Blood pressure variability and microvascular dysfunction

Original Article

Blood pressure variability and microvascular dysfunction: the Maastricht Study

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Background: Microvascular dysfunction (MVD) contributes to stroke, dementia, depression, retinopathy and chronic kidney disease. However, the determinants of MVD are incompletely understood. Greater blood pressure variability (BPV) may be one such determinant.

Methods and results: We used cross-sectional data of The Maastricht Study ($n = 2773$, age 59.9 years; 51.9% men) to investigate whether greater very short- to mid-term BPV is associated with various MVD measures. We standardized and averaged within-visit, 24-h and 7-day BPV into a systolic and a diastolic BPV composite score. MVD measures included a composite score of MRI cerebral small vessel disease (CSVD) features (total brain parenchymal volume, white matter hyperintensity volume, lacunar infarcts and cerebral microbleeds), a composite score of flicker light-induced retinal arteriolar and venular dilation response, albuminuria, heat-induced skin hyperemia and a composite score of plasma biomarkers of MVD (sICAM-1, sVCAM-1, sE-selectin and von Willebrand Factor). We used linear regression adjusted for age, sex, glucose metabolism status, mean 24-h systolic or DBP, cardiovascular risk factors and antihypertensive medication. We found that higher systolic and diastolic BPV composite scores (per SD) were associated with higher albuminuria [higher ratio, 1.04 (95% CI 1.00–1.08) and 1.07 (1.03–1.11), respectively], but not with other measures of MVD tested.

Conclusion: Greater systolic and diastolic BPV was associated with higher albuminuria, but not with CSVD features, flicker light-induced retinal arteriolar and venular dilation response, heat-induced skin hyperemia and plasma biomarkers of MVD. This suggests that the microvasculature of the kidneys is most vulnerable to the detrimental effects of greater BPV.

Keywords: albuminuria, blood pressure, cardiovascular disease, cerebral small vessel diseases, cohort study, endothelium, epidemiology, imaging, magnetic resonance, nitric oxide, type 2 diabetes mellitus

Abbreviations: BPV, blood pressure variability; CSVD, cerebral small vessel disease; MVD, microvascular dysfunction; sE-selectin, soluble E-selectin; sICAM-1, soluble intercellular adhesion molecule-1; sVCAM-1, soluble vascular adhesion molecule-1; UAE, urinary albumin excretion; vWF, von Willebrand factor

INTRODUCTION

Microvascular dysfunction (MVD) is an important contributor to various diseases that are (in part) of microvascular origin, including stroke [1], dementia [1], depression [1], retinopathy [2], and chronic kidney disease [3]. However, the determinants of MVD are incompletely understood. Greater blood pressure variability (BPV), that is, greater fluctuations of blood pressure over time, may be one such determinant.

Greater BPV may lead to MVD both via increases in pulsatile pressure that can penetrate distally and damage the microcirculation [4], and sudden falls in blood pressure leading to reduced microvascular perfusion [5]. The microvascular beds of organs with low vascular impedance (i.e. the microvasculature of the brain, eyes and kidneys) may be particularly vulnerable for these fluctuations in blood pressure [4].

Microvascular function can be measured noninvasively in various organs. These measures include MRI features of

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cerebral small vessel disease (CSVD, that is, lower total brain parenchyma volume, higher white matter hyperintensity volume, and presence of lacunar infarcts and cerebral microbleeds) [6]; flicker light-induced retinal arteriolar and venular dilation response [7]; albuminuria ('urinary albumin excretion', UAE) [8]; heat-induced skin hyperemia [7]; and plasma biomarkers of MVD [i.e. soluble intercellular adhesion molecule-1 (sICAM-1), soluble vascular adhesion molecule-1 (sVCAM-1), soluble E-selectin (sE-selectin) and von Willebrand factor (vWF)] [9].

The associations between BPV and most of these various MVD measures remain, however, incompletely understood. To date, only five studies have evaluated the association between BPV and CSVD features. These studies found an association between greater very short-term to short-term systolic and diastolic BPV and cerebral atrophy [10,11], higher white matter hyperintensity volume [10–13], lacunar infarcts [10,12], and enlarged perivascular spaces [10,14]. However, these studies were relatively small ($n \leq 155$) [11,13], done in selected populations (i.e. individuals with hypertension [12], aged 70 years and older [15], or admitted to the hospital [10,14]) or did not adjust for potentially important confounders (i.e. mean blood pressure [11,13] or lifestyle factors [12]). For UAE, most previous studies [16–27], but not all [28–30], found an association with greater very short-to mid-term systolic or diastolic BPV. However, these studies did not adjust for potentially important confounders, including dietary habits and physical activity. For plasma biomarkers of MVD, only one study has been done, which included 190 individuals with newly diagnosed hypertension. This study found an association between greater short-term systolic BPV and higher sE-selectin [31]. Currently, no studies have investigated the association between BPV and flicker light-induced retinal arteriolar and venular dilation or heat-induced skin hyperemia.

In view of the above, we investigated, in a large population-based cohort, whether very short-term to mid-term BPV (i.e. within-visit, 24-h and 7-day BPV) is associated with a comprehensive set of MVD measures, including CSVD features, flicker light-induced retinal arteriolar and venular dilation response, UAE, heat-induced skin hyperemia and plasma biomarkers of MVD. We hypothesized that greater BPV would be more strongly associated with MVD in organs with a low vascular impedance, that is, brain, eyes and kidneys, and would not be associated with MVD in organs with a high vascular impedance, for example, skin.

MATERIAL AND METHODS

Study population and design

We used data from The Maastricht Study, an observational population-based cohort study. The rationale and methodology have been described previously [32]. In brief, the study focuses on the cause, pathophysiology, complications and comorbidities of diabetes mellitus type 2 (T2D) and is characterized by an extensive phenotyping approach. Eligible for participation were all individuals aged between 40 and 75 years and living in the southern part of the Netherlands. Participants were recruited through mass media campaigns, the municipal registries and the regional Diabetes Patient Registry via mailings. Recruitment was stratified according to known T2D status, with an oversampling of individuals with T2D for reasons of efficiency. The present report includes cross-sectional data from 3451 participants who completed the baseline survey between November 2010 and September 2013. The examinations of each participant were performed within a time window of 3 months. The study has been approved by the institutional medical ethical committee (NL31329.068.10) and the Minister of Health, Welfare, and Sports of the Netherlands (Permit 131088-105234-PG). All participants gave written informed consent. Data are available from The Maastricht Study for any researcher who meets the criteria for access to confidential data, and the corresponding author may be contacted to request data.

Blood pressure measurements and determination of blood pressure variability

A detailed description of the office, 24-h ambulatory and 7-day home blood pressure measurements and determination of BPV has been reported previously [33]. Briefly, within-visit BPV was calculated as the standard deviation (SD) of three consecutive office blood pressure measurements assessed in the sitting position, with a 1-min interval, after 10 min of rest [34]. The 24-h BPV was calculated as the average real variability of blood pressure readings taken every 15 min between 0800 and 2300 h, and every 30 min between 2300 and 0800 h [34]. Seven-day BPV was calculated as the SD of home blood pressure measurements taken twice, with a 1-min interval, each morning and evening, for 7 consecutive days [34].

Microvascular dysfunction measures

For all MVD measures, participants were asked to refrain from smoking and drinking caffeine-containing beverages 3 h before the measurement [35]. A light meal was allowed until at least 90 min prior to the examination. For retinal measurements, pupils were dilated with 0.5% tropicamide and 2.5% phenylephrine at least 15 min before the start of the examination. Skin blood flow measurements were performed in a climate-controlled room at 24 °C [36]. Here, we briefly describe the MVD measures used; a detailed description, including the reproducibility of the MVD measures, is provided in the Extended Methods (Supplementary Material, http://links.lww.com/HJH/B333).

Features of cerebral small vessel disease

Brain MRI measurements were implemented from December 2013 onwards and were available in 2313 of the 3451 participants (67%). Brain MRI was performed on a 3T MRI scanner (Siemens Magnetom Prisma-fit Syngo MR D13D, Erlangen, Germany). We evaluated four MRI CSVD features, that is. total brain parenchyma volume, white matter hyperintensity volume, lacunar infarcts and cerebral microbleeds. Briefly, the MRI protocol consisted of a 3D T1-weighted sequence, T2-weighted fluid-attenuated inversion recovery (FLAIR), and a gradient recalled echo (GRE) pulse sequence with susceptibility-weighted imaging (SWI) [37]. T1-weighted images and FLAIR images were analyzed by use of an automated method [38,39]. T1-

weighted images were segmented into grey matter, white matter and cerebrospinal fluid volumes [38]. Intracranial volume was calculated as the sum of grey matter, white matter (including white matter hyperintensity volume) and cerebrospinal fluid volumes. Total brain parenchyma volume was calculated as the sum of grey and white matter volumes. T1-weighted and FLAIR images were used to identify white matter hyperintensities [39]. White matter hyperintensity volume was summed to assess total white matter hyperintensity burden, and expressed relative to intracranial volume. Lacunar infarcts were defined as focal brain parenchyma defects of at least 3 mm and less than 15 mm in size with a similar signal intensity as cerebrospinal fluid on all sequences and a hyperintense rim on FLAIR images [6]. Cerebral microbleeds were rated on three-dimensional T2* GRE imaging with SWI by use of the Microbleed Anatomical Rating Scale [40], and were defined as focal lesions of at least 2 mm and 10 mm or less in size with a hypointense signal [6]. The presence of lacunar infarcts and cerebral microbleeds was rated manually by three neuroradiologists.

Flicker light-induced retinal arteriolar and venular dilation response

We measured retinal arteriolar and venular dilation to flicker light exposure by the Dynamic Vessel Analyzer (Imedos, Jena, Germany), as previously described [7,41]. Briefly, a baseline recording of 50 s was followed by 40-s flicker light exposure followed by a 60-s recovery period. We calculated baseline diameters (in measurement units) as the average diameter during the 20–50 s recording. For both the arteriolar and venular dilation, percentage dilation over baseline was calculated using the average dilation achieved at time points 10 and 40 s during the flicker stimulation period.

Urinary albumin excretion

To assess UAE, participants were requested to collect two 24-h urine samples. Urinary albumin concentration was measured with a standard immunoturbidimetric assay by an automatic analyzer (because of a change of supplier, by the Beckman Synchron LX20 and the Roche Cobas 6000) and multiplied by collection volume to obtain 24-h UAE. A urinary albumin concentration below the detection limit of the assay was set at 1.5 mg/l (2 mg/l for the Beckman Synchron LX20 and 3 mg/l for the Roche Cobas 6000) before multiplying by collection volume. Only urine collections with a collection time between 20 and 28 h were considered valid. If needed, UAE was extrapolated to 24-h excretion. For this study, UAE was preferably based on the average of two (available in 91.3% of participants) 24-h urine collections.

Heat-induced skin hyperemia

We measured heat-induced skin hyperemia by laser Doppler flowmetry (Perimed, Järfälla, Sweden), as previously described [7]. Briefly, skin blood flow at the wrist, expressed in arbitrary perfusion units, was recorded unheated for 2 min to serve as a baseline. After 2 min, the temperature of the laser Doppler probe was rapidly and locally increased to 44 °C and was kept constant until the end of the registration. Skin hyperemia was expressed as the percentage increase in average perfusion unit during the 23 min heating phase over the 2 min average baseline perfusion unit.

Plasma biomarkers of microvascular dysfunction

We measured four plasma biomarkers of MVD: sICAM-1, sVCAM-1, sE-selectin and vWF [42]. sICAM-1, sVCAM-1 and sE-selectin were measured in EDTA plasma samples with commercially available 4-plex sandwich immunoassay kits with different standards and antibodies (Meso Scale Discovery, Rockville, Maryland, USA).

Covariates

We determined glucose metabolism status according to the WHO 2006 criteria as normal glucose metabolism, prediabetes or T2D [43]. Education level was classified into three groups: low (none, primary or lower vocational education only), intermediate (intermediate general secondary, intermediate vocational or higher general secondary education) and high (higher vocational education or university level of education). We determined alcohol consumption [none, low (women $\leq$7, men $\leq$14 units/week), high (women >7, men >14 units/week)], smoking status (never, former, current), medication use, BMI, total/high density lipoprotein (HDL) cholesterol ratio and prior cardiovascular disease as described previously [7,8,32]. We defined hypertension as use of antihypertensive medication, and/or systolic office blood pressure At least 140 mmHg and/or diastolic office blood pressure at least 90 mmHg [44]. Estimated glomerular filtration rate (eGFR) was computed with the CKD-EPI (Chronic Kidney Disease Epidemiology collaboration) formula using serum creatinine and cystatin C [45]. Plasma biomarkers of low-grade inflammation (i.e. high-sensitive C-reactive protein, serum amyloid A, interleukin-6, interleukin-8 and tumor necrosis factor alpha) were determined as described previously [32,46]. Carotid–femoral pulse wave velocity, a measure of aortic stiffness [44], was measured according to international guidelines [47] with the use of applanation tonometry (Sphygmocor; Atcor Medical, Sydney, Australia) at the right common carotid and right common femoral arteries. As described previously, we used questionnaires to assess the Mediterranean diet score ('diet score') [48], moderate-to-vigorous physical activity [32] and socioeconomic status (income level and occupation status) [49].

Statistical analysis

We inversed (multiplying by −1) total brain parenchyma volume, flicker light-induced retinal arteriolar and venular dilation response and heat-induced skin hyperemia so that higher values indicated worse microvascular function. White matter hyperintensity volume and UAE were log-transformed (base 2) to normalize their skewed distribution.

We summarized the three BPV measures (i.e. within-visit, 24-h and 7-day BPV) into a systolic and diastolic BPV composite score, as done previously [50]. We hypothesized that each BPV measure is associated with MVD according to similar underlying mechanisms, that is, each greater BPV measure may be related to an increased pulsatile load, and

these increased pulsatile loads may damage the microvascular beds of various organs in a similar way. Furthermore, a composite score reduces the influence of noise, or measurement error, of its components [51], and it reduces the chance of a type 1 error. The BPV composite scores were calculated when at least data on two of the three BPV measures were available. The scores were calculated by summation and subsequent standardization of the *z*-scores of the three systolic and diastolic BPV measures, respectively, so that a 1-unit increment is expressed as a 1-SD increment in the BPV composite score.

We also calculated separate composite scores for the CSVD features, for the flicker light-induced retinal arteriolar and venular dilation response and for the plasma biomarkers of MVD, respectively. The CSVD composite score was calculated as described previously [52]; one point per CSVD feature was assigned based on the following cut-offs: for lower total brain parenchyma volume quartile 1 vs. quartiles 2–4; for higher white matter hyperintensity volume quartile 4 vs. quartiles 1–3; and for lacunar infarcts and cerebral microbleeds presence vs. absence. The points for each feature were combined to compute the CSVD composite score (range 0–4). The composite scores for retinal arteriolar and venular dilation and plasma biomarkers of MVD were calculated by summation and averaging of the *z*-scores of the flicker light-induced retinal arteriolar and venular dilation responses and the four plasma biomarkers of MVD, respectively.

We used Poisson regression to investigate the association between the systolic and diastolic BPV composite scores and the CSVD composite score. We used linear regression to investigate the association between the systolic and diastolic BPV composite scores and the retinal arteriolar and venular dilation composite score, UAE, skin hyperemia and the plasma biomarkers of MVD composite score. All analyses were adjusted for age and sex (model 1), and additionally for glucose metabolism status (model 2), mean 24-h SBP or DBP (wherever appropriate) (model 3), and education level, BMI, smoking status, alcohol consumption, total/HDL cholesterol ratio, lipid-modifying medication and the individual classes of antihypertensive medication (i.e. beta blockers, diuretics, calcium channel blockers, angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers) (model 4). For analyses with the CSVD composite score, results were exponentiated to represent the risk ratio per point higher score. For analyses with log-transformed UAE as the outcome, regression coefficients were back-transformed and expressed as higher ratio per SD higher systolic and diastolic BPV.

We tested interaction terms of the BPV composite scores with age [53], sex [54], glucose metabolism status [55] and hypertension status [12] to evaluate whether the associations between the BPV composite scores and the MVD measures differed according to these factors.

Several sensitivity and additional analyses were performed. First, we repeated the analysis with the individual BPV measures as the determinant, that is, within-visit, 24-h and 7-day systolic and diastolic BPV. Second, we repeated the analysis using as the outcome the individual CSVD features, the individual retinal arteriolar and venular dilation response and the individual plasma biomarkers of MVD, respectively. Third, we repeated the analysis with additional adjustment for eGFR, prior cardiovascular disease, plasma biomarkers of low-grade inflammation and carotid–femoral pulse wave velocity. These covariates were entered into a separate model because of the risk of overadjustment bias: these factors may be confounders, but may also mediate any association between BPV and MVD. Fourth, we repeated the analysis additionally adjusting for the diet score, and moderate-to-vigorous physical activity and for income level and occupation status (instead of education level). Adjustment for these potential confounders was not included in the main analysis, as data were missing in a relatively large number of participants ($n = 1133$ missed data on one or more of these variables). Fifth, we used microalbuminuria defined as at least 30 mg/24 h vs. less than 30 mg/24 h as the outcome instead of UAE per mg/24 h [56]. Sixth, we studied the association between BPV and eGFR [continuously and categorically ($\geq$60 vs. $<$60 ml/min/1.73 m^2)].

All statistical analyses were performed with Statistical Package for Social Sciences (v22.0; IBM, Chicago, Illinois, USA). A *P* value of less than 0.05 was considered statistically significant [57].

RESULTS

Study population

Figure 1 shows the derivation of the study population. In total, 2773 participants had data available on the BPV composite scores, all potential confounders and at least one MVD measure, and were included in the analysis. CSVD features were available in 1837 participants, retinal arteriolar and venular dilation response in 1844, UAE in 2748, skin hyperemia in 1320 and plasma biomarkers of MVD in 2726. These subpopulations were comparable with regard to age, sex and cardiovascular risk profile (Supplemental Table S1, http://links.lww.com/HJH/B333). Participants excluded because of missing data had greater BPV and higher BMI and more often had prior cardiovascular disease compared with those without missing data (Supplemental Table S1, http://links.lww.com/HJH/B333).

Table 1 and Supplemental Table S2, http://links.lww.com/HJH/B333 show the general characteristics for the total study population and according to tertiles of the systolic BPV composite score. Supplemental Table S3, http://links.lww.com/HJH/B333 shows the characteristics according to tertiles of the diastolic BPV composite score. The mean age was 59.9 years, 51.9% were men and 26.9% had T2D. In general, participants with the highest compared with the lowest tertile of the systolic BPV composite score were older, less often men, had a worse cardiovascular risk profile and more often used lipid-modifying and antihypertensive medication.

Blood pressure variability and microvascular dysfunction

Higher systolic and diastolic BPV composite scores were associated with higher UAE [1.04 (95% CI 1.00–1.08) and 1.07 (1.03–1.11) higher ratio per 1 SD higher systolic and diastolic BPV composite score, respectively], after adjustment for all potential confounders (Table 2, model 4).

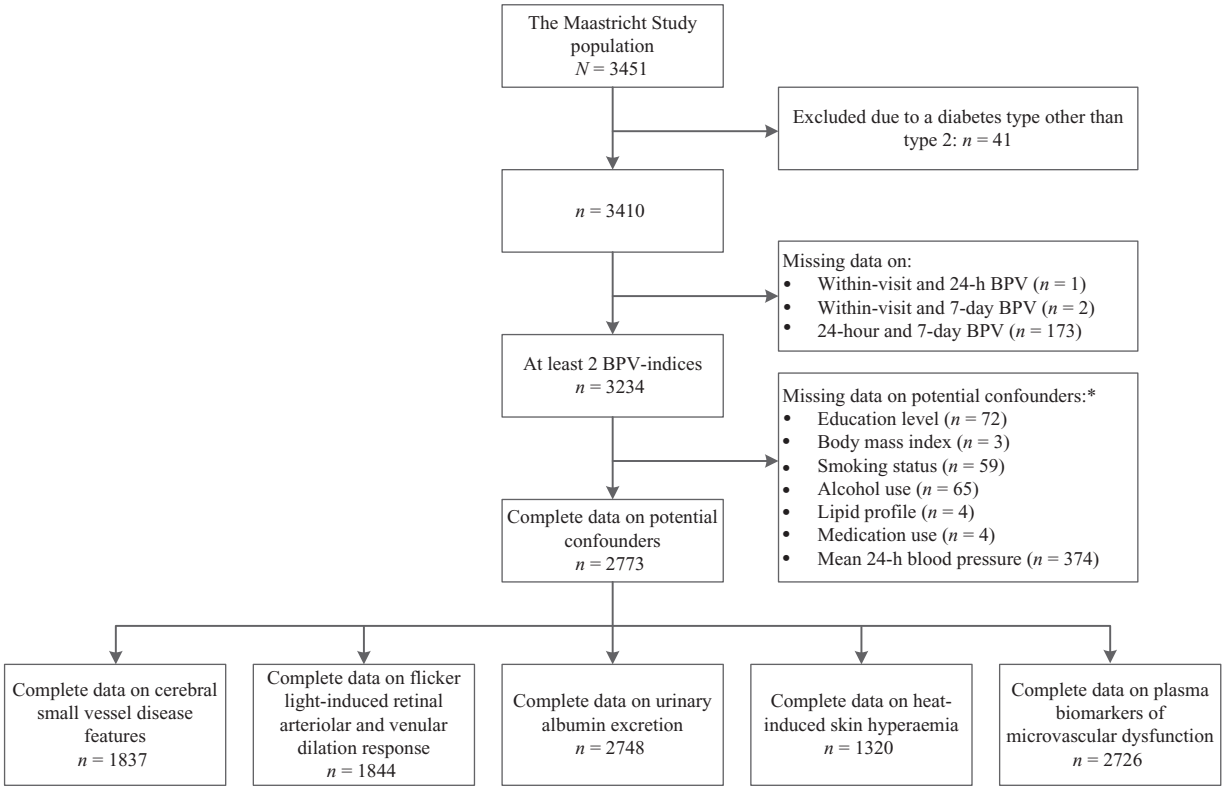

FIGURE 1 Flowchart delineating the derivation of the study population. *Not mutually exclusive. BPV, blood pressure variability.

Systolic and diastolic BPV composite scores were not associated with the other MVD measures: the CSVD composite score, the retinal arteriolar and venular dilation response composite score, skin hyperemia, and the plasma biomarkers of MVD composite score, after full adjustment (Table 2, model 4).

We did not observe consistent interactions with age, sex, glucose metabolism status or hypertension status for the associations between systolic and diastolic BPV and any of the MVD measures (Supplemental Table S4, http://links.lww.com/HJH/B333).

Sensitivity and additional analyses

For individual systolic and diastolic BPV measures, we found the following results after full adjustment: systolic and diastolic within-visit BPV were both not associated with any measure of MVD; 24-h systolic BPV was not associated with any measure of MVD; diastolic 24-h, BPV was associated with a higher CSVD composite score, retinal arteriolar and venular dilation response composite score and UAE but not with any other measure of MVD; 7-day systolic BPV was associated with a higher CSVD composite score and plasma biomarkers of MVD composite score, but not with any other measure of MVD; and 7-day diastolic BPV was associated with higher UAE and a higher plasma biomarker of MVD composite score, but not with any other measure of MVD (Supplemental Table S5, http://links.lww.com/HJH/B333). When we repeated the analysis using each individual MVD measure as the outcome, the systolic and diastolic BPV composite scores were associated with higher levels of sVCAM-1 and the systolic BPV composite score with higher levels of vWF (Supplemental Table S6, http://links.lww.com/HJH/B333). Results were similar when we additionally adjusted for eGFR, prior cardiovascular disease, plasma biomarkers of low-grade inflammation, carotid–femoral pulse wave velocity, diet score, moderate-to-vigorous physical activity, or income level and occupation status (Supplemental Tables S7–S14, http://links.lww.com/HJH/B333). Each SD higher BPV composite score was associated with higher odds of UAE at least 30 mg/24 h; odds ratios were 1.19 (95% CI 1.02–1.38) for systolic BPV and 1.19 (95% CI 1.02–1.37) for diastolic BPV (Fig. 2 and Supplemental Table S15, http://links.lww.com/HJH/B333). The systolic and diastolic BPV composite scores were not associated with eGFR (Supplemental Table S16, http://links.lww.com/HJH/B333).

DISCUSSION

We found that greater very short-term to mid-term systolic and diastolic BPV are associated with higher UAE, but not with other measures of MVD tested, that is, the CSVD composite score, flicker light-induced retinal arteriolar and venular dilation response composite score, heat-induced skin hyperemia and the plasma biomarkers of MVD composite score. The association with higher UAE was independent of age, sex, mean 24-h systolic or diastolic blood pressure, education level, and lifestyle and cardiovascular risk factors. The strength of this association corresponds to a 1.2 higher odds of UAE at least 30 mg/24 h as compared with a UAE of less than 30 mg/24 h per SD higher systolic or diastolic BPV composite score.

TABLE 1. General study population characteristics

Characteristic	Total study population ($n = 2773$)	Tertiles of systolic BPV composite score		
		Lowest tertile ($n = 921$)	Middle tertile ($n = 934$)	Highest tertile ($n = 918$)
Demographics				
Age (years)	59.9 ± 8.2	57.8 ± 8.6	60.3 ± 7.8	61.7 ± 7.6
Men	1,40 (51.9)	490 (53.2)	486 (52.0)	464 (50.5)
Lifestyle factors				
Smoking status				
Never	980 (35.3)	366 (39.7)	297 (31.8)	317 (34.5)
Former	1441 (52.0)	453 (49.2)	506 (54.2)	482 (52.5)
Current	352 (12.7)	102 (11.1)	131 (14.0)	119 (13.0)
Alcohol consumption				
None	509 (18.4)	148 (16.1)	179 (19.2)	182 (19.8)
Low (women ≤7, men ≤14 units/week)	1550 (55.9)	562 (61.0)	516 (55.2)	472 (51.4)
High (women >7, men >14 units/week)	714 (25.7)	211 (22.9)	239 (25.6)	264 (28.8)
BMI (kg/m^2)	27.0 ± 4.4	26.3 ± 4.3	27.0 ± 4.3	27.6 ± 4.5
Cardiovascular risk factors				
Total/HDL cholesterol ratio	3.7 ± 1.2	3.6 ± 1.2	3.6 ± 1.2	3.8 ± 1.2
Glucose metabolism status				
Normal glucose metabolism	1575 (56.8)	612 (67.4)	522 (55.9)	432 (47.1)
Prediabetes	416 (15.0)	112 (12.2)	151 (16.2)	153 (16.7)
Type 2 diabetes	782 (28.2)	188 (20.4)	261 (27.9)	333 (36.3)
Use of lipid-modifying medication	1004 (36.2)	278 (30.2)	330 (35.3)	396 (43.1)
Use of antihypertensive medication	1101 (39.7)	284 (30.8)	371 (39.7)	446 (48.6)
Beta blockers	488 (17.6)	130 (14.1)	162 (17.3)	196 (21.4)
Diuretics	448 (16.2)	104 (11.3)	170 (18.2)	174 (19.0)
Calcium channel blockers	244 (8.8)	72 (7.8)	88 (9.4)	84 (9.2)
Angiotensin-converting enzyme inhibitors	342 (12.3)	77 (8.4)	107 (11.5)	158 (17.2)
Angiotensin II receptor blockers	491 (17.7)	122 (13.2)	174 (18.6)	195 (21.2)
Mean BP				
24-h SBP (mmHg	120.1 ± 11.7	115.9 ± 9.7	120.0 ± 11.7	124.3 ± 12.7
24-h DBP (mmHg)	74.4 ± 7.1	72.7 ± 6.3	74.4 ± 7.2	76.1 ± 7.4
BPV measures				
Within-visit systolic BPV (mmHg)	4.69 ± 2.91	2.77 ± 1.46	4.43 ± 1.99	6.88 ± 3.30
Within-visit diastolic BPV (mmHg)	2.51 ± 1.68	2.14 ± 1.31	2.41 ± 1.46	2.99 ± 2.07
24-h systolic BPV (mmHg)	10.03 ± 2.50	8.16 ± 1.32	9.88 ± 1.58	12.07 ± 2.61
24-h diastolic BPV (mmHg)	7.01 ± 1.86	6.24 ± 1.35	6.88 ± 1.65	7.91 ± 2.10
7-day systolic BPV (mmHg)	9.25 ± 3.83	6.91 ± 1.70	8.84 ± 2.28	12.15 ± 4.80
7-day diastolic BPV (mmHg)	5.76 ± 2.93	4.76 ± 1.65	5.37 ± 1.80	7.24 ± 4.14
Measures of MVD				
Cerebral small vessel disease composite score, per point	0.66 ± 0.84	0.52 ± 0.77	0.70 ± .086	0.78 ± 0.87
Flicker light-induced retinal arteriolar and venular dilation response composite score, SD	−0.01 ± 1.00	−0.05 ± 1.01	−0.04 ± 0.99	0.05 ± 0.99
Urinary albumin excretion (mg/24 h)	6.8 [4.1–11.8]	5.8 [3.7–9.9]	6.9 [4.0–12.5]	7.6 [4.7–13.6]
Heat-induced skin hyperemia (%)	1124 ± 781	1164 ± 841	1130 ± 745	1083 ± 756
Plasma biomarkers of MVD composite score (SD)	−0.01 ± 0.99	−0.12 ± 0.99	−0.04 ± 0.98	0.12 ± 0.99

Data are presented as mean ± standard deviation, median [interquartile range] or *n* (%). Data were available for: within-visit blood pressure variability, $n = 2768$; 24-h blood pressure variability, $n = 2773$ 7-day blood pressure variability, $n = 1950$; cerebral small vessel disease composite score, $n = 1837$; flicker light-induced arteriolar and venular dilation, $n = 1844$; urinary albumin excretion, $n = 2748$; skin hyperemia, $n = 1320$, and plasma biomarkers of microvascular dysfunction, $n = 2685$. BP, blood pressure; BPV, blood pressure variability; HDL, high-density lipoprotein; MVD, microvascular dysfunction.

Our study findings are in agreement with most [16–27], but not all [28–30], previous studies that investigated the association between BPV and UAE. Our study adds to the existing literature on UAE, as we were able to study this association in the context of various other MVD measures, and adjusted for potentially important confounders, including dietary habits and physical activity. Previous studies on BPV and UAE did not adjust for these potential confounders.

In disagreement with our hypothesis, we did not find an association between greater BPV and MVD measured in organs with low microvascular impedance other than the kidneys, that is, the brain and eyes, and with plasma biomarkers of MVD, which at least partly reflect MVD in organs with low microvascular impedance. A possible explanation is that the kidney microvasculature has a lower impedance than the brain and eye microvasculature, for example, blood flow to the kidneys relative to organ weight (360 ml/min per 100 g kidney tissue) is higher than to the brain (50 ml/min per 100 g brain tissue) [58]. The kidney microvasculature may, therefore, in comparison be most vulnerable to the detrimental effects of BPV.

Although we found no significant associations between greater BPV and CSVD features, flicker light-induced retinal arteriolar and venular dilation response and plasma biomarkers of MVD, these measures nevertheless reflect MVD in organs with low vascular impedance, and may thus be vulnerable to an increased pulsatile load [59], albeit to a lesser extent than UAE. Indeed, we found positive associations that were quantitatively similar for CSVD features,

TABLE 2. Associations between SBP and DBP variability composite scores and microvascular dysfunction measures

Microvascular dysfunction measure	Model	SBP variability composite score, per SD β (95% CI)	DBP variability composite score, per SD β (95% CI)
Cerebral small vessel disease composite score, per point	1	**1.07 (1.01–1.13)**	**1.07 (1.00–1.13)**
	2	1.06 (1.00–1.12)	1.06 (0.99–1.12)
	3	1.03 (0.97–1.10)	1.03 (0.97–1.10)
	4	1.02 (0.96–1.09)	1.03 (0.97–1.10)
Flicker light-induced retinal arteriolar and venular dilation composite score, per SD	1	0.033 (−0.014 to 0.081)	0.021 (−0.030 to 0.071)
	2	0.021 (−0.027 to 0.069)	0.014 (−0.036 to 0.064)
	3	0.030 (−0.020 to 0.081)	0.027 (−0.023 to 0.078)
	4	0.031 (−0.019 to 0.082)	0.025 (−0.025 to 0.076)
Urinary albumin excretion, higher ratio	1	**1.14 (1.10–1.18)**	**1.13 (1.09–1.17)**
	2	**1.11 (1.07–1.15)**	**1.11 (1.09–1.15)**
	3	**1.05 (1.01–1.09)**	**1.09 (1.09–1.13)**
	4	**1.04 (1.00–1.08)**	**1.07 (1.03–1.11)**
Heat-induced skin hyperemia, per SD	1	0.027 (−0.029 to 0.083)	0.007 (−0.050 to 0.064)
	2	0.006 (−0.051 to 0.063)	−0.009 (−0.066 to 0.048)
	3	−0.001 (−0.060 to 0.058)	−0.006 (−0.064 to 0.052)
	4	0.005 (−0.054 to 0.065)	−0.003 (−0.061 to 0.055)
Plasma biomarkers of microvascular dysfunction composite score, per SD	1	**0.089 (0.052–0.126)**	**0.082 (0.043 0.120)**
	2	**0.052 (0.015–0.088)**	**0.054 (0.017–0.092)**
	3	**0.057 (0.019–0.095)**	**0.056 (0.018–0.093)**
	4	0.035 (−0.001 to 0.072)	0.023 (−0.013 to 0.060)

Results [β (95% confidence interval)] are expressed as rate ratio for higher cerebral small vessel disease composite score, SD lower flicker light-induced retinal arteriolar and venular dilation composite score, higher ratio urinary albumin excretion, SD lower heat-induced skin hyperemia, and SD higher plasma biomarkers of microvascular dysfunction composite score (all indicating worse microvascular function), and per SD higher SBP or DBP variability composite score. Model 1: adjusted for age, sex; model 2: model 1 + glucose metabolism status; model 3: model 2 + mean 24-h SBP or DBP (wherever appropriate); model 4: model 3 + education level, BMI, smoking status, alcohol consumption, total/high density lipoprotein cholesterol ratio, lipid-modifying medication, and the individual classes of antihypertensive medication (i.e. beta blockers, diuretics, calcium channel blockers, angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers). Bold denotes *P* value less than 0.05. CI, confidence interval; SD, standard deviation.

flicker light-induced retinal arteriolar and venular dilation response, and plasma biomarkers of MVD. Estimations of these associations may have been more inaccurate (i.e. larger confidence intervals), because of higher measurement errors in these MVD measures as compared with UAE: CSVD features, flicker light-induced retinal arteriolar and venular dilation response, and plasma biomarkers of MVD were measured only once, whereas UAE was based on two 24-h urine samples. In addition, estimations of the associations may have been more inaccurate with CSVD features and retinal arteriolar and venular dilation response because of relatively less available data ($n = 1837$ and $n = 1844$, respectively) as compared with UAE ($n = 2748$).

As expected, we did not find an association between BPV and heat-induced skin hyperemia. The skin has relatively high microvascular impedance [4], and, therefore, most of the increased pulsatile energy related to greater BPV may be dissipated by arteries and large arterioles proximal to the skin capillaries [60].

Strengths of this study include the large study population of community-dwelling participants, assessment of microvascular function in various vascular beds and the extensive adjustment for potential confounders.

Our study has several limitations. First, our cross-sectional data preclude reaching causal conclusions about the study findings. Indeed, the reverse association may hold

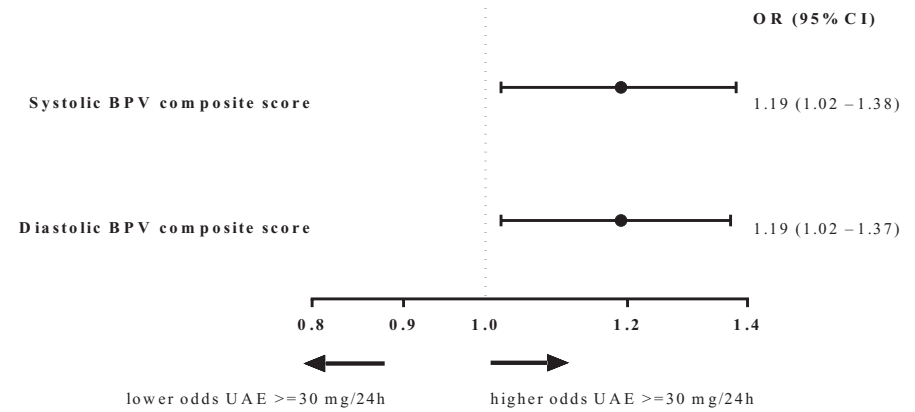

FIGURE 2 Associations of SBP and DBP variability composite scores with urinary albumin excretion dichotomized as at least 30 mg/24 h vs. less than 30 mg/24 h. Point estimates represent the odds ratio of urinary albumin excretion per standard deviation higher systolic or diastolic BPV composite score. Results are adjusted for age, sex, glucose metabolism status, mean 24-h SBP or DBP (wherever appropriate), education level, BMI, smoking status, alcohol consumption, total/high density lipoprotein cholesterol ratio, lipid-modifying medication, and the individual classes of antihypertensive medication. BPV, blood pressure variability; CI, confidence interval; OR, odds ratio; UAE, urinary albumin excretion.

true as well, that is, higher UAE (as a reflection of worse kidney function) may lead to greater BPV [61]. However, when we additionally adjusted our analyses for estimated glomerular filtration rate, results were similar. Second, as we performed a large number of tests in interaction analyses, we cannot exclude that some findings may reflect the play of chance because of multiple testing. Future validation of these inconsistent (hypothesis-generating) observations is warranted. Third, the use of a BPV composite score assumes that all BPV measures share similar underlying mechanisms that lead to MVD, which may not necessarily be true. However, when we repeated the analyses with the individual BPV measures, results were qualitatively similar. This may suggest that BPV measures share similar underlying mechanisms that lead to MVD (even though individual measures of BPV are determined by different haemodynamic mechanisms) [62]. Fourth, the association between greater BPV and UAE may be the result of residual confounding because of low-grade inflammation [63,64], arterial stiffening [4,65], activation of the renin–angiotensin system [66,67], unhealthy dietary habits [68,69], physical inactivity [70,71] and lower socioeconomic status [72,73]. However, when we adjusted for low-grade inflammation, carotid–femoral pulse wave velocity, the diet score, moderate-to-vigorous physical activity and factors related to socioeconomic status (i.e. education, income level and occupation status), results did not materially change. In this study, no data were available on activation of the renin–angiotensin system; however, and this issue requires further study. Fifth, we may have underestimated the association between greater BPV and MVD as individuals excluded for the present analysis because of missing data had greater BPV and a higher prevalence of prior cardiovascular disease than those included in the analysis. Finally, the study population consisted mainly of middle-aged individuals who were relatively well educated and whose cardiovascular risk factors were relatively well controlled. This may have led to an underestimation of the association between BPV and MVD.

Perspectives

In conclusion, this large, relatively healthy population-based study showed that greater very short-term to mid-term systolic and diastolic BPV was associated with higher UAE, but not with other measures of MVD tested, that is, CSVD features, flicker light-induced retinal arteriolar and venular dilation response, heat-induced skin hyperemia and plasma biomarkers of MVD. This may suggest that the microvasculature of the kidneys is most vulnerable to the detrimental effects of greater BPV. Future longitudinal studies should confirm these associations and, if verified, intervention studies should assess whether lowering BPV may prevent albuminuria.

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Conflicts of interest

There are no conflicts of interest.

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