# Cardiovagal baroreflex sensitivity, blood pressure and blood pressure variability - the Maastricht study

# Cardiovagal baroreflex sensitivity, blood pressure and blood pressure variability – the Maastricht study

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**Objective:** Low baroreflex sensitivity (BRS) has been hypothesized to underlie high blood pressure (BP) and greater BP variability on the longer term, but evidence is scarce. In addition, these associations may differ by sex and (pre)diabetes. Therefore, we investigated whether cardiovagal BRS is associated with short- to mid-term mean BP and BP variability, and differs according to sex and (pre)diabetes.

**Methods:** Cross-sectional data from the population-based Maastricht study (age 60 ± 8 years, 52% men), where office ($n = 2846$), 24-h ($n = 2404$) and 7-day BP measurements ($n = 2006$) were performed. Spontaneous BRS was assessed by cross-correlating systolic BP and instantaneous heart rate. We used linear regression with adjustments for age, sex, BP or BP variability, and cardiovascular risk factors.

**Results:** With regard to BP, 1-SD (standard deviation) lower BRS (−5.75 ms/mmHg) was associated with higher office, 24-h and 7-day systolic BP (2.22 mmHg [95% confidence interval [CI]: 1.59; 2.80], 0.95 mmHg [0.54; 1.36], and 1.48 mmHg [0.99; 1.97], respectively) and diastolic BP (1.31 mmHg [0.97; 1.66], 0.57 mmHg [0.30; 0.84], and 0.86 mmHg [0.54; 1.17], respectively). Per 1-SD lower BRS, these associations were stronger in women (0.5–1.5 mmHg higher compared to men), and weaker in those with type 2 diabetes (1–1.5 mmHg lower compared to normal glucose metabolism). With regard to BP variability, BRS was not consistently associated with lower BP variability.

**Conclusions:** Lower cardiovagal BRS is associated with higher mean BP from the short- to mid-term range, and not consistently with BP variability. The associations with mean BP are stronger in women and weaker in those with type 2 diabetes.

**Keywords:** average real variability, baroreflex, blood pressure, blood pressure variability, epidemiology, population-based

**Abbreviations:** BP, blood pressure; BRS, baroreflex sensitivity; CVD, cardiovascular disease; SD, standard deviation; T2D, type 2 diabetes; xBRS, cross-correlation baroreflex sensitivity

## INTRODUCTION

High blood pressure (BP) and greater BP variability are both independently associated with incident cardiovascular disease (CVD) [1,2]. To improve treatment and prevention of CVD, it is thus important to investigate potential determinants of high BP and BP variability. This is especially true for those who are undertreated or at increased risk, such as women [3] and individuals with type 2 diabetes (T2D), respectively [4]. It has been proposed that baroreflex sensitivity (BRS) may be such a determinant [5,6], as the baroreflex has an essential role in very short-term BP regulation.

However, it has been debated whether the baroreflex also contributes to BP regulation in the longer term [7]. There is some evidence that supports this notion. For example, in cases of complete baroreflex failure (surgically resected carotid body tumors [8] or neck irradiation [9]), BP increased acutely but normalized over time. The variability of BP, however, remained increased at least over a period of several months. The baroreflex may buffer BP changes in various ways, via cardiac function (heart rate and contractility) and changes in vascular tone via the sympathetic nervous system [10].

Whether baroreflex function is associated with BP and BP variability in the long term in the general population, and whether women and individuals with type 2 diabetes are affected differently, is largely unknown. Some studies measured BRS in normotensive and hypertensive populations [11,12], but included relatively few participants ($n \sim 50$) and measured BP only up to 24 h. In addition, previous studies have suggested that autonomic regulation of BP may differ

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according to sex [13] and diabetes status [14], but no studies have investigated such associations.

Therefore, we investigated, in the population-based Maastricht Study, whether lower cardiovagal BRS was associated with higher BP and BP variability over a range of time (i.e., by use of office, 24-h ambulatory, and 7-day home BP measurements). In addition, we investigated whether these associations differed according to sex or glucose metabolism status.

# METHODS

## Study design and population

We used data from The Maastricht Study, an observational prospective population-based cohort study. The rationale and methodology have been described elsewhere [15]. In brief, the study focuses on the etiology, pathophysiology, complications and comorbidities of 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 and from 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 statistical efficiency. The present report includes cross-sectional data from the first 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 collection

### Blood pressure measurements and determination of blood pressure variability

A detailed description of the office, 24-h ambulatory and 7-day home BP measurements and the variability indices have been reported previously [16]. Briefly, for BP variability indices, within-visit BP variability was calculated as the standard deviation (SD) of three consecutive office blood pressure measurements, with a 1-min interval, after 10 min of rest. 24-h BP variability was calculated as the average real variability of BP readings taken every 15 min between 0800 and 2300 h, and every 30 min between 2300 and 0800 h. Seven-day BP variability was calculated as the SD of home BP measurements taken twice, with a 1-min interval, each morning and evening, for 7 consecutive days.

### Measurement of cardiovagal baroreflex sensitivity

Cardiovagal BRS was quantified using the cross-correlation BRS (xBRS) method [17]. In brief, systolic BP and heart rate intervals (RRi) were continuously measured with a Nexfin HD Monitor (BMEYE, Amsterdam, the Netherlands). Systolic BP was obtained by using an inflatable cuff placed around the left index finger, and RRi was obtained by detecting consecutive ECG-derived QRS-complex intervals. Recordings were taken in supine position for at least 600 heart beats. xBRS computes the linear correlation between beat-to-beat systolic BP and RRi intervals resampled at 1 Hz. This in a 10-s sliding window with 0–5 s delays for the window between both variables. The delay with the greatest positive correlation is selected and, when statistically significant ($P$ value $\leq 0.01$), slope and delay are noted as one xBRS value. Hence, the xBRS method observes systolic BP and RRi variability over a fixed 10-s time period, as opposed to the sequential BRS method, where the number of beats is variable. Each successive 1 s of the recording marks a new computation. To interpret, a lower xBRS value indicates a worse baroreflex function. We standardized xBRS to facilitate comparisons in the associations between BP and BP variability.

### Covariates

We assessed alcohol consumption, smoking status, history of CVD and moderate-to-vigorous physical activity by questionnaire. Alcohol consumption was defined as non-consumer, low consumer ($\leq$7 alcoholic drinks/week for women; $\leq$14 alcoholic drinks/week for men) or high consumer (>7 alcoholic drinks/week for women; >14 alcohol drinks/week for men). Smoking status was categorized into never, former and current smoker. We determined body mass index (BMI), waist circumference, total cholesterol, high-density lipoprotein cholesterol (HDL), and fasting and postload glucose as described elsewhere [15]. Glucose metabolism status was categorized into normal glucose metabolism, prediabetes (impaired fasting glucose and/or impaired glucose tolerance) and T2D, according to the World Health Organization 2006 criteria [18]. Estimated glomerular filtration rate was computed with the CKD-EPI (Chronic Kidney Disease Epidemiology collaboration) formula, using serum creatinine and cystatin C [19]. We collected information on the use of lipid-modifying and antihypertensive medication, that is, generic names, doses and frequencies, during an interview.

## Analytical sample

Figure 1 shows the delineation of the final study populations. In total, we analyzed office BP/within-visit BP variability in 2846 participants, 24-h ambulatory BP/24-h BP variability in 2404 participants and 7-day home BP/7-day BP variability in 2006 participants). The clinical characteristics of the included and excluded participants were similar (Tables S1–S3, Supplemental Digital Content, http://links.lww.com/HJH/C98).

## Statistical analysis

For the main analysis, we used standardized xBRS values to determine the association of BRS with mean BP and BP variability. To this end, we performed two linear regression analyses. First, we used linear regression to investigate the associations between xBRS, and office, 24-h and 7-day mean systolic and diastolic BP. Second, we used linear regression to investigate the associations between xBRS, and within-visit, 24-h and 7-day systolic and diastolic BP variability. We adjusted all analyses for age, sex and glucose metabolism status (model 1); plus systolic or diastolic BP variability (within-visit, 24-h or 7-day, where appropriate)

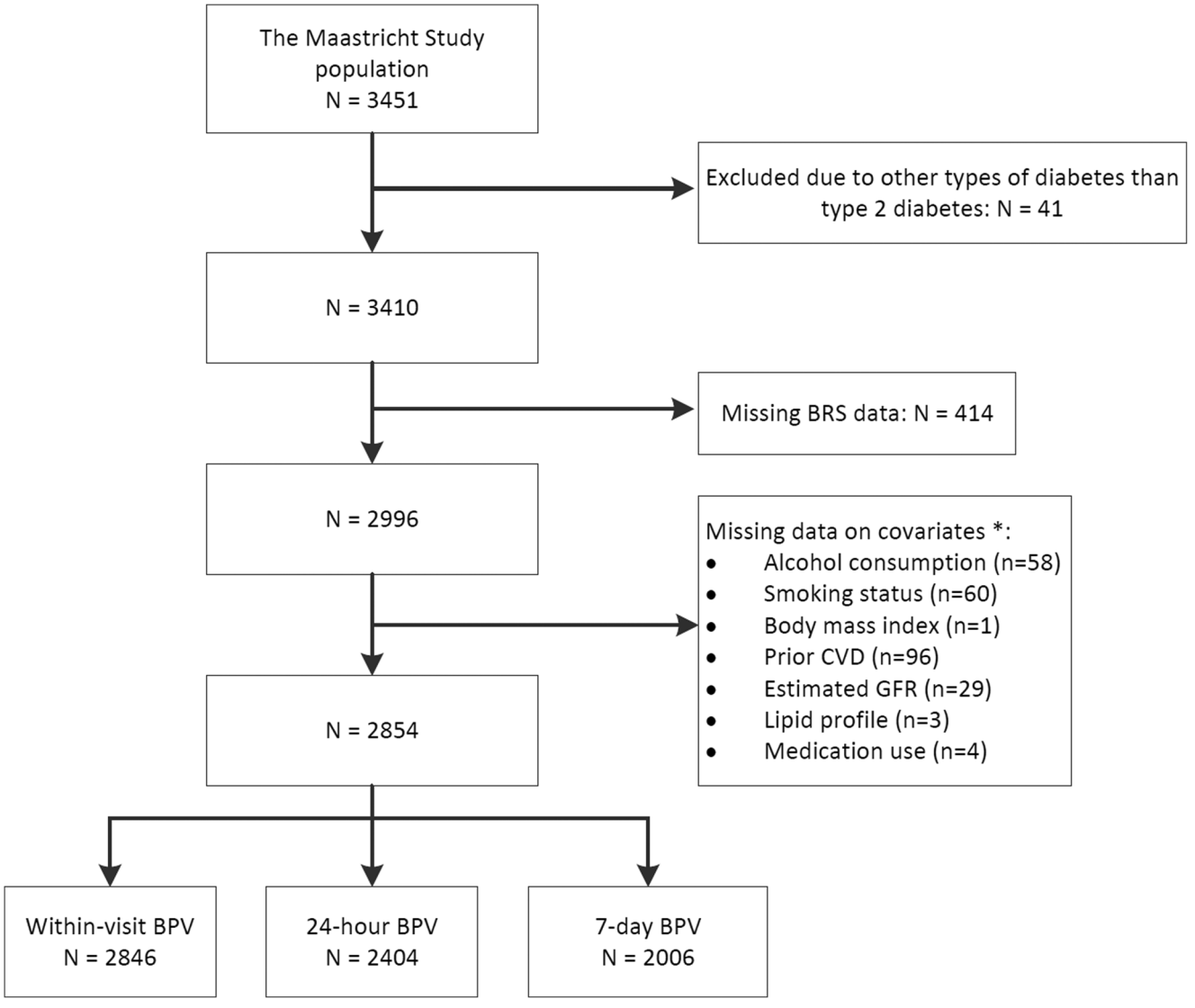


**FIGURE 1** Flowchart delineating the final study populations. ∗ denotes not mutually exclusive. BP, blood pressure; BRS, baroreflex sensitivity; CVD, cardiovascular disease; GFR, glomerular filtration rate.

in analyses with mean BP as outcome, and mean systolic or diastolic BP (office, 24-h or 7-day, where appropriate) in analyses with BP variability as outcome (model 2); plus BMI, smoking behavior and alcohol consumption (model 3); and in addition for prior CVD, estimated glomerular filtration rate, total-to-HDL cholesterol ratio, lipid-modifying medication and antihypertensive medication (beta-blockers, calcium channel blockers, ACE inhibitors, angiotensin II receptor blockers and diuretics entered separately into the model) (model 4).

We tested for interactions with sex and glucose metabolism status by adding the interaction terms BRS∗sex or BRS∗prediabetes and BRS∗T2D, because sex and (pre) diabetes may modify the association of BRS with mean BP and BP variability [20,21].

Several additional analyses were performed to test the robustness of our findings: we adjusted for waist circumference instead of BMI, as it may more accurately reflect visceral fat, which has been associated with sympathetic overactivity [22]; we additionally adjusted for physical activity (not in the main analysis due to the relatively large number of missing data; $n = 343$); and we additionally adjusted for resting heart rate as they differed between BRS tertiles.

All data were analyzed with the use of IBM SPSS software version 23.0 for Windows (IBM Corp., Somers, New York, USA). Data are presented as $n$ (%), mean ± SD or median [interquartile range]. A two-sided $P$ value of $<0.05$ was considered statistically significant.

## RESULTS

### Study population characteristics

Table 1 shows the clinical characteristics of the xBRS study population according to tertiles of xBRS (tertile 1: lowest xBRS). Generally, participants with the lowest as compared to the highest xBRS tertile were older, more often had T2D and more often used antihypertensive medication. In

**TABLE 1. Clinical characteristics of the within-visit study population**

| | Within-visit study population ($n = 2846$) | Tertiles of xBRS | | |
|---|---|---|---|---|
| | | Tertile 1 ($n = 947$) | Tertile 2 ($n = 950$) | Tertile 3 ($n = 949$) |
| Demographics | | | | |
| Age, years | 59.6 ± 8.2 | 62.3 ± 7.3 | 59.5 ± 7.8 | 56.9 ± 8.5 |
| Men | 1487 (52.2%) | 577 (60.9%) | 484 (50.9%) | 426 (44.9%) |
| History of CVD | 479 (16.8%) | 182 (19.2%) | 150 (15.8%) | 147 (15.5%) |
| Lifestyle variables | | | | |
| Smoking behavior | | | | |
| Never | 983 (34.5%) | 280 (29.6%) | 330 (34.7%) | 373 (39.3%) |
| Former | 1479 (52.0%) | 540 (57.0%) | 491 (51.7%) | 448 (47.2%) |
| Current | 384 (13.5%) | 127 (13.4%) | 129 (13.6%) | 128 (13.5%) |
| Alcohol consumption | | | | |
| None | 532 (18.7%) | 196 (20.7%) | 159 (16.7%) | 177 (18.7%) |
| Low | 1558 (54.7%) | 497 (52.5%) | 527 (55.5%) | 534 (56.3%) |
| High | 756 (26.6%) | 254 (26.8%) | 264 (27.8%) | 238 (25.1%) |
| Moderate-to-vigorous physical activity (h/week)* | 4.5 [2.3–8.0] | 3.8 [1.5–7.0] | 4.8 [2.5–8.3] | 5.0 [3.0–8.3] |
| Cardiovascular risk factors | | | | |
| BMI (kg/m$^2$) | 27.0 ± 4.5 | 28.5 ± 4.9 | 26.8 ± 4.2 | 25.7 ± 3.9 |
| Waist circumference (cm)* | 95.7 ± 13.7 | 101.2 ± 14.0 | 95.1 ± 12.6 | 91.0 ± 12.5 |
| Heart rate (bpm) | 67.9 ± 11.0 | 72.1 ± 11.7 | 67.3 ± 9.8 | 64.5 ± 10.0 |
| Glucose metabolism status | | | | |
| Normal glucose metabolism | 1632 (57.3%) | 388 (41.0%) | 569 (59.9%) | 675 (71.1%) |
| Prediabetes | 436 (15.3%) | 157 (16.6%) | 158 (16.6%) | 121 (12.8%) |
| Type 2 diabetes | 778 (27.3%) | 402 (42.4%) | 223 (23.5%) | 153 (16.1%) |
| Total-to-HDL cholesterol ratio | 3.7 ± 1.2 | 3.8 ± 1.2 | 3.7 ± 1.2 | 3.7 ± 1.1 |
| eGFR (ml/min per 1.73 m$^2$) | 88.3 ± 14.8 | 85.7 ± 15.3 | 88.6 ± 14.0 | 90.7 ± 14.6 |
| Medication | | | | |
| Use of antihypertensive medication | 1108 (38.9%) | 479 (50.6%) | 329 (34.6%) | 300 (31.6%) |
| Beta-blockers | 497 (17.5%) | 195 (20.6%) | 154 (16.2%) | 148 (15.6%) |
| Calcium channel blockers | 250 (8.8%) | 113 (11.9%) | 71 (7.5%) | 66 (7.0%) |
| ACE inhibitors | 321 (11.3%) | 138 (14.6%) | 94 (9.9%) | 89 (9.4%) |
| Angiotensin II receptor blockers | 512 (18.0%) | 235 (24.8%) | 138 (14.5%) | 139 (14.6%) |
| Diuretics | 456 (16.0%) | 219 (23.1%) | 136 (14.3%) | 101 (10.6%) |
| Lipid-modifying medication | 1003 (35.2%) | 442 (46.7%) | 319 (33.6%) | 242 (25.5%) |
| Blood pressure measurements | | | | |
| Office SBP (mmHg) | 134.8 ± 18.0 | 141.0 ± 18.3 | 134.8 ± 16.8 | 128.7 ± 16.8 |
| Office DBP (mmHg) | 76.2 ± 9.8 | 78.5 ± 9.8 | 76.6 ± 9.7 | 73.6 ± 9.2 |
| 24-h SBP (mmHg)[c] | 120.2 ± 11.8 | 123.9 ± 12.2 | 119.3 ± 10.9 | 117.2 ± 11.1 |
| 24-h DBP (mmHg)[c] | 74.5 ± 7.1 | 75.7 ± 7.5 | 74.3 ± 6.9 | 73.5 ± 6.7 |
| 7-day home SBP (mmHg)[d] | 127.6 ± 13.6 | 132.7 ± 13.5 | 126.7 ± 12.2 | 122.6 ± 12.5 |
| 7-day home DBP (mmHg)[d] | 77.3 ± 8.2 | 79.3 ± 8.3 | 77.4 ± 7.7 | 75.5 ± 8.3 |
| Blood pressure variability parameters | | | | |
| Within-visit systolic BP variability (mmHg) | 4.65 ± 2.90 | 4.75 ± 2.92 | 4.58 ± 2.53 | 4.35 ± 2.81 |
| Within-visit diastolic BP variability (mmHg) | 2.52 ± 1.75 | 2.48 ± 1.65 | 2.52 ± 1.69 | 2.45 ± 1.70 |
| 24-h systolic BP variability (mmHg)† | 10.04 ± 2.48 | 10.53 ± 2.63 | 9.92 ± 2.39 | 9.54 ± 2.29 |
| 24-h diastolic BP variability (mmHg)† | 6.98 ± 1.84 | 7.00 ± 1.78 | 6.92 ± 1.91 | 6.76 ± 1.81 |
| 7-day systolic BP variability (mmHg)‡ | 9.34 ± 3.87 | 9.72 ± 3.67 | 9.10 ± 3.61 | 8.91 ± 4.18 |
| 7-day diastolic BP variability (mmHg)‡ | 5.87 ± 3.07 | 5.97 ± 2.79 | 5.65 ± 2.77 | 5.64 ± 3.19 |
| Baroreflex sensitivity | | | | |
| xBRS (ms/mmHg) | 7.37 ± 5.76 | 3.18 ± 1.00 | 6.04 ± 0.86 | 12.88 ± 6.93 |

Data are presented as mean ± SD, median [interquartile range] or *n* (%).
CVD, cardiovascular disease; HDL, high-density lipoprotein; SD, standard deviation; xBRS, cross-correlation baroreflex sensitivity.
*Data available for: moderate-to-vigorous physical activity, $n = 2502$; waist circumference, $n = 2845$.
†Values presented for 24-h BP variability study population.
‡Values presented for 7-day BP variability study population.

addition, office, 24-h and 7-day mean BP and BP variability were greater from the highest to the lowest xBRS tertile.

## Associations between baroreflex sensitivity, and systolic and diastolic blood pressure

After adjustments for age, sex, glucose metabolism status, systolic or diastolic BP variability smoking status, alcohol consumption, BMI, total-to-HDL cholesterol ratio, prior CVD, lipid-modifying and antihypertensive medication and estimated glomerular filtration rate (Table 2, model 4; Fig. 2, panels a–c), a 1 SD lower xBRS (equivalent to −5.75 ms/mmHg) was associated with higher office, 24-h and 7-day systolic (2.22 mmHg [95% confidence interval (CI): 1.59; 2.80], 0.95 mmHg [0.54; 1.36], and 1.48 mmHg [0.99; 1.97], respectively) and diastolic BP (1.31 mmHg [0.97; 1.66], 0.57 mmHg [0.30; 0.84], and 0.86 mmHg [0.54; 1.17], respectively, for diastolic mean BP; Figure S1, Supplemental Digital Content, http://links.lww.com/HJH/C98, panels A–C).

**TABLE 2. Associations between cross-correlation baroreflex sensitivity, and systolic and diastolic blood pressure**

| | | Systolic blood pressure (mmHg) | | | Diastolic blood pressure (mmHg) | | |
|---|---|---|---|---|---|---|---|
| | | Office | 24-h | 7-day | Office | 24-h | 7-day |
| | Model | β (95%CI) | β (95% CI) | β (95% CI) | β (95% CI) | β (95% CI) | β (95% CI) |
| xBRS (SD) | Crude | 3.69 (3.04; 4.33) | 1.87 (1.40; 2.35) | 2.87 (2.30; 3.43) | 1.59 (1.23; 1.95) | 0.61 (0.33; 0.90) | 1.13 (0.78; 1.48) |
| | 1 | 2.40 (1.79; 3.01) | 1.29 (0.85; 1.72) | 1.97 (1.11; 2.50) | 1.56 (1.21; 1.91) | 0.75 (0.47; 1.02) | 1.14 (0.81; 1.48) |
| | 2 | 2.36 (1.76; 2.97) | 1.06 (0.65; 1.47) | 1.86 (1.36; 2.35) | 1.59 (1.24; 1.94) | 0.76 (0.49; 1.03) | 1.13 (0.81; 1.45) |
| | 3 | 2.14 (1.54; 2.75) | 1.09 (0.68; 1.50) | 1.56 (1.10; 2.07) | 1.37 (1.02; 1.71) | 0.71 (0.44; 0.99) | 0.99 (0.67; 1.31) |
| | 4 | 2.22 (1.59; 2.80) | 0.95 (0.54; 1.36) | 1.48 (0.99; 1.97) | 1.31 (0.97; 1.66) | 0.57 (0.30; 0.84) | 0.86 (0.54; 1.17) |

Regression coefficients (β) represent β mmHg difference in blood pressure for every 1 SD lower xBRS. 1 SD xBRS was equivalent to 5.75 ms/mmHg.
Model 1: age, sex and glucose metabolism status; model 2: model 1 + mean systolic or diastolic blood pressure variability (office, 24-h or 7-day, where appropriate); model 3: model 2 + smoking status, alcohol consumption and body mass index; model 4: model 3 + total-to-HDL cholesterol ratio, history of CVD, antihypertensive medication (with the individual classes separately), lipid-modifying medication and estimated glomerular filtration rate.
95% CI, 95% confidence interval; BP variability, blood pressure variability; CVD, cardiovascular disease; HDL, high-density lipoprotein; SD, standard deviation; xBRS, cross-correlation baroreflex sensitivity.



### Associations between baroreflex sensitivity, and systolic and diastolic blood pressure variability

After adjustments for the covariates of model 4, xBRS was not associated with within-visit, 24-h and 7-day systolic BP variability (−0.01 mmHg [−0.12; 0.10, 0.02 mmHg [−0.07; 0.12], −0.08 mmHg [−0.24; 0.07], respectively). A 1 SD lower xBRS was associated with lower within-visit and 24-h diastolic BP variability (−0.07 mmHg [−0.14; 0.00] and −0.08 mmHg [−0.15; −0.01], respectively), but not with 7-day diastolic BP variability (−0.09 mmHg [−0.22; 0.04]) (Table 3, model 4).

### Interaction analyses

Sex and glucose metabolism status consistently modified the association between xBRS and BP, but not between xBRS and BP variability (Table S4, Supplemental Digital Content, http://links.lww.com/HJH/C98). When we stratified the analysis for the association between xBRS and mean BP, we observed that, with regard to sex, after full adjustment, a 1 SD lower xBRS was more strongly associated with higher systolic and diastolic BP in women than in men (approximately 0.5–1.5 mmHg higher per SD xBRS for women; Fig. 2, panels d–f; Table S5, Supplemental Digital Content, http://links.lww.com/HJH/C98, model 4 and Figure S1, panels D–F, Supplemental Digital Content, http://links.lww.com/HJH/C98). With regard to glucose metabolism status, after full adjustment, a 1 SD lower xBRS was more weakly associated with higher systolic and diastolic BP in individuals with T2D than in those with normal glucose metabolism (approximately 1.0–1.5 mmHg lower per SD xBRS for individuals with T2D; Fig. 2, panels h–j; Table S6, Supplemental Digital Content, http://links.lww.com/HJH/C98, model 4 and Figure S1, panels H–J, Supplemental Digital Content, http://links.lww.com/HJH/C98).

### Additional analyses

Results remained similar when we adjusted for waist circumference instead of BMI (Table S7, Supplemental Digital Content, http://links.lww.com/HJH/C98) or additionally adjusted for moderate-to-vigorous physical activity (Table S8, Supplemental Digital Content, http://links.lww.com/HJH/C98), or resting heart rate (Table S9, Supplemental Digital Content, http://links.lww.com/HJH/C98).

## DISCUSSION

The present study had two main findings. First, lower cardiovagal BRS was associated with higher mean systolic and diastolic BP in the short-term (office and 24-h) to mid-term (7 days) measurements, with the strongest association with office BP. These associations were stronger in women than in men, and weaker in individuals with (pre)diabetes than in those with normal glucose metabolism. Second, we found that cardiovagal BRS was not consistently associated with BP variability. Taken together, these findings suggest that lower cardiovagal BRS is a determinant of higher mean BP, even in mid-term measurements, but not for greater BP variability.

Our results are in agreement with the findings of Hesse *et al.* [11], who reported that lower BRS was associated with higher 24-h mean BP in normotensive individuals. We extend their findings in that the baroreflex is associated with BP in an even longer term, i.e. 7 days, and by observing this association in a population-based cohort. In contrast to our findings, Floras *et al.* [12] reported that lower BRS was associated with greater 24-h BP variability, but did not adjust for important confounders, such as mean BP.

The present study supports the hypothesis that the baroreflex plays a role in short-term BP regulation, but also in the longer term. Among the mechanisms of long-term BP regulation by baroreflex activation are inhibitory effects on the renal sympathetic nerve activity, which increases renal excretory functions, i.e. sodium excretion, and inhibition of the renin-angiotensin-aldosterone system [7]. Other hemodynamic and hormonal mechanisms may also play a role, and these potential underlying mechanisms require further study. In addition, other factors may underlie the association between BRS and mean BP, including excess visceral fat (which is associated with sympathetic overactivity [22]) and high physical activity [23]. However, our results did not materially change when we adjusted for waist circumference, a more accurate marker of visceral fat than BMI [24], or additionally adjusted for physical activity.

We found that lower cardiovagal BRS was not consistently associated with greater BP variability, which can be explained by several factors. First, the antioscillatory capacity of the baroreflex may be preserved with lower BRS due to intact efferent sympathetic branches of the baroreflex [25]. Indeed, it has been suggested that the parasympathetic branches of the baroreflex, assessed by cardiovagal BRS,

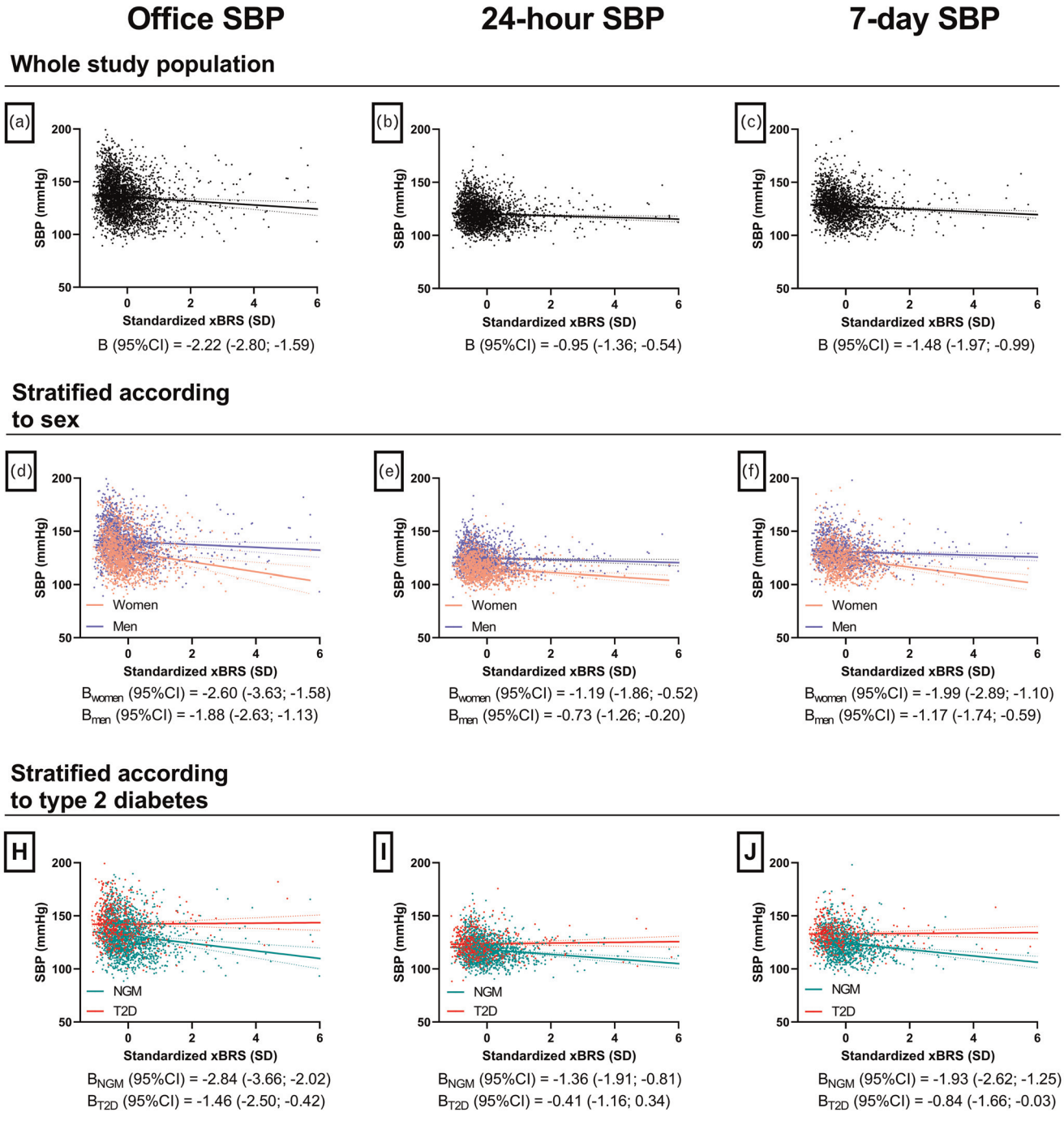


**FIGURE 2** Associations between xBRS and office (left column), 24-h (middle column) and 7-day (right column) systolic BP. Panels a–c: association between BRS and office, 24-h and 7-day systolic BP in the whole study population, respectively. Panels d–f: associations between BRS and office, 24-h and 7-day systolic BP stratified according to sex, respectively. Panels h–j: associations between BRS and office, 24-h and 7-day systolic BP stratified according to T2D status. Note: regression coefficients are inversed as compared with tables, i.e. regression coefficients (*B*) indicate mmHg difference in systolic BP per 1 SD increment in xBRS. BP, blood pressure; CI, confidence interval; NGM, normal glucose metabolism; SBP, systolic blood pressure; SD, standard deviation; T2D, type 2 diabetes; xBRS, cross-correlation baroreflex sensitivity.

deteriorate earlier than the sympathetic branches [26]. Thus, despite lower cardiovagal BRS, the baroreflex sympathetic outflow to the heart, peripheral vasculature and kidneys remains unchanged, which ensures that BP is kept at a constant level. Second, our study population does not include individuals with severe or complete baroreflex failure. These individuals, for example, after surgical resection of carotid body tumors or neck irradiation [8,9], do experience extreme BP variability. To our surprise, we found a weak association between lower cardiovagal BRS and lower diastolic within-visit and 24-h BP variability. Hesse *et al.* [11] found similar results and argued that this may be due to BP changes during physical activity. However, when we additionally adjusted for moderate-to-vigorous physical activity, the association remained similar. Such findings may also represent the play of chance. Hence,

**TABLE 3. Associations between cross-correlation baroreflex sensitivity, and systolic and diastolic blood pressure variability**

| | | Systolic blood pressure variability (mmHg) | | | Diastolic blood pressure variability (mmHg) | | |
|---|---|---|---|---|---|---|---|
| | | Within-visit | 24-h | 7-day | Within-visit | 24-h | 7-day |
| | Model | β (95% CI) | β (95% CI) | β (95% CI) | β (95% CI) | β (95% CI) | β (95% CI) |
| xBRS (SD) | Crude | 0.10 (−0.01; 0.20) | 0.25 (0.15; 0.35) | 0.26 (0.09; 0.42) | −0.03 (−0.10; 0.03) | 0.03 (−0.05; 0.10) | 0.10 (−0.03; 0.23) |
| | 1 | 0.05 (−0.06; 0.15) | 0.15 (0.05; 0.25) | 0.11 (−0.06; 0.27) | −0.05 (−0.12; 0.01) | −0.02 (−0.10; 0.06) | 0.03 (−0.11; 0.16) |
| | 2 | −0.02 (−0.13; 0.09) | 0.05 (−0.04; 0.15) | −0.10 (−0.26; 0.05) | −0.08 (−0.15; −0.01) | −0.05 (−0.13; 0.03) | −0.10 (−0.23; 0.03) |
| | 3 | −0.01 (−0.12; 0.10) | 0.01 (−0.08; 0.11) | −0.11 (−0.27; 0.05) | −0.07 (−0.14; −0.01) | −0.08 (−0.16; −0.01) | −0.11 (−0.24; 0.02) |
| | 4 | −0.01 (−0.12; 0.10) | 0.02 (−0.07; 0.12) | −0.08 (−0.24; 0.07) | −0.07 (−0.14; 0.00) | −0.08 (−0.15; −0.01) | −0.09 (−0.22; 0.04) |

Regression coefficients (β) represent β mmHg difference in blood pressure variability for every 1 SD lower xBRS. 1 SD xBRS is equivalent to 5.75 ms/mmHg.
Model 1: age, sex and glucose metabolism status; model 2: model 1 + mean systolic or diastolic blood pressure (office, 24-h or 7-day, where appropriate); model 3: model 2 + smoking status, alcohol consumption and body mass index; model 4: model 3 + total-to-HDL cholesterol ratio, history of CVD, antihypertensive medication (with the individual classes separately), lipid-modifying medication and estimated glomerular filtration rate.
95% CI, 95% confidence interval; BP variability, blood pressure variability; CVD, cardiovascular disease; HDL, high-density lipoprotein; SD, standard deviation; xBRS, cross-correlation baroreflex sensitivity.



this issue requires further study in other population-based studies.

Sex and glucose metabolism modified the association between cardiovagal BRS and BP. With regard to sex, we found that the association between BRS and BP was stronger in women as compared with men. Previous studies have shown that women exhibit higher levels of BRS than men due to higher levels of circulating estrogen in women inhibiting angiotensin II in the brain [27,28]. However, the mechanisms involved in sex-specific BP modulation by the baroreflex are still unknown and further research is needed. With regard to glucose metabolism status, we found that the association between lower cardiovagal BRS and higher BP weakened from normal glucose metabolism status to (pre)diabetes. This may be due to the fact that individuals with diabetes may have damaged efferent autonomic nerve fibers that innervate the heart and blood vessels (i.e. diabetes-associated cardiac autonomic dysfunction), which we have observed in the Maastricht study [29]. Here, individuals with (pre)diabetes had lower heart rate variability, which reflects cardiac autonomic dysfunction. Therefore, despite increased afferent signals from the baroreflex, efferent signals may be damaged to such an extent so that BP cannot differ anymore.

We speculate that the findings of our study may suggest that specific groups of patients with hypertension may experience greater effects of baroreceptor activation therapy [30] than others. Because associations between BRS and BP were stronger in women and weaker in those with T2D, it could imply that female patients may experience greater effects from baroreceptor activation therapy (or may need less electric stimulation) than male patients, and the opposite may apply to patients with T2D.

Strengths of the present study include its large sample size, population-based design, adjustments for a large series of potential confounders to test the robustness of our associations, for instance additional adjustment for physical activity and heart rate did not change results, and the large time range of BP measurements (i.e. up to 7 days).

Several limitations of this study need to be addressed. First, due to the cross-sectional design of this study, any causal inference should be made with caution. Second, we did not have data on sympathetic BRS measurements, which would have extended the findings of the present report. Third, beat-to-beat BPs as a measure for very short-term BP regulation were not used in the current analyses due to multicollinearity, as these data were also used to calculate BRS. In addition, data on visit-to-visit BP as a measure for very long-term BP were unavailable. Thereby, our results may not be extended to very short- or very long-term BP regulation.

Lower cardiovagal BRS is associated with higher BP in the short- to the mid-term range, but not with greater BP variability. In addition, we found that the association between lower cardiovagal BRS and higher BP is stronger in women than in men, whereas the association is weaker in those with T2D. In general, our findings suggest that the baroreflex may be a potential treatment target to lower BP, even in the longer term, and that such therapies may be more effective in women and in those without T2D. Further studies may include BP measurements over visit-to-visit, and future therapeutic studies may account for sex and diabetes-associated differences.

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### Conflicts of interest

There are no conflicts of interest.

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