2012; **114**: 1170–6
19. Bilimoria KY, Liu Y, Paruch JL, *et al*. Development and evaluation of the universal ACS NSQIP surgical risk calculator: a decision aid and informed consent tool for patients and surgeons. *J Am Coll Surg* 2013; **217**: 833–42.e1–3
20. Sanders RD, Bottle A, Jameson SS, *et al*. Independent preoperative predictors of outcomes in orthopedic and vascular surgery: the influence of time interval between an acute coronary syndrome or stroke and the operation. *Ann Surg* 2012; **255**: 901–7
21. Lee TH, Marcantonio ER, Mangione CM, *et al*. Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. *Circulation* 1999; **100**: 1043–9
22. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987; **40**: 373–83
23. Sutton R, Bann S, Brooks M, Sarin S. The Surgical Risk Scale as an improved tool for risk-adjusted analysis in comparative surgical audit. *Br J Surg* 2002; **89**: 763–8
24. Brooks MJ, Sutton R, Sarin S. Comparison of Surgical Risk Score, POSSUM and p-POSSUM in higher-risk surgical patients. *Br J Surg* 2005; **92**: 1288–92
25. Harrell FE Jr, *Regression Modeling Strategies: With Applications to Linear Models, Logistic Regression, and Survival Analysis*. New York: Springer, 2013
26. Aronow WS, Fleg JL, Pepine CJ, *et al*. ACCF/AHA 2011 expert consensus document on hypertension in the elderly: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus documents developed in collaboration with the American Academy of Neurology, American Geriatrics Society, American Society for Preventive Cardiology, American Society of Hypertension, American Society of Nephrology, Association of Black Cardiologists, and European Society of Hypertension. *J Am Coll Cardiol* 2011; **57**: 2037–114
27. Denardo SJ, Gong Y, Nichols WW, *et al*. Blood pressure and outcomes in very old hypertensive coronary artery disease patients: an INVEST substudy. *Am J Med* 2010; **123**: 719–26
28. Andersson C, Shilane D, Go AS, *et al*. Beta-blocker therapy and cardiac events among patients with newly diagnosed coronary heart disease. *J Am Coll Cardiol* 2014; **64**: 247–52
29. Jorgensen ME, Hlatky MA, Kober L, *et al*. Beta-blocker-associated risks in patients with uncomplicated hypertension undergoing noncardiac surgery. *JAMA Intern Med* 2015; **175**: 1923–31.
30. Franklin SS, Larson MG, Khan SA, *et al*. Does the relation of blood pressure to coronary heart disease risk change with aging? The Framingham Heart Study. *Circulation* 2001; **103**: 1245–9
31. Devereaux PJ, Chan MT, Alonso-Coello P, *et al*. Association between postoperative troponin levels and 30-day mortality among patients undergoing noncardiac surgery. *JAMA* 2012; **307**: 2295–304
32. Weksler N, Klein M, Szendro G, *et al*. The dilemma of immediate preoperative hypertension: to treat and operate, or to postpone surgery? *J Clin Anesth* 2003; **15**: 179–83
33. Sterne JA, White IR, Carlin JB, *et al*. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ* 2009; **338**: b2393

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