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CARDIOVASCULAR DISEASE

Systolic blood pressure variability as a risk factor for abdominal aortic aneurysm: a prospective cohort study with genomic and proteomic profiling

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Abstract

Elevated blood pressure is an established risk factor for abdominal aortic aneurysm (AAA), yet traditional measures inadequately capture dynamic hemodynamic stress. This study examined the association between visit-to-visit systolic blood pressure variability (SBPV) and incident AAA, assessed whether genetic susceptibility modified this association, and explored protein-specific indirect associations. Visit-to-visit SBPV was calculated from ≥3 systolic blood pressure measurements in 189,770 UK Biobank participants with linked primary care records. Cox proportional hazards models evaluated SBPV-AAA associations, adjusting for cardiovascular risk factors and mean systolic blood pressure. Polygenic risk scores stratified genetic susceptibility. Proteomic profiling was used for exploratory protein-specific indirect-effect analyses. Over median follow-up of 10.7 years, 1,036 incident AAA cases occurred. Higher SBPV was independently associated with increased AAA risk across all metrics (all P for trend ≤0.003), with 33%–54% increased risk comparing the highest versus lowest tertile. Dose-response relationships were approximately linear (all P for non-linearity >0.05). High SBPV conferred elevated risk even with mean systolic blood pressure <130 mmHg. Participants with both high SBPV and high genetic risk had more than two-fold increased AAA risk (hazard ratio 2.07–2.28, all P<0.001). Ten circulating proteins showed FDR-significant protein-specific indirect effects in separate exploratory models, with descriptive coefficient-attenuation estimates ranging from 6.7% to 30.4%; these protein-specific estimates are non-additive and do not establish causal mediation. Associations remained robust across multiple sensitivity analyses. Higher visit-to-visit SBPV was associated with increased AAA risk, particularly among genetically susceptible individuals. These findings support

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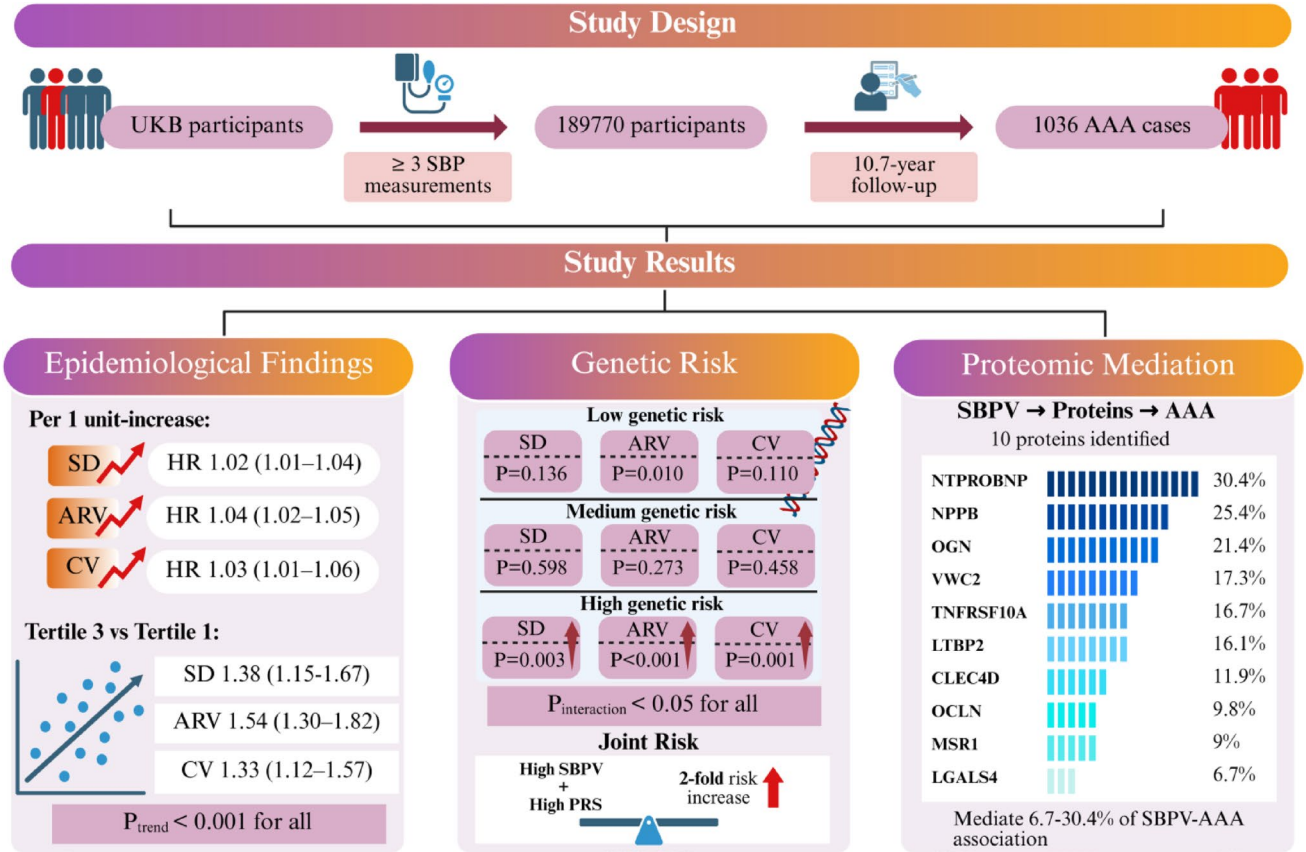
SBPV as a potential AAA risk marker and warrant external validation, but do not establish that reducing SBPV would prevent AAA.

Graphical abstract



Highlights

- Higher systolic blood pressure variability (SBPV) linked to increased AAA risk.
- SBPV-AAA relationship consistent across multiple sensitivity analyses.
- High SBPV amplified AAA risk in individuals with high genetic predisposition.
- Ten proteins identified as mediators between SBPV and AAA risk.
- SBPV associated with AAA even with mean systolic pressure <130 mmHg.
- Results support blood pressure variability management in AAA prevention.

Keywords Hypertension · Blood pressure variability · Abdominal aortic aneurysm · Polygenic risk score · Proteomic analysis · Prevention

Introduction

Abdominal aortic aneurysm (AAA) is defined as a localized dilation of the abdominal aorta with a diameter more than 3.0 cm [1]. It typically remains asymptomatic until rupture, an event associated with exceedingly high mortality, even with prompt intervention [2]. AAA is responsible for an estimated 160,000 deaths and 3 million disability-adjusted life years annually, highlighting its substantial global health burden [3]. Patho-physiologically, AAA is characterized by progressive inflammation, vascular smooth muscle cell depletion, and extracellular matrix degradation. Genetic predisposition and age-related biological processes further contribute to its pathogenesis [4]. Although screening and surgical or endovascular repair have improved outcomes, effective approaches to prevent AAA formation or halt its early progression remain elusive. Thus, elucidating modifiable risk factors underlying AAA development is crucial for improving early prevention and mitigating disease burden.

Elevated blood pressure is an established risk factor for major cardiovascular diseases, such as stroke, coronary heart disease, and heart failure [5]. Epidemiological evidence demonstrates that elevated systolic blood pressure (SBP) or diastolic blood pressure, as well as a history of hypertension, are linked to an increased risk of AAA [6]. Nevertheless, several studies have reported weak or inconsistent associations between elevated blood pressure parameters and AAA, and meta-analyses show considerable heterogeneity across different populations [7, 8]. The heterogeneity in these associations suggests that elevated blood pressure may represent only one component of the hemodynamic stress affecting the aortic wall. In reality, blood pressure exhibits dynamic fluctuations influenced by physical activity, autonomic nervous tone, emotional state, medication adherence, and arterial stiffness—a phenomenon termed blood pressure variability [9]. Unlike mean arterial pressure, which reflects a time-averaged hemodynamic load, blood pressure variability captures the oscillations in cardiovascular homeostasis. Emerging evidence indicates that elevated blood pressure variability is independently associated with an increased risk of cardiovascular events, beyond the effect of elevated blood pressure [5, 9, 10]. However, whether blood pressure variability contributes to the development of AAA remains unclear.

Genetic factors represent a major determinant in the pathogenesis of AAA [11–13]. Evidence from family and twin studies indicates a substantial heritable component, indicating a significant contribution of genetic factors to AAA onset. Genome-wide association studies have identified multiple risk loci and implicated biological pathways involved in lipid metabolism, vascular remodeling, and inflammatory processes [13]. Polygenic risk scores (PRS) have emerged as promising tools for identifying individuals at high risk of developing AAA, highlighting the potential of genetic profiling to enhance early risk stratification [12]. Recent findings have provided evidence that AAA is a multifactorial disorder influenced by the interplay of genetic predisposition and environmental factors such as smoking, dyslipidemia, and elevated blood pressure [14]. However, it remains unknown whether genetic susceptibility interacts with blood pressure variability in the development of AAA.

Proteomic profiling provides a comprehensive analysis of the entire repertoire of expressed proteins under defined conditions, enabling a systematic insight into molecular pathways underlying disease pathogenesis [15]. In AAA, proteomic studies have revealed significant alterations in proteins involved in extracellular matrix remodeling, inflammation, vascular smooth muscle cell dysfunction, and lipid metabolism [16]. These observations underscore the central role of dynamic protein-level changes in the pathobiology of AAA. Proteomic analyses have been utilized to identify key protein alterations associated with both elevated blood pressure and AAA progression, offering novel insights into the pathophysiological mechanisms through which chronic hypertension exacerbates aortic wall injury [17]. However, the mechanisms through which blood pressure variability modulates protein expression, and the signaling pathways that connect oscillatory hemodynamic stress to AAA risk remain incompletely understood. The proteomic mechanisms underlying this relationship constitute an important knowledge gap and merit further rigorous investigation.

Therefore, we designed a large prospective cohort study using UK Biobank data to examine the association of blood pressure variability with AAA risk, and determined whether genetic susceptibility modifies this risk. In addition, proteomic profiling was employed to identify key proteins potentially linking blood pressure variability to AAA formation. Together, this study offers a comprehensive framework for elucidating how hemodynamic variability, genetic predisposition, and molecular mechanisms collectively contribute to AAA pathogenesis.

Methods

Study population

This study used data from the UK Biobank, which recruited ~500,000 participants between 2006 and 2010 with detailed baseline socio-demographic, lifestyle, and clinical assessments. Linked primary care records from general practitioners were available for ~200,000 participants up to September 2017. All participants provided written informed consent, and ethical approval was granted by the North West-Haydock Research Ethics Committee. For the present analysis, we included 219,242 participants with linked primary care data. SBP records were cleaned following standardized procedures: values underwent range validation, and repeated measurements taken during the same visit were averaged. We then excluded participants with fewer than three valid SBP records (n = 6,829), and/or follow-up < 1 year (n = 10,622), leaving 201,791 participants with sufficient data to calculate visit-to-visit systolic blood pressure variability (SBPV). From this cohort, we further excluded those with baseline AAA (n = 69) and missing covariate data (n = 11,952), yielding a final analytical sample of 189,770 participants for incident AAA analyses (Fig. 1).

SBP ascertainment and SBPV definition

SBP values were obtained from UK Biobank primary care records (Supplementary Figure S1). To reduce measurement error, we [1] excluded values < 60 or > 300 mmHg and [2]

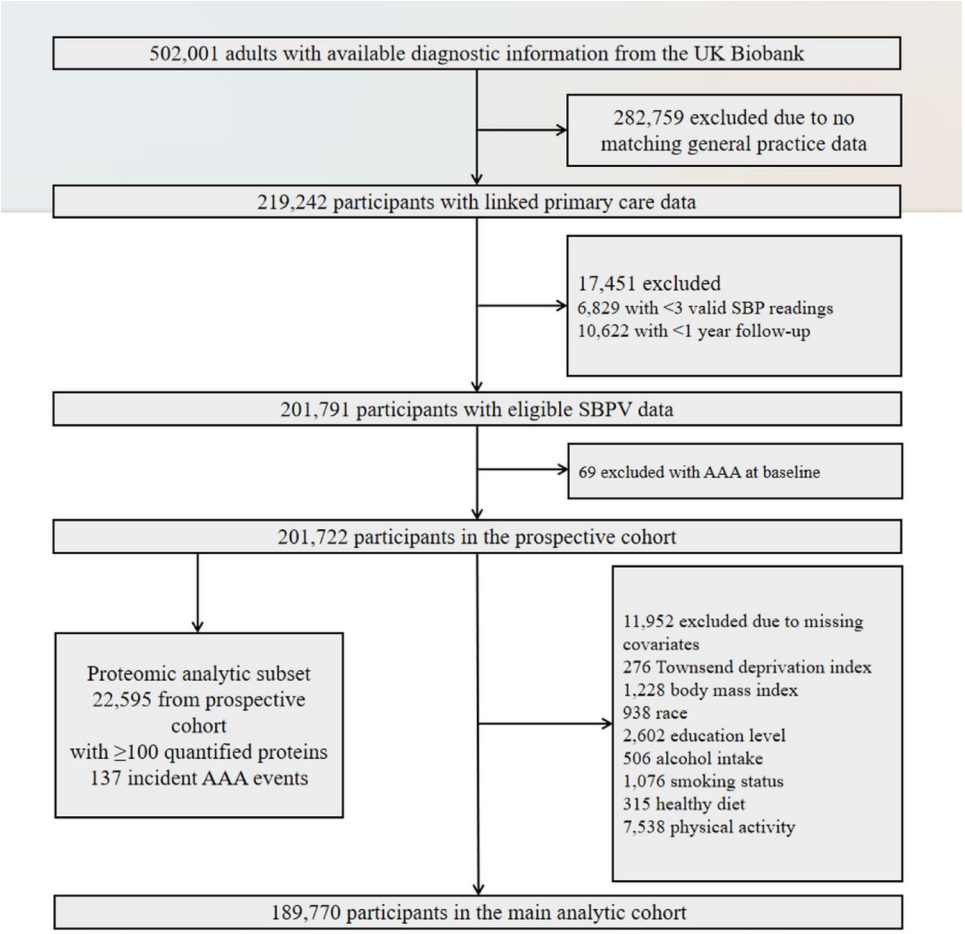


Fig. 1 Derivation of the prospective cohort, main analytic cohort, and proteomic analytic subset. The prospective cohort included 201,722 participants after exclusion of prevalent abdominal aortic aneurysm. The main analytic cohort included 189,770 participants after exclusion of 11,952 participants with missing covariates. The proteomic analytic subset was derived separately from the prospective cohort and included 22,595 participants with at least 100 quantified proteins, among whom 137 incident abdominal aortic aneurysm events occurred. AAA, abdominal aortic aneurysm; SBP, systolic blood pressure; SBPV, systolic blood pressure variability. Participants could have missing data for more than one covariate; therefore, the missing-covariate category counts are not mutually exclusive

averaged multiple readings recorded at the same visit to avoid overestimating visit-to-visit variability. Among participants included in the SBPV analysis, the median SBP was 136 mmHg (1st-99th percentile: 100–184 mmHg). SBP was measured a median of 13 times per participant at 147-day intervals (1st-99th percentiles: 3–78 measurements; 2–2977 days). Baseline SBP was taken as the first recorded value for each participant. Visit-to-visit variability was measured by standard deviation (SD), coefficient of variation (CV = SD/mean × 100), and average real variability (ARV, the mean absolute difference between consecutive values). Effect sizes were reported per 1 mmHg increase in SD or ARV and per 1% increase in CV. For categorical analyses, each metric was split into tertiles, with higher tertiles indicating greater variability.

Ascertainment of outcomes

Medical history in the UK Biobank was ascertained through linkage to national hospital admission and death registry data. Hospital diagnoses and procedures were coded using ICD-10 and OPCS-4, respectively. Consistent with previous UK Biobank studies [2], AAA was defined as the first recorded hospital diagnosis, AAA-related death, and/or AAA-related surgical procedure (Supplementary Table S1). Follow-up started from the first available SBP record and continued until the occurrence of incident AAA, AAA-related death, or the end of the study period (September 27, 2021). Participants without AAA were censored at the date of their last available record or the end of the study period.

Assessment of covariates

Socio-demographic and lifestyle factors were collected at baseline using a self-administered touchscreen questionnaire. Covariates included age, sex, body mass index (BMI), ethnicity, Townsend deprivation index (TDI), education level, smoking status, alcohol intake, physical activity, a healthy diet score based on modified American Heart Association guidelines, and mean SBP. Baseline comorbidities included stroke, ischaemic heart disease (IHD), type 2 diabetes (T2DM), and chronic kidney disease (CKD), identified from the earliest available record before the start of follow-up. Detailed definitions of all variables were provided in Supplementary Table S2.

Genome-wide PRS construction

Genome-wide PRS for AAA were constructed using summary statistics from the FinnGen Release 12 GWAS and the Bayesian LDpred2 framework. FinnGen, a Finnish founder cohort, was used to minimise sample overlap with the UK Biobank and to increase power for European-ancestry analyses. GWAS summary statistics were harmonised and matched to UK Biobank imputed genotypes, which served as both the target dataset and LD reference. Chromosome-specific sparse LD matrices and SNP-heritability estimates were derived in a subset of UK Biobank participants, and LDpred2-auto was run with multiple independent chains per chromosome. LDpred2-inf estimates were used when LDpred2-auto did not converge. Individual PRS were calculated as weighted sums of risk-allele dosages, standardised (mean 0, SD 1), and categorised into tertiles (low, middle, high) for descriptive analyses. Further implementation details were provided in Supplementary Table S3.

Proteomics data

We utilized proteomic data from the UK Biobank Pharma Proteomics Project, which comprised 53,017 participants broadly representative of the overall UK Biobank cohort. Circulating proteins were quantified using the Olink platform, employing a proximity extension assay coupled with next-generation sequencing for parallel protein measurement. Results were reported as normalized protein expression values on a $\log_2$ scale. For proteomic analysis, we included participants with at least 100 successfully quantified proteins, yielding 22,595 eligible individuals. We excluded eight proteins with >20% missing data, resulting in 2,915 proteins retained for analysis. All protein measurements were standardized prior to statistical modeling.

Statistical analysis

Continuous variables were summarised as mean ± SD or median (interquartile range, IQR), and categorical variables as counts (percentages). Baseline characteristics in Table 1 were summarised descriptively, without hypothesis-test P values. Standardized differences were used to compare the main analytic cohort with the proteomic subset. Associations between SBPV and incident AAA were estimated using Cox proportional hazards models with follow-up time as the time scale, and the proportional hazards assumption was checked using Schoenfeld residuals. Covariate adjustment was performed hierarchically: unadjusted, Model 1 (age, sex, BMI, ethnicity), Model 2 (Model 1 plus TDI, educational attainment, smoking, alcohol, physical activity, healthy diet, and baseline stroke, IHD, T2DM, and CKD), and Model 3 (Model 2 plus mean SBP). Each SBPV metric was analysed both continuously and in tertiles (lowest tertile as reference). Trend across tertiles was tested by assigning the median of each tertile as a continuous term (Wald P values). Dose-response was examined using restricted cubic splines with knots at the 10th, 50th, and 90th percentiles, and non-linearity was assessed by likelihood ratio tests comparing spline and linear models. Potential threshold effects of SBPV on AAA risk were explored using segmented Cox models with a data-driven change-point in SBPV, estimated from partial likelihood-based methods.

Sensitivity analyses were performed to evaluate the robustness of the primary findings: (i) exclusion of the first follow-up year to reduce reverse causation; (ii) recalculation of SBPV using alternative minimum measurement thresholds to assess consistency in effect estimates; (iii) exclusion of participants with initial SBP records before 1987 (the 1 st percentile of measurement dates) to limit early temporal artifacts; (iv) multiple imputation with chained equations (five datasets combined via Rubin's rules) to address missing data; (v) Fine-Gray subdistribution models to account for competing risks; (vi) use of diastolic BPV as an alternative exposure to examine specificity; and (vii) a discordance analysis categorizing participants by mean SBP (≥130 vs. < 130 mmHg) and SBPV (high vs. low) to clarify the independent contribution of SBPV, with hazard ratios (HR) compared across groups; and (viii) an assessment-date landmark analysis in participants with valid pulse wave arterial stiffness index (ASI; UK Biobank Field 21021) to evaluate residual confounding by arterial stiffness. Because ASI was measured at the UK Biobank baseline assessment and was available only in a subset, this analysis was restricted to participants with valid ASI (0 < ASI < 29.59 m/s), no AAA diagnosis on or before assessment, and positive follow-up thereafter. Follow-up began on the assessment date, and the fully adjusted Model 3 was refitted before and after adding ASI standardized to a 1-SD increase (Supplementary Table S10).

Genetic analysis was performed to examine whether inherited risk modified the association between SBPV and AAA. All genetic models were adjusted for genotyping array and the first 10 genetic principal components to reduce population stratification bias. We stratified participants by PRS tertiles and re-estimated SBPV-AAA associations within each stratum using Cox models adjusted as in Model 3. To evaluate joint effects, SBPV was cross-classified with PRS tertiles. Cox models estimated HRs using the low-SBPV/low-PRS group as reference. An ordinal joint score (range 0–5) was derived by summing SBPV (0/1) and PRS (0/2/4) codes and modeled continuously to test for trend. Multiplicative interaction was assessed using a product term (continuous SBPV × continuous PRS).

Table 1 Baseline characteristics of the analytic cohort, overall and stratified by incident abdominal aortic aneurysm during follow-up

Characteristic	Overall (N = 189,770)	No incident AAA (n = 188,734)	Incident AAA (n = 1,036)
Age, mean (SD), years	56.88 (7.93)	56.84 (7.93)	63.50 (4.85)
Sex, n (%)			
Female	104,742 (55.2)	104,596 (55.4)	146 (14.1)
Male	85,028 (44.8)	84,138 (44.6)	890 (85.9)
Race, n (%)			
White	181,597 (95.7)	180,570 (95.7)	1027 (99.1)
Non-White	8173 (4.3)	8164 (4.3)	9 (0.9)
BMI, mean (SD), kg/m^2	27.56 (4.82)	27.55 (4.82)	28.71 (4.45)
Townsend deprivation index, mean (SD)	−1.42 (2.98)	−1.42 (2.98)	−1.30 (3.13)
Education level, n (%)			
None of the listed qualifications	33,895 (17.9)	33,543 (17.8)	352 (34.0)
Low	31,914 (16.8)	31,764 (16.8)	150 (14.5)
Medium	33,369 (17.6)	33,214 (17.6)	155 (15.0)
High	90,592 (47.7)	90,213 (47.8)	379 (36.6)
Alcohol intake, n (%)			
No	107,478 (56.6)	106,908 (56.6)	570 (55.0)
Yes	82,292 (43.4)	81,826 (43.4)	466 (45.0)
Current smoking, n (%)			
No	170,478 (89.8)	169,764 (89.9)	714 (68.9)
Yes	19,292 (10.2)	18,970 (10.1)	322 (31.1)
Physical activity, n (%)			
No	44,322 (23.4)	44,053 (23.3)	269 (26.0)
Yes	145,448 (76.6)	144,681 (76.7)	767 (74.0)
Healthy diet, n (%)			
No	103,262 (54.4)	102,604 (54.4)	658 (63.5)
Yes	86,508 (45.6)	86,130 (45.6)	378 (36.5)
T2DM at baseline, n (%)			
No	188,883 (99.5)	187,854 (99.5)	1029 (99.3)
Yes	887 (0.5)	880 (0.5)	7 (0.7)
CKD at baseline, n (%)			
No	189,673 (99.9)	188,640 (100.0)	1033 (99.7)
Yes	97 (0.1)	94 (0.0)	3 (0.3)
Stroke at baseline, n (%)			
No	189,425 (99.8)	188,397 (99.8)	1028 (99.2)
Yes	345 (0.2)	337 (0.2)	8 (0.8)
IHD at baseline, n (%)			
No	187,444 (98.8)	186,461 (98.8)	983 (94.9)
Yes	2326 (1.2)	2273 (1.2)	53 (5.1)
Baseline SBP, mean (SD), mmHg	128.65 (18.02)	128.60 (18.00)	137.09 (19.26)
Mean SBP, mean (SD), mmHg	131.65 (11.78)	131.62 (11.79)	135.66 (10.20)
SD of SBP, mean (SD), mmHg	12.20 (4.29)	12.19 (4.29)	13.68 (3.92)
CV of SBP, mean (SD), %	9.22 (3.00)	9.22 (3.00)	10.07 (2.73)
ARV of SBP, mean (SD), mmHg	12.17 (4.59)	12.17 (4.59)	13.07 (4.04)
PRS (raw), mean (SD)	6.15 (0.59)	6.15 (0.59)	6.30 (0.58)
PRS tertile, n (%)			
Low	59,597 (31.4)	59,353 (31.4)	244 (23.6)
Middle	59,361 (31.3)	59,041 (31.3)	320 (30.9)

Table 1 (continued)

Characteristic	Overall (N = 189,770)	No incident AAA (n = 188,734)	Incident AAA (n = 1,036)
High	59,298 (31.2)	58,874 (31.2)	424 (40.9)
Missing	11,514 (6.1)	11,466 (6.1)	48 (4.6)

AAA abdominal aortic aneurysm; *ARV* average real variability; *BMI* body mass index; *CKD* chronic kidney disease; *CV* coefficient of variation; *IHD* ischaemic heart disease; *PRS* polygenic risk score; *SBP* systolic blood pressure; *SD* standard deviation; *T2DM* type 2 diabetes mellitus

Values are presented as mean (SD) for continuous variables and number (percentage) for categorical variables. PRS was available for 178,256 participants in the main analytic cohort. PRS tertiles were defined using cut points derived from the PRS distribution among prospective-cohort participants with available PRS. Missing indicates participants without an available PRS; percentages for PRS categories were calculated using the full column totals

Educational attainment was classified by the highest reported qualification as high (college or university degree or NVQ/HND/HNC or equivalent), medium (A/AS levels or other professional qualifications), low (O levels/GCSEs or CSEs or equivalent), or none of the listed qualifications ("None of the above"); "Prefer not to answer" and missing responses were treated as missing

For proteomic analyses, we restricted all models to participants with available proteomic data and controlled multiple testing using the Benjamini-Hochberg false discovery rate (FDR) procedure. Within this subset, we related SBPV to each circulating protein using multivariable linear regression (Model 3), and related each protein to incident AAA using Cox models adjusted for SBPV and the same covariates. Proteins associated with both SBPV and AAA were considered candidates for exploratory mediation analysis. To address high dimensionality and correlation among proteins, candidate proteins were entered into LASSO regression with 10-fold cross-validation, and the selection was repeated 1000 times with different random seeds; only proteins selected in all runs were retained as representative proteins. Separate protein-specific regression-based mediation models were then fitted as exploratory analyses. For each protein, path a was estimated using multivariable linear regression, whereas path b was estimated using a Cox proportional hazards model conditional on SBPV and the Model 3 covariates. The indirect effect was estimated as the product of coefficients (a×b) on the log-hazard scale; its SE and P value were obtained using the Sobel method, and Benjamini-Hochberg FDR correction was applied to these indirect-effect P values. Total and direct SBPV coefficients (c and c′) were estimated from the corresponding Cox models without and with the protein, respectively. Separately, coefficient attenuation was calculated as $100\times(c-c')/c$. Because Cox models were used, a×b and $c-c'$ are not algebraically equivalent; the attenuation estimates are descriptive rather than causal natural indirect effects. A formal multiple-mediator model was not fitted because the joint complete-case sample contained 15,799 participants but only 90 AAA events for approximately 27 model parameters, creating substantial overfitting concerns, and because no prespecified causal ordering among the concurrently measured proteins was available. Accordingly, all reported estimates are protein-specific and non-additive and do not represent a joint mediated effect. All analyses were performed in R version 4.3.0.

Results

Baseline characteristics

Table 1 presented the baseline characteristics of the analytic cohort (n = 189,770) according to incident AAA status. The majority of participants (95.7%) were of White ethnicity. Individuals who subsequently developed AAA (n = 1,036) were older (mean age 63.5 vs. 56.8 years), male (85.9%), and had a higher BMI (28.71 ± 4.45 vs. 27.55 ± 4.82) compared to those without AAA. The AAA group exhibited a higher prevalence of current smoking (31.1% vs. 10.1%), a lower adherence to a healthy dietary pattern (36.5% vs. 45.6%), and a moderately lower rate of regular physical activity (74.0% vs. 76.7%). Educational attainment was also lower in this group, with fewer participants attaining higher education (36.6% vs. 47.8%) and a greater proportion having none of the listed qualifications (34.0% vs. 17.8%). Clinically, future AAA cases demonstrated higher baseline and long-term mean SBP, as well as greater SBPV across all assessed metrics (SD, CV, and ARV). The comorbidities were more prevalent at baseline, including stroke (0.8% vs. 0.2%), IHD (5.1% vs. 1.2%), and CKD (0.3% vs. 0.0%). T2DM was rare (< 1%) and comparable between groups. Additionally, participants who developed AAA had a higher genetic predisposition, reflected by a higher PRS (6.30 vs. 6.15) and a greater proportion in the highest PRS tertile (40.9% vs. 31.2%).

Associations of SBPV with AAA

Elevated SBPV was consistently associated with an increased risk of AAA across all metrics (SD, CV, and ARV), with associations remaining statistically significant across sequentially adjusted models (Table 2). In the fully adjusted model, each 1-mmHg increase in SD corresponded to an HR of 1.023 (95% CI: 1.006–1.040; P = 0.006). The highest tertile of SD was associated with an HR of 1.381 (95% CI:

Table 2 Association between long-term systolic blood pressure variability and incident abdominal aortic aneurysm

SBPV	Ncase/Ntotal	Crude Model		Model 1		Model 2		Model 3	
		HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
SD Continuous, per 1-mmHg increase	1036/189,770	1.051 (1.036–1.065)	**<0.001**	1.025 (1.010–1.040)	**0.001**	1.016 (1.001–1.032)	**0.034**	1.023 (1.006–1.040)	**0.006**
SD Categorical, tertiles									
Low	174/63,739	reference	reference	reference	reference	reference	reference	reference	reference
Middle	395/63,227	1.643 (1.385–1.950)	**<0.001**	1.299 (1.093–1.544)	**0.003**	1.317 (1.100–1.576)	**0.003**	1.348 (1.124–1.616)	**0.001**
High	467/62,804	1.846 (1.563–2.181)	**<0.001**	1.341 (1.132–1.589)	**0.001**	1.303 (1.092–1.556)	**0.003**	1.381 (1.145–1.665)	**0.001**
ARV Continuous, per 1-mmHg increase	1036/189,770	1.044 (1.030–1.058)	**<0.001**	1.040 (1.025–1.055)	**<0.001**	1.033 (1.018–1.048)	**<0.001**	1.037 (1.022–1.053)	**<0.001**
ARV Categorical, tertiles									
Low	216/63,596	reference	reference	reference	reference	reference	reference	reference	reference
Middle	386/63,617	1.395 (1.188–1.637)	**<0.001**	1.136 (0.966–1.335)	0.123	1.123 (0.950–1.327)	**0.175**	1.152 (0.973–1.364)	0.101
High	434/62,557	1.753 (1.498–2.050)	**<0.001**	1.521 (1.299–1.781)	**<0.001**	1.464 (1.243–1.726)	**<0.001**	1.538 (1.298–1.822)	**<0.001**
CV Continuous, per 1% increase	1036/189,770	1.055 (1.034–1.077)	**<0.001**	1.048 (1.026–1.071)	**<0.001**	1.032 (1.010–1.055)	**0.005**	1.034 (1.012–1.057)	**0.003**
CV Categorical, tertiles									
Low	208/63,623	reference	reference	reference	reference	reference	reference	reference	reference
Middle	380/63,237	1.319 (1.120–1.554)	**0.001**	1.209 (1.025–1.425)	**0.024**	1.201 (1.013–1.424)	**0.035**	1.212 (1.022–1.439)	**0.027**
High	448/62,910	1.516 (1.294–1.777)	**<0.001**	1.403 (1.195–1.647)	**<0.001**	1.305 (1.105–1.541)	**0.002**	1.328 (1.122–1.571)	**0.001**

AAA abdominal aortic aneurysm; *ARV* average real variability; *CI* confidence interval; *CV* coefficient of variation; *HR* hazard ratio; *SBP* systolic blood pressure; *SBPV* systolic blood pressure variability; *SD* standard deviation

HRs and 95% CIs were estimated using Cox proportional hazards models, with follow-up time as the underlying time scale. Continuous effects represent the relative hazard associated with a 1-unit increase in each SBPV metric. For categorical analyses, tertiles were defined based on the distribution of SBPV measures in the analytic cohort, with the lowest tertile serving as the reference group

Covariate adjustment was performed hierarchically: unadjusted, Model 1 (age, sex, BMI, ethnicity), Model 2 (Model 1 plus TDI, educational attainment, smoking, alcohol intake, physical activity, healthy diet, and baseline stroke, ischaemic heart disease, chronic kidney disease, and type 2 diabetes), and Model 3 (Model 2 plus mean SBP). P values are from Wald tests. Boldface indicates statistically significant results ($P < 0.05$).

1.145–1.665; $P=0.001$; P for trend = 0.003) compared to the lowest tertile. For ARV, each 1-unit increase was related to an HR of 1.037 (95% CI: 1.022–1.053; $P<0.001$), and the highest tertile demonstrated significantly elevated risk (HR: 1.538, 95% CI: 1.298–1.821; $P<0.001$; P for trend < 0.001). Similarly, each 1% increase in CV was associated with an HR of 1.034 (95% CI: 1.012–1.057; $P=0.003$), with the highest tertile exhibiting an HR of 1.328 (95% CI: 1.122–1.571; $P=0.001$; P for trend = 0.001). When modeled continuously using restricted cubic splines, all SBPV metrics

showed a graded increase in AAA risk with increasing variability (Fig. 2; Supplementary Table S4). HR exceeded 1.0 slightly above the cohort median, reaching approximately 1.2–1.3 at the upper ranges of SD and CV, and exceeding 1.5 at the upper range of ARV. Likelihood ratio tests did not provide strong evidence of non-linearity (SD: $P=0.137$; CV: $P=0.217$; ARV: $P=0.295$). Segmented Cox models with data-driven change-points yielded consistent conclusions (Supplementary Table S4; Fig. 3). Estimated thresholds were located in the mid-range of SBPV distributions, and slopes above these points were attenuated or non-significant. Overall, the association between SBPV and AAA risk appeared to be gradual and largely linear across the observed variability range.

Sensitivity analyses

The association between SBPV and AAA risk remained consistent across multiple sensitivity analyses. Similar results were observed after excluding the first year of follow-up, recalculating SBPV using different thresholds (≥2 or ≥4 SBP measurements), excluding participants with very early SBP records, applying multiple imputation for missing data, and accounting for competing risks using Fine-Gray subdistribution hazard models (Supplementary Tables S5-S9; Supplementary Figure S2). In all scenarios, elevated SBPV was consistently associated with increased AAA risk. In an assessment-date landmark subset of 67,316 participants with 298 incident AAA events, further adjustment for standardized ASI did not attenuate the associations: HRs were 1.040 (95% CI 1.010–1.071; $P=0.009$) for SD, 1.032 (95% CI 1.004–1.060; $P=0.026$) for ARV, and 1.054 (95% CI 1.013–1.097; $P=0.010$) for CV (Supplementary Table S10). Parallel analyses of diastolic blood pressure variability (DBPV) were performed in 156,488 participants, including 859 incident AAA cases (Supplementary Table S11). DBPV exhibited a pattern similar to SBPV, with higher variability associated with greater AAA risk. In fully adjusted models, all three DBPV metrics were significantly associated with AAA risk when analyzed continuously (SD: HR 1.053, 95% CI 1.025–1.083, $P<0.001$; ARV: HR 1.062, 95% CI 1.034–1.091, $P<0.001$; CV: HR 1.036, 95% CI 1.013–1.059, $P=0.002$). Participants in the highest tertile of each DBPV metric also showed increased risk compared to the lowest tertile (SD: HR 1.346, 95% CI 1.118–1.621, $P=0.002$; ARV: HR 1.411, 95% CI 1.183–1.681, $P<0.001$; CV: HR 1.325, 95% CI 1.102–1.593, $P=0.003$). Dose-response analyses using restricted cubic splines indicated an approximately linear increase in risk across DBPV levels (all $P>0.05$; Supplementary Table S12; Supplementary Figure S3).

Discordance analysis revealed that higher SBPV was associated with significantly elevated AAA risk even among participants with mean SBP<130 mmHg. Compared to the low SBP/low SBPV reference group, the low SBP/high SBPV group exhibited an HR of 1.597 (95% CI 1.258–2.027) for SD, 1.730 (95% CI 1.342–2.232) for CV, and 1.469 (95% CI 1.227–1.758) for ARV (all $P<0.001$). Risk estimates in this group were comparable to those in the high SBP/high SBPV group and approached those in the high SBP/low SBPV group (Supplementary Table S13). These results indicate that visit-to-visit SBPV is an important independent marker of AAA risk, beyond the effect of mean SBP alone.

Combined effects of SBPV and PRS on AAA

To evaluate whether the association between SBPV and AAA risk was modified by genetic susceptibility, analyses were stratified by PRS (Table 3). In the highest PRS tertile (424events among 59298 participants), each unit increase in SBPV was consistently associated with elevated AAA risk across all metrics (SD: HR 1.039, 95% CI 1.013–1.066, $P=0.003$; ARV: HR 1.056, 95% CI 1.033–1.080, $P<0.001$; CV: HR 1.059, 95% CI 1.023–1.095, $P=0.001$), whereas the associations were weaker and generally not statistically significant in the lower and intermediate PRS tertiles. We further evaluated the joint effects of SBPV and genetic susceptibility (Table 4). Participants with both high SBPV and high PRS exhibited substantially elevated AAA risk compared with those with low SBPV and low PRS (SD: HR 2.22, 95% CI 1.73–2.84; ARV: HR 2.28, 95% CI 1.80–2.88; CV: HR 2.07, 95% CI 1.64–2.61; all $P<0.001$). A combined SBPV–PRS score (range 0–5) demonstrated a graded increase in risk per point (HR 1.16, P for trend<0.001). Interaction results are reported in Supplementary Table S14. No significant multiplicative interaction was detected (all interaction P values≥0.12). Positive additive-interaction estimates were observed for all three SBPV metrics (SD: RERI 0.053, 95% CI 0.001–0.086, $P=0.047$; ARV: RERI 0.071, 95% CI 0.040–0.095, $P<0.001$; CV: RERI 0.075, 95% CI 0.001–0.119, $P=0.049$).

Exploratory proteomic analyses linking SBPV to AAA risk

The proteomic analytic subset comprised 22,595 participants, including 137 incident AAA events. Compared with the main analytic cohort (189,770 participants and 1,036 incident AAA events), the proteomic subset was broadly comparable across key demographic, clinical, lifestyle, and SBPV characteristics; all absolute standardized differences were below 0.05. The proportions of incident AAA events

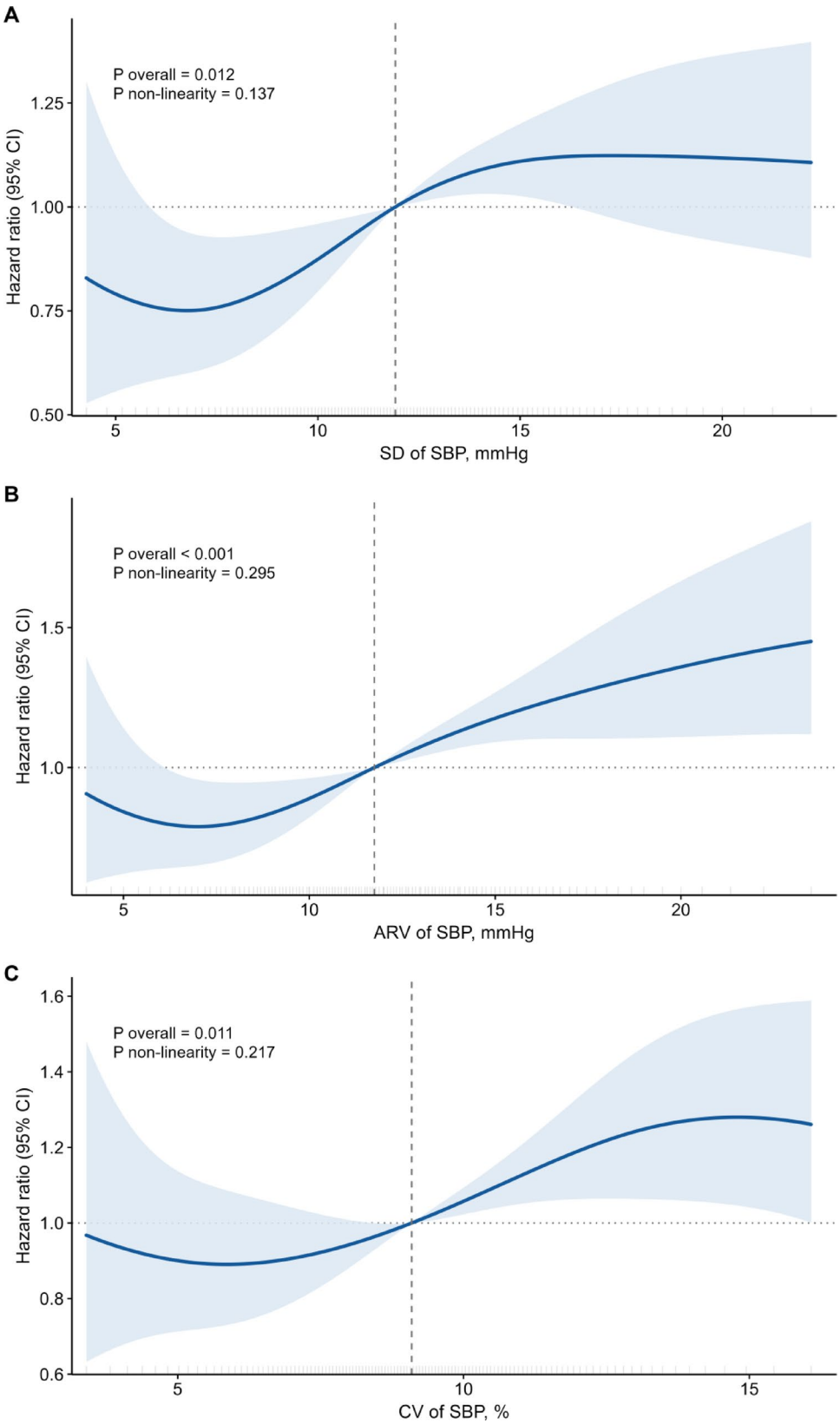


Fig. 2 Dose-response associations of systolic blood pressure variability with incident abdominal aortic aneurysm. Restricted cubic spline analyses show the associations of **A** standard deviation, **B** average real variability, and **C** coefficient of variation of systolic blood pressure with incident abdominal aortic aneurysm. Hazard ratios were estimated using Cox proportional hazards models adjusted for sex, age, body mass index, race, Townsend deprivation index, education level, current smoking, alcohol intake, physical activity, healthy diet, baseline stroke, ischemic heart disease, chronic kidney disease, type 2 diabetes, and mean systolic blood pressure. Knots were placed at the 10th, 50th, and 90th percentiles, with the median used as the reference. Solid blue lines indicate hazard ratios, shaded areas indicate 95% confidence intervals, and rug marks indicate the exposure distributions. P overall was obtained using a likelihood ratio test comparing the spline model with the corresponding covariate-only model; P non-linearity was obtained by comparing the spline model with the linear exposure model. Analyses included 189,770 participants and 1,036 incident abdominal aortic aneurysm events. ARV, average real variability; CI, confidence interval; CV, coefficient of variation; HR, hazard ratio; SBP, systolic blood pressure; SD, standard deviation

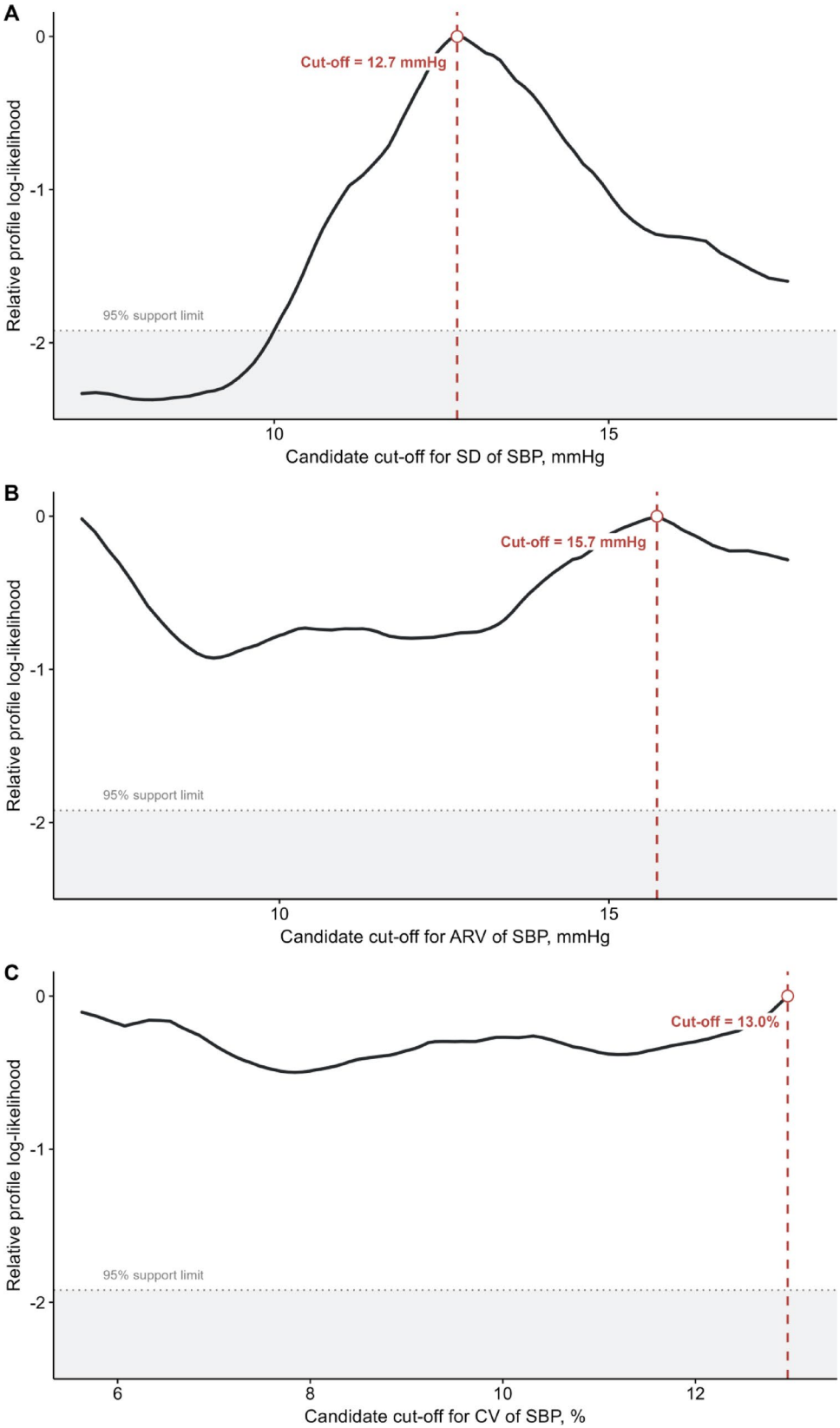


Fig. 3 Profile-likelihood determination of cut-off values for systolic blood pressure variability indices. Panels **A**–**C** show the relative profile partial log-likelihoods for candidate change points in segmented Cox proportional hazards models for **A** standard deviation, **B** average real variability, and **C** coefficient of variation of systolic blood pressure. Candidate change points were evaluated from the 10th to the 90th percentile of each variability index. Profile log-likelihoods were normalized so that the maximum was zero. Red dashed lines and open circles indicate the maximum-likelihood cut-off estimates: 12.7 mmHg for standard deviation (95% profile-likelihood support interval, 10.0–17.7), 15.7 mmHg for average real variability (7.0–17.7), and 13.0% for coefficient of variation (5.6–13.0). Horizontal dotted lines at −1.92 denote the approximate 95% profile-likelihood support limit; light-grey regions fall below this limit. Models were adjusted for sex, age, body mass index, race, Townsend deprivation index, education level, current smoking, alcohol intake, physical activity, healthy diet, baseline stroke, ischemic heart disease, chronic kidney disease, type 2 diabetes, and mean systolic blood pressure. Analyses included 189,770 participants and 1,036 incident abdominal aortic aneurysm events. ARV, average real variability; CV, coefficient of variation; SBP, systolic blood pressure; SD, standard deviation

Table 3 Association between systolic blood pressure variability and incident abdominal aortic aneurysm within strata of polygenic risk score

SBPV	Low genetic risk (244/59597)		Medium genetic risk (320/59361)		High genetic risk (424/59298)	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
SD	1.026 (0.992–1.062)	0.136	1.008 (0.978–1.039)	0.598	1.039 (1.013–1.066)	0.003
ARV	1.041 (1.010–1.073)	0.010	1.016 (0.988–1.045)	0.273	1.056 (1.033–1.080)	<0.001
CV	1.038 (0.992–1.086)	0.110	1.015 (0.975–1.057)	0.458	1.059 (1.023–1.095)	0.001

AAA abdominal aortic aneurysm; *ARV* average real variability; *CI* confidence interval; *CV* coefficient of variation; *HR* hazard ratio; *PRS* polygenic risk score; *SBPV* systolic blood pressure variability; *SD* standard deviation; *TDI* townsend deprivation index

HRs and 95% CIs for incident AAA per 1-unit increase in each SBPV metric were estimated using Model 3-adjusted Cox models within AAA PRS tertiles. Analyses included 178,256 participants with available PRS and complete Model 3 covariates (988 events); tertile cut points were derived in the PRS-available prospective cohort. P values are from Wald tests for SBPV terms

Table 4 Combined effects of systolic blood pressure variability and polygenic risk score on incident abdominal aortic aneurysm

SBPV	Results	Low SBPV + Low PRS	High SBPV + Low PRS	Low SBPV + Medium PRS	High SBPV + Medium PRS	Low SBPV + High PRS	High SBPV + High PRS	Trend test (Joint score)
SD	Event/N	85/30,151	159/29,446	112/29,819	208/29,542	130/29,726	294/29,572	-
	HR (95% CI), P	Reference	1.185 (0.906–1.548), 0.215	1.275 (0.961–1.690), 0.092	1.518 (1.174–1.963), 0.001	1.562 (1.188–2.053), 0.001	2.217 (1.733–2.836), <0.001	HR = 1.163, P-trend < 0.001
ARV	Event/N	95/29,896	149/29,701	137/29,804	183/29,557	161/29,671	263/29,627	-
	HR (95% CI), P	Reference	1.300 (1.003–1.685), 0.048	1.387 (1.068–1.803), 0.014	1.575 (1.227–2.021), <0.001	1.769 (1.372–2.280), <0.001	2.280 (1.799–2.880), <0.001	HR = 1.161, P-trend < 0.001
CV	Event/N	96/30,225	148/29,372	118/29,714	202/29,647	149/29,630	275/29,668	-
	HR (95% CI), P	Reference	1.104 (0.852–1.429), 0.454	1.203 (0.919–1.576), 0.179	1.467 (1.149–1.873), 0.002	1.595 (1.233–2.061), <0.001	2.067 (1.636–2.611), <0.001	HR = 1.160, P-trend < 0.001

AAA abdominal aortic aneurysm; *ARV* average real variability; *CI* confidence interval; *CV* coefficient of variation; *HR* hazard ratio; *PRS* polygenic risk score; *SBPV* systolic blood pressure variability; *SD* standard deviation; *SBP* systolic blood pressure; *TDI* townsend deprivation index

HRs and 95% CIs for incident AAA were estimated using Cox proportional hazards models with follow-up time as the underlying time scale. Joint categories of SBPV and genetic risk were defined by cross-classifying each SBPV metric dichotomized at the median in the prospective cohort with PRS tertiles (low, medium, and high), with individuals in the lowest SBPV and lowest PRS category serving as the reference group. Event/participant counts and Cox models were based on 178,256 participants with available PRS and complete data for the covariates included in Model 3, including 988 incident AAA events. Models were further adjusted for genetic principal components 1–10 (PC1–PC10) and genotyping batch to account for population structure and technical artefacts based on the full Model 3. The trend test evaluates the linear increase in AAA risk across ordered joint categories (low SBPV + low PRS to high SBPV + high PRS), treated as an ordinal score. P values are from Wald tests

were also similar (0.6% vs. 0.5%; standardized difference = 0.008) (Supplementary Table S15). Within the proteomic subset, 843 circulating proteins were significantly associated with SBPV after FDR correction. LASSO regression narrowed these candidates to 73 proteins, of which 14 were also significantly associated with incident AAA. Ten proteins—NT-proBNP, NPPB, VWC2, TNFRSF10A, LTBP2, OGN, CLEC4D, MSR1, LGALS4, and OCLN—showed FDR-significant protein-specific indirect effects in separate exploratory models (Table 5), with descriptive coefficient-attenuation estimates ranging from 6.7% to 30.4% (Fig. 4). When individually added to a fully adjusted Cox model containing SBPV, all 10 proteins were associated with AAA (all $P < 0.05$), whereas the SBPV coefficient was no longer statistically significant in those protein-specific models (Supplementary Table S16). This pattern should not be interpreted as evidence of a joint mediated effect. Although the SBPV-only models showed high discrimination (C-index 0.904–0.907), adding individual proteins yielded only small improvements (ΔC-index 0.001–0.009). LTBP2 improved the 5- and 10-year AUCs and TNFRSF10A improved the 15-year AUC, whereas most other changes were small and statistically unstable (Supplementary Table S17).

Discussion

AAA remains a major threat to public health, contributing to substantial clinical and economic burdens due to the limited availability of effective preventive measures [18]. Accumulating evidence indicates that blood pressure variability provides important information for cardiovascular diseases [19]. Nonetheless, the role of blood pressure variability in AAA development remains poorly understood. In this large prospective cohort study, higher visit-to-visit SBPV was consistently associated with an increased risk of incident AAA, independent of mean SBP and a wide range of established risk factors. This association was broadly linear

Table 5 Exploratory protein-specific indirect-effect and coefficient-attenuation estimates for the association between systolic blood pressure variability and incident abdominal aortic aneurysm

Protein	Path a βa (SE)	Path b βb (SE)	HR of total	HR of direct	Indirect effect a×b (SE)	Descriptive coefficient attenuation (%)	FDR *P* for indirect effect
NTPROBNP	0.027 (0.002)	0.221 (0.076)	1.060	1.042	0.006 (0.002)	30.4	0.005
NPPB	0.020 (0.002)	0.283 (0.089)	1.060	1.044	0.006 (0.002)	25.4	0.003
VWC2	0.014 (0.002)	0.361 (0.088)	1.057	1.047	0.005 (0.001)	17.3	<0.001
TNFRSF10A	0.015 (0.002)	0.305 (0.076)	1.057	1.047	0.005 (0.001)	16.7	<0.001
LTBP2	0.014 (0.002)	0.334 (0.093)	1.060	1.050	0.005 (0.001)	16.1	0.002
OGN	0.018 (0.002)	0.333 (0.086)	1.060	1.047	0.006 (0.002)	21.4	<0.001
CLEC4D	0.011 (0.002)	0.255 (0.090)	1.064	1.056	0.003 (0.001)	11.9	0.010
MSR1	0.009 (0.002)	0.351 (0.094)	1.061	1.056	0.003 (0.001)	9	0.003
LGALS4	0.016 (0.002)	0.274 (0.083)	1.066	1.061	0.004 (0.001)	6.7	0.003
OCLN	0.015 (0.002)	0.265 (0.088)	1.048	1.043	0.004 (0.001)	9.8	0.005

AAA abdominal aortic aneurysm; *CI* confidence interval; *FDR* false discovery rate; *HR* hazard ratio; *SBPV* systolic blood pressure variability; *SE* standard error; *TDI* townsend deprivation index

Exploratory protein-specific analyses were performed to evaluate indirect associations between SBPV and incident AAA. Path a (βa) represents the association of SBPV with each protein (exposure–mediator path), and Path b (βb) represents the association of each protein with AAA conditional on SBPV (mediator–outcome path). The indirect effect was assessed using the product-of-coefficients estimate a×b on the log-hazard scale, with its SE and P value obtained using the Sobel method. Total and direct HRs were exp(c) and exp(c′), respectively. Descriptive coefficient attenuation was calculated separately using the difference-in-coefficients formula 100×(c − c′)/c and should not be interpreted as a causal natural indirect effect. Because Cox models were used, a×b and c − c′ are not algebraically equivalent. All mediation models were based on the full Model 3. FDR-adjusted P values are Benjamini–Hochberg-adjusted P values for the product-of-coefficients indirect effect (a×b) only; they do not refer to the total effect, direct effect, or coefficient-attenuation estimate. Each protein was evaluated in a separate model, and the reported coefficient-attenuation estimates are protein-specific and non-additive and do not represent a joint mediated effect

across the distribution of SBPV and was robust to multiple sensitivity analyses, including alternative SBPV definitions, exclusion of early follow-up, competing-risk models, and analyses using DBPV. The association was strongest among participants with high polygenic risk: those with both high SBPV and high genetic risk had more than twice the AAA risk of participants with low SBPV and low genetic risk. Exploratory proteomic analyses identified 10 circulating proteins associated with both higher SBPV and AAA risk. Collectively, these observational findings support SBPV as a potentially useful AAA risk marker but do not establish causality or the benefit of interventions targeting SBPV.

AAA represents a leading cause of cardiovascular morbidity and mortality, and its development and rupture are shaped by multiple cardiovascular risk factors [20]. Although elevated SBP contributes to aneurysm formation, it inadequately represents the dynamic mechanical stresses exerted on the aortic wall, particularly under conditions of blood pressure variability [21]. The increased blood pressure variability is associated with arterial stiffness and adverse remodeling—key processes in vascular injury [22]. Cheng et al. demonstrated in a large UK Biobank cohort that persistently high blood pressure variability elevated the risk of cardiovascular disease, chronic kidney disease, dementia, and mortality, independent of mean arterial pressure [9]. These findings highlight the value of blood pressure variability in improving risk stratification and identifying high-risk individuals overlooked by conventional blood pressure assessment. Nonetheless, the role of blood pressure variability in AAA onset remained unclear. Our study addresses this gap by demonstrating that higher visit-to-visit SBPV was consistently associated with increased AAA risk, after adjusting for mean SBP and traditional risk factors. A graded dose-response relationship was observed, even among individuals with normal mean SBP, suggesting that hemodynamic fluctuation may contribute to AAA formation independently of sustained hypertension. Clinically, integrating blood pressure variability into AAA risk evaluation could improve early identification of high-risk individuals who might be missed by conventional assessments. Additional adjustment for ASI in the assessment-date landmark subset did not attenuate these associations, suggesting that measured arterial stiffness did not materially explain the observed findings.

Genetic studies have established that inherited susceptibility strongly influences AAA formation [11]. Early familial cohort studies reveal a significantly elevated AAA risk among first-degree relatives of affected individuals, supporting a substantial heritable component [14]. Subsequent genome-wide association studies have identified common risk variants involved in the biological pathways underlying aortic degeneration [23]. More recently, meta-analyses have confirmed that polygenic risk—rather than single mutations—accounts for major inherited risk and helps identify

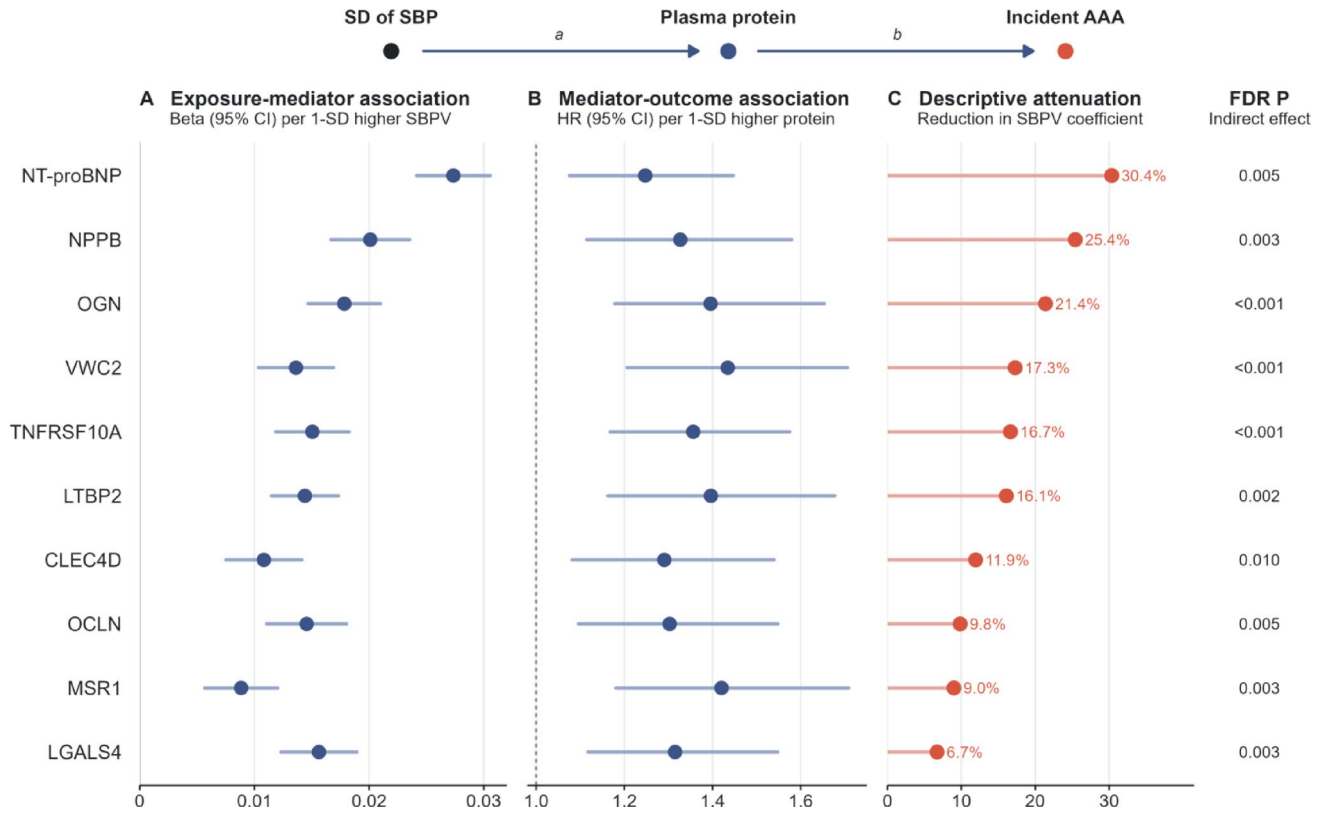


Fig. 4 Exploratory protein-specific indirect-effect analyses of the association between the standard deviation of systolic blood pressure and incident abdominal aortic aneurysm. Panel a shows the association between a 1-SD higher standard deviation of systolic blood pressure and each standardized plasma protein (path a), expressed as beta coefficients with 95% confidence intervals. Panel b shows the association between each 1-SD higher standardized protein and incident abdominal aortic aneurysm conditional on the standard deviation of systolic blood pressure (path b), expressed as hazard ratios with 95% confidence intervals. Panel c shows the descriptive coefficient-attenuation estimate in each separate single-protein model, calculated as $100 \times (c - c')/c$, where c and c′ are the total and direct systolic blood pressure variability coefficients, respectively. Benjamini-Hochberg FDR-adjusted P values in the right column refer exclusively to the product-of-coefficients indirect effect (a×b), evaluated using the Sobel method; they do not refer to the coefficient-attenuation estimate. Path-a and path-b models were adjusted for the covariates included in Model 3, and path-b models additionally included the standard deviation of systolic blood pressure. Proteins are ordered by coefficient attenuation. Protein-specific complete-case samples ranged from 18,177 to 20,945 participants, with 104 to 124 incident abdominal aortic aneurysm events. Each protein was evaluated separately; the estimates are protein-specific and non-additive and do not represent a joint mediated effect. Because Cox models were used, coefficient attenuation should not be interpreted as a causal natural indirect effect. AAA, abdominal aortic aneurysm; CI, confidence interval; FDR, false discovery rate; HR, hazard ratio; SBP, systolic blood pressure; SBPV, systolic blood pressure variability

individuals with accelerated aneurysm growth and higher rupture risk [2, 24–28]. PRS have thus emerged as a valuable tool for refining AAA risk stratification [11–14, 23, 29, 30]. For instance, recent UK Biobank analyses showed that PRS was a strong predictor of incident AAA, with individuals in the high PRS group having up to a 65% higher risk than those with low genetic burden [1]. In addition, the PRS identified individuals who were more vulnerable to environmental exposures such as long-term air pollution, leading to a substantially greater increase in AAA risk [2]. These advances highlight that incorporating both genetic and clinical risk factors provide superior risk stratification compared to either alone. Nonetheless, no research had evaluated potential interactions between SBPV and genetic susceptibility in AAA development. In this study, SBPV and polygenic risk acted synergistically, with individuals exhibiting both high SBPV and high genetic risk having the greatest AAA risk—exceeding that associated with either factor alone. This suggests that genetic predisposition may amplify the detrimental vascular effects of hemodynamic fluctuation. Incorporating both SBPV and polygenic risk into clinical assessment could improve early identification of high-risk individuals who may benefit from personalized monitoring or preventive interventions.

Proteomic profiling can provide hypothesis-generating clues to molecular pathways associated with haemodynamic stress and vascular injury [31]. In AAA research, proteomic studies have identified protein alterations associated with aneurysm pathogenesis before clinical presentation [32]. For example, Steffen et al. linked lower circulating

neogenin and kit ligand levels to higher AAA risk, Zhang et al. reported proteins associated with aneurysm development through Mendelian-randomization analyses, and Yuan et al. evaluated circulating proteins potentially linking smoking to AAA risk [16, 17, 33]. In the present study, 10 proteins were associated with both SBPV and AAA risk and showed FDR-significant protein-specific indirect effects in separate exploratory models. The observed patterns were consistent with pathways involving haemodynamic load, TGF-β-related extracellular-matrix integrity, fibrotic remodelling, innate immunity, apoptosis, and barrier function. However, these observational associations do not establish that SBPV caused downstream vascular damage or that the proteins jointly mediated the SBPV–AAA association. The coefficient-attenuation estimates are protein-specific and non-additive. Adding individual proteins to SBPV models produced only small and inconsistent gains in discrimination, so these findings should be viewed as hypothesis-generating and require replication and mechanistic validation.

This study has several notable strengths. It leverages the large sample size, long follow-up, and rich phenotyping of the UK Biobank, enabling well-powered analyses of SBPV and AAA with careful adjustment for confounders. The availability of linked primary care records permitted construction of long-term visit-to-visit SBPV metrics using multiple blood pressure measurements per participant, which arguably better reflect chronic haemodynamic instability than single clinic readings. The integration of epidemiological, genomic, and proteomic data provides a multidimensional perspective on AAA pathogenesis, allowing us to move beyond traditional risk factors and explore mechanistic pathways and interactions. Standardized assessment of baseline characteristics and centrally measured proteomic biomarkers further enhances internal validity. Several limitations should also be acknowledged. First, AAA cases are identified from hospital admission, procedure, and death records rather than from self-report. This approach improves the accuracy of case definition and avoids recall bias, but it is likely to miss asymptomatic or small aneurysms detected only on imaging. Such under-ascertainment would probably bias our estimates towards the null and makes it harder to distinguish effects on disease onset from effects on detection. Second, SBPV is based on intermittent clinic measurements rather than ambulatory monitoring, potentially missing short-term fluctuations. Third, the predominantly European ancestry of the cohort may restrict generalizability to other populations. Fourth, we could not fully account for antihypertensive treatment. In this long-term cohort, individuals with higher or more variable blood pressure are more likely to start or intensify antihypertensive therapy. This means that treatment is strongly related to both SBPV and AAA risk and may partly lie on the causal pathway from SBPV to aneurysm formation. In exploratory analyses, adding a simple indicator of antihypertensive use made the SBPV estimates much weaker and unstable, suggesting overadjustment and confounding by indication rather than a true absence of association. Due to the lack of detailed longitudinal data on drug type, dose, treatment changes, or adherence, we did not adjust for antihypertensive treatment in the main models, and some residual confounding by treatment may remain. Arterial stiffness was assessed only in a subset (36.2% of the main cohort); therefore, although the ASI-adjusted sensitivity analysis showed no attenuation, residual confounding by arterial stiffness or other unmeasured vascular factors cannot be excluded. Finally, the observational nature of the analysis precludes causal conclusions, and further mechanistic studies are needed to validate the biological roles of implicated proteins.

Conclusion

In this large prospective cohort, higher long-term visit-to-visit SBPV was independently associated with incident AAA. The association was strongest in participants with high genetic risk, and exploratory protein-specific analyses identified indirect associations and descriptive coefficient attenuation involving pathways related to extracellular-matrix remodelling, inflammation, and vascular injury. These observational results do not establish causal mediation. Future studies should evaluate whether SBPV improves risk prediction across diverse populations and should validate the implicated protein pathways experimentally.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10654-026-01459-2.

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Author contributions Writing manuscript: QH; Data extraction and Statistical analysis: ZQC; Conceptualization and supervision: YFZ, WBN, and YJL; Reviewing and editing: XPC, Baimei He and ZYP. All authors read and approved the final manuscript. XPC and ZYP are the guarantors of this work, had full access to and verified all the data in the study, and took responsibility for data integrity and the accuracy of the data analysis.

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Data availability The data that we used in this study can be accessed

by researchers on application. Requests for data access should be made directly to the UK Biobank.

Declarations

Conflict of interest The authors declare that they have no competing interests.

Ethical approval and consent to participate The UK Biobank received ethical approval from the North West Multi-Centre Research Ethical Committee. All participants provided written informed consent. No specific ethical approval was required for this study due to use of publicly available data. This research has been conducted using the UK Biobank Resource under Application Number 617672.

Consent for publication All authors listed above approved the manuscript for publication.

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