The Heart of the Matter: Discovery of new genetic loci for heart rate variability and its relationship with blood pressure and mortality

Tegegne, Balewgizie

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Chapter 4

Spontaneous baroreflex sensitivity and its association with age, gender, obesity indices and hypertension: a population study

Tengfei Man, Balewgizie S Tegegne, Arie M van Roon, Judith G M Rosmalen, Ilja M Nolte, Harold Snieder, Harriëtte Riese

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Abstract

Background: Low baroreflex sensitivity (BRS) is an established risk factor for cardiovascular disorders. We investigated determinants of BRS in a large sample from general population.

Methods: In a population-based study (n=901) data were collected on BRS, arm cuff blood pressure (BP) and obesity indices including body mass index (BMI), waist-to-hip ratio (WHR), waist circumference and percentage body fat (%BF). BRS was calculated by spectral analysis software based on continuously recorded spontaneous fluctuations in beat-to-beat finger BP for 10 to 15 minutes. Correlations and multivariable regression analyses were used to test associations of age, sex, obesity indices and hypertension with BRS while considering effects of lifestyle factors (smoking, alcohol consumption and physical activity).

Results: In multivariable analysis, age, sex, %BF, and hypertension were independently associated with BRS. BRS decreased with -0.10 (95% confidence interval [CI]: -0.15 to -0.06) ms/mmHg with each year of increase in age. Women had -1.55 (95% CI: -2.28 to -0.73) ms/mmHg lower mean BRS than men. The effects of %BF (per 10% increase) and hypertension on BRS were -0.55 (95% CI: -0.97 to -0.13) ms/mmHg and -1.23 (95% CI: -1.92 to -0.46) ms/mmHg, respectively. There was no evidence of associations between BRS and lifestyle factors. Age, age^2, sex, and their interactions plus %BF and hypertension contributed 16.9% of total variance of BRS.

Conclusions: In this large general population study, we confirm prior findings that age and sex are important factors associated with BRS and find %BF is more strongly related to less favorable BRS levels than BMI.

Keywords: age; baroreflex sensitivity; hypertension; obesity indices; sex.

Introduction

The baroreflex loop was an important cardiovascular control mechanism for short-term blood pressure (BP) regulation. Baroreflex sensitivity (BRS) can be estimated from the transfer function between interbeat intervals (IBI) and systolic BP (SBP) changes[1]. Together with other well- known risk factors, decreased BRS played a role in the development and progression of hypertension and other cardiovascular diseases[2], and physiologically as a marker for sympathetic and parasympathetic autonomic regulation[1] .For this reason, revealing factors associated with a decreased baroreceptor reflex function, indexed as lower BRS, is important.

Previous studies indicated that age (i.e., lower BRS in older age) and sex (i.e., men had higher BRS than women) were both independent determinants of spontaneous BRS with age contributing 21.3% and sex contributing 1% to the explained variance of BRS[3].

Lower BRS was also associated with less favorable values of several obesity indices[4] and high BP or hypertension[3,5,6]. However, studies on the associations of BRS with age and obesity indices were mostly conducted in rather small samples with a limited number of obesity indices until now, which makes replication in a larger population-based sample with a wider age range and more sophisticated measures of obesity advisable.

Data of a subsample of the population-based Prevention of REnal and Vascular ENd stage Disease (PREVEND) study were used for the current study[7]. The aim of the current study is to extend on previous findings by comprehensively characterizing the association of BRS with age, sex, hypertension, and multiple obesity indices.

METHODS

Study design and population

PREVEND was a population-based cohort study investigating micro-albuminuria as a risk factor for renal and cardiovascular disease. All inhabitants of the city of Groningen between the ages of 28 and 75 years (85,421 subjects) were invited, and 40,856 (48%) subjects responded. After exclusion of subjects with insulin dependent diabetes mellitus and pregnant women, all subjects with an elevated urinary albumin concentration of ≥10 mg/L (n = 7,768), together with a randomly selected control group with a urinary albumin concentration of <10 mg/L

(n = 3,395), were invited for further investigations (total n = 11,163). Finally, 8,592 subjects completed the total screening program, making up the PREVEND study cohort in 1997–1998. Since the PREVEND study population was enriched for albuminuria, to get a representative sample of general population, all albuminuria-negative participants (<10 mg/L) and a random sample of albuminuria-positive participants (≥10 mg/L) were combined to counterbalance the oversampling for albuminuria. In the second screening in 2001–2002, 2,554 subjects from this representative sample were invited to participate in the Study of Allostatic Load as a UnifyingTheme (SALUT[8]), which aimed to examine the extent to which propensity to ill health of any kind was attributable to liability, susceptibility or chains of risk models of morbidity accumulation (Figure 1). A total of 1,091 (43%) subjects finally participated in the SALUT study. In our analysis, 158 (14.5%) subjects were excluded as they did not have BRSmeasurements available due to logistic reasons.

The study was approved by the Ethics Committee of the University Medical Center Groningen and conducted in accordance with the guidelines of the declaration of Helsinki. The informed consent procedure consisted of 2 parts. For the screening phase of the PREVEND study, informed consent was obtained at the first outpatient visit in 1997–1998. For further investigations in the context of SALUT, informedconsent was obtained at the outpatient visit in 2001–2002.

Questionnaires and BP measurements

The subjects completed a self-administered questionnaire regarding demographics, family history on hypertension, and the use of medication for hypertension, lifestyle factors (alcohol use, smoking, and physical activity). BP was measured twice for 10 minutes in supine position with an automatic Dinamap XL Model 9300 series device (Johnson and Johnson, Medical Inc., Arlington, TX). We defined hypertension as SBP ≥ 140 mm Hg and/or diastolic BP ≥ 90 mmHg and/or current antihypertensive treatment.

Anthropometric measurements and calculation ofobesity indices

Anthropometric measurements included measures on weight, height, waist, and hip circumference (centimeter). Minimum waist circumference was measured on bare skin at the natural indentation between the 10th rib and the iliac crest. Body mass index (BMI) was calculated as the ratio between weight (kilograms) and height (meters) squared, and waist-to-hip ratio (WHR) was calculated as the ratio between waist and hip circumference (assessed in centi- meter). A single frequency bioelectrical impedance analysis device (BIA 101, RJL systems, Akern SRL, Italy) was used to measure whole-body electrical impedance at 50 kHz between

the hand and the foot. The bioelectrical impedancemeasures obtained were used to estimate %BF (%BF = (bodyweight – fat free mass)/body weight)[9].

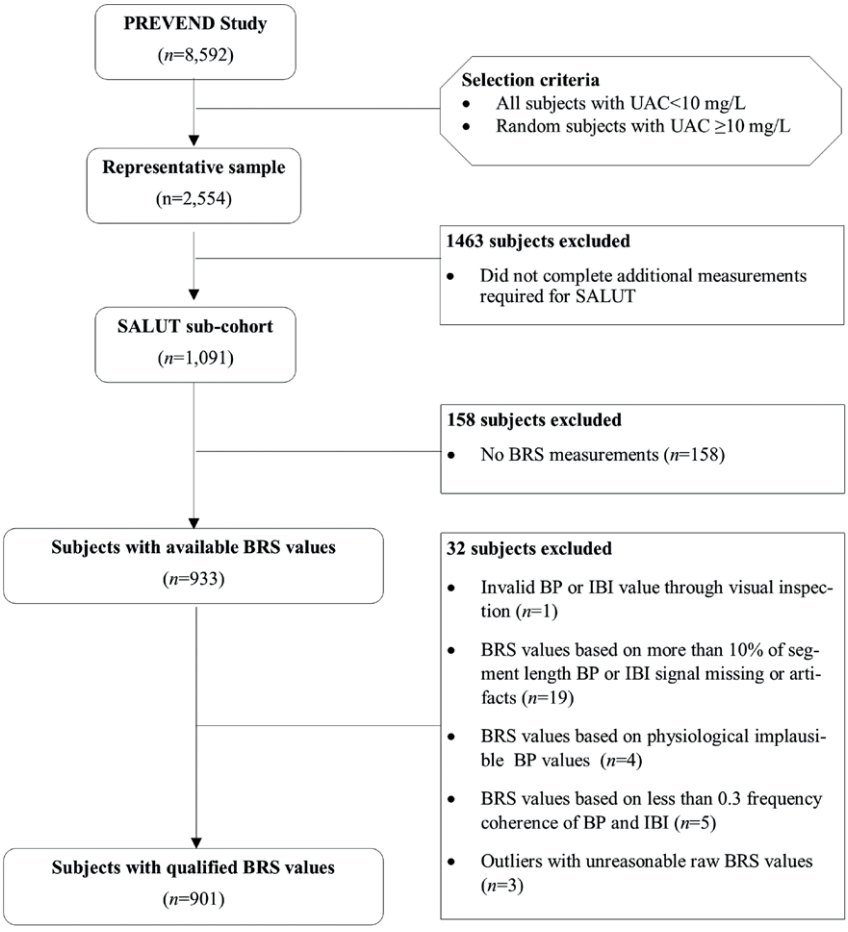

Figure 1: A schematic of how the study cohort was established. A representative sample of 2,554 subjects from the PREVEND study cohort (n = 8,592) were invited to participate in SALUT which aimed to examine the extent to which propensity to ill health of any kind is attributable to liability, susceptibility, or chains of risk models of morbidity accumulation. One thousand and ninety-one subjects finally participated in the SALUT subcohort study and 901 subjects were finally included into analysis (158 subjects without BRS measurements and 32 subjects with unqualified BRS values were excluded). Abbreviations: PREVEND, Prevention of REnal and Vascular ENd stage Disease; SALUT, Study of Allostatic Load as a Unifying Theme; BRS, baroreflex sensitivity; IBI, inter beat interval; BP, blood pressure; UAC, urinary albumin concentration.

BRS calculation

Subjects were in supine position in a quiet room and encouraged to relax and asked not to move or speak during data acquisition. A cuff was fixed around the middle phalanx of the third finger on the right hand, which was kept at heart level. The Portapres device (FMS Finapres Medical Systems BV)[10] continuously recorded spontaneous fluctuations in beat-to-beat finger BP for 10–15 minutes. The average block length used for BRS calculation was 278.9 (SD = 66.1) seconds. The CARSPAN spectral analysis program was used for BRS calculation[11]. This program allows for discrete Fourier transformation of nonequidistant SBP and IBI time series. The time series were corrected for artifacts and checked for stationarity. BRS was defined as the mean modulus between SBP and IBI in the 0.07–0.14 Hz frequency band for frequencies with a coherence of 0.3 or higher and expressed in ms/mm Hg, which was applied in our previous studies[12,13].

BRS quality control

Of the 933 subjects with BRS measurements, invalid values were rejected when adequate signal recording failed. Detected artifacts, such as outliers and missing values for continuous BP and heart rate, were corrected by means of linear interpolation of 4 data points surrounding the artifact. Visual inspection of BP and IBI signals yielded 932 valid values. After BRS calculation, the quality of the dataset was assured by exclusion of (i) BRS values that were based on more than 10% of segment length BP or IBI signal missing or artifacts (n = 19); (ii) BRS values that were based on physiological implausible BP values (n = 4); (iii) BRS values that were based on less than 0.3 frequency coherence of BP and IBI (n = 5); and (iv) outliers with unreasonable raw BRS values (n = 3). We obtained 901 measurements that met our quality criteria (Figure 1).

Statistical analyses

Distributions of all variables were checked for normality and transformed by natural logarithm when needed prior to analysis. For normally distributed variables mean and SD and for non-normally distributed variables median and interquartile range were provided to describe the distribution. For categorical data, we reported counts and frequencies.

These descriptive statistics were provided for men and women separately as sex differences in obesity indices and BRS have been reported[14,15]. A *t*-test, Mann–Whitney *U*-test, or Pearson's chi-square tests were used to test for group differences on continuous normally, non-normally distributed, and categorical variables, respectively. Since age and sex were well-known factors associated with BRS, for

illustrative purposes we plotted mean log-transformed BRS values and their 95% confidence intervals (CI) for men and women separately in 10-year age bins.

We calculated Spearman's correlations of BRS with age, sex, obesity indices, hypertension, lifestyle variables (i.e., current smoking, alcohol consumption and frequency of exercise). We classified effect size of correlations (*r*) as small if *r* was below 0.3, medium if *r* was between 0.3 and 0.5, and large if *r* was larger than 0.5[16]. Multivariable linear regression analyses were used to test for the effects of obesity indices and hypertension and their interactions with age, age^2, and sex on log-transformed BRS. We included age^2 into the multivariable regression model to allow for nonlinear effects of age on BRS[17]. We analyzed 6 models to test their associations with BRS: (i) model 1 (base model): age, age^2, sex, age × sex, age^2 × sex; (ii) model 1 plus the strongest correlated obesity index; (iii) model 2 plus age × obesity index, age^2 × obesity index, sex × obesity index; (iv) model 2 or 3 plus hypertension (depending on whether the interactions were significant or not); (v) model 4 plus age × hypertension, age^2 × hypertension, sex × hypertension; (vi) model 4 or 5 plus lifestyle variables (current smoking, alcohol consumption, frequency of exercise) (depending on whether the interactions from model 5 were significant or not). For the sake of interpretability, we converted effect sizes from the most parsimonious model, back to the raw BRS scale around the means of each of the continuous variables and for women and persons with hypertension regarding the categorical ones (see Supplementary Material).

All analyses were performed in SPSS 20 (SPSS Inc, Chicago, IL). *P*-values of <0.05 were considered statistically significant.

RESULTS

Subjects' characteristics

The median age of the study cohort (*n* = 901) was 52 years (ranging from 33 to 78); 411 (45.6%) subjects were men. The majority (98.0%) of the subjects were Caucasian with very few black (0.6%), Asian (0.7%), or other ethnicities (0.8%). Men had a higher SBP, diastolic BP, prevalence of hypertension, and a lower heart rate than women (Table 1). In addition, men more often drank alcohol, but they were not different from women on smoking behavior and frequency of physical exercise. There were no sex differences in BMI, but this was not true for the other obesity measures: men had larger waist circumference, higher WHR, and a lower %BF compared with women. The cardiovascular data obtained during supine rest

revealed that men had longer IBIs and higher BRS values compared with women. There were no sex differences in the use of antihypertension, lipid lowering, or antidiabetic medication. The subjects excluded from the analysis (n = 190) were similar on demographic characteristics compared with subjects included in the study: subjects had the same median age (both groups were 52 years old) and %BF (both were 31%) and similar proportions of men (50% vs. 46%) and prevalence of hypertension (27% vs. 23%).

BRS values in different age groups

Visual inspection showed that the log-transformed BRS values initially decreased steeply with older age. After the age of 70 years, they continued to decline with age in men, but in women, they became flat. Except for the 30–39 years age bin, women had lower mean BRS values in each age bin compared with men (Figure 2).

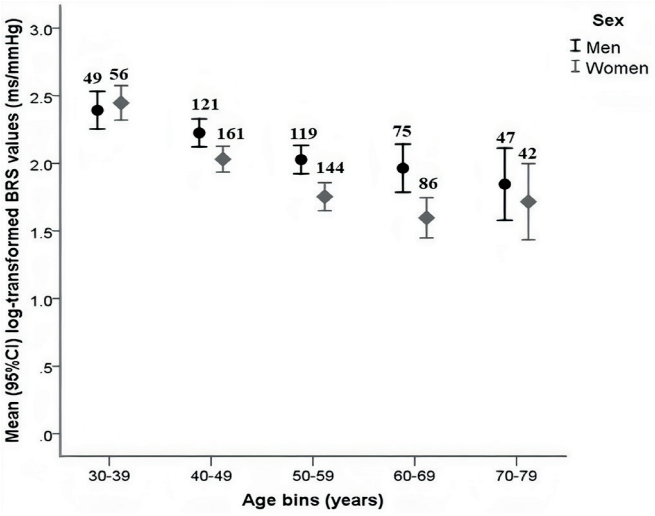

Figure 2: Mean log-transformed BRS values and 95% CI in the different 10-year age bins, for men and women separately. The black dots represented mean log-transformed BRS values in different age bins (10 years) of men, and green diamonds represented those for women. Error bars represented 95% CI. Number of male and female subjects among the different age bins was given on the top of each bar. The log- transformed BRS values initially decreased steeply with older age and continued to decline with age in men, but in women, they became flat after the age of 70. Abbreviations: BRS, baroreflex sensitivity; CI, confidence interval.

Table 1: *Characteristics of the study population*

	Men (*n* = 411)	**Women (*n* = 490)**	***P* value**
Age (in years)	52.0 [45.0–62.0]	51.0 [44.0–60.0]	n.s.
Race (*n*, %)			
Caucasian	402 [97.8]	477 [98.1]	n.s.
Black	1 [0.2]	4 [0.8]	
Asian	3 [0.7]	3 [0.6]	
Other	5 [1.2]	2 [0.4]	
Heart rate[a] (bpm)	66.0 [59.0–73.0]	69.0 [63.0–75.0]	<0.001
SBP[a] (mm Hg)	126.0 [116.0–135.0]	116.0 [108.0–129.0]	<0.001
DBP[a] (mm Hg)	75.0 [70.0–81.0]	69.0 [64.0–75.0]	<0.001
Hypertension (*n*, %)	107 [26.0]	98 [20.0]	0.019
Antihypertension medication (*n*, %)	51 [12.5]	56 [11.5]	n.s.
Lipid lowering medication (*n*, %)	36 [8.8]	31 [6.3]	n.s.
Antidiabetic medication (*n*, %)	10 [2.4]	4 [0.8]	n.s.
Obesity indices			
BMI (kg/m^2)	25.9 [23.9–28.2]	25.5 [23.4–28.9]	n.s.
Waist circumference (in cm)	95.0 [89.0–102.0]	85.0 [78.0–93.0]	<0.001
WHR	0.95 [0.91–0.99]	0.84 [0.80–0.88]	<0.001
%BF	26.5 [22.1–30.6]	35.8 [30.5–41.4]	<0.001
Spectral analysis measures			
IBI (ms)	901.3 [809.4–1016.1]	864.0 [783.8–961.0]	<0.001
BRS (ms/mm Hg)	7.9 [5.0–12.2]	6.6 [4.1–10.7]	<0.001
Lifestyle (*n*, %)			
Current smoker	108 [26.3]	106 [21.7]	
Ex-smoker	185 [45.1]	209 [42.7]	n.s.
Never smoked or stopped >10 years ago	117 [28.5]	174 [35.6]	
Alcohol			
Not/<1 drink per day	55 [13.4]	126 [25.8]	<0.001
1 or more drinks per day	354 [86.6]	363 [74.2]	
Frequency of exercise			
Not/hardly	53 [13.0]	43 [8.8]	
<1 time/week	43 [10.5]	48 [9.8]	n.s.
Twice or more/week	313 [76.5]	397 [81.4]	

Mean (SD) were given for normally distributed variables, median [25%–75% percentile] for non-normally distributed variables, and count [percentage] for categorical variables. Gender differences were tested, and P values given (t-test, Mann–Whitney U-test, or Pearson Chi-Squaretests were used). n.s., nonsignificant (P > 0.05). Abbreviations: BMI, body mass index; BRS, baroreflex sensitivity; DBP, diastolic blood pressure; SBP, systolic blood pressure; % BF, percentage body fat; IBI, interbeat interval; WHR, waist-to-hip ratio.

[a]Measured with an arm cuff device.

Correlations

Women (r = −0.12) and persons with hypertension (r = −0.20) had negative correlations with BRS compared with men and persons without hypertension, respectively. Additionally, BRS was also negatively correlated with age, BMI, waist circumference, and %BF. Age showed the highest negative correlation with BRS (r = −0.35), followed by %BF (r = −0.26), which was notably higher correlated than the other obesity indices (range between −0.05 and −0.17) (Table 2). Therefore, %BP was included into the multivariable regression model representing the effect of obesity. There was no evidence of association of BRS with WHR, currentsmoking, alcohol drinking, or physical exercise.

Table 2: *Spearman's correlations of BRS with age, sex,hypertension, obesity indices, and lifestyle variables*

	Correlation with BRS (95% CI)	*P*-value
Age	−0.35 (−0.41, −0.29)	<0.01
Sex (women)[a]	−0.12 (−0.18, −0.05)	<0.01
Hypertension[b]	−0.20 (−0.26, −0.14)	<0.01
BMI	−0.17 (−0.23, −0.11)	<0.01
Waist circumference	−0.14 (−0.20, −0.08)	<0.01
WHR	−0.05 (−0.11, 0.02)	n.s.
%BF	−0.26 (−0.32, −0.20)	<0.01
Current smoking	0.02 (−0.05, 0.09)	n.s.
Alcohol drinking	0.06 (−0.01, 0.12)	n.s.
Physical exercise	0.02 (−0.05, 0.09)	n.s

Abbreviations: BMI, body mass index; BRS, baroreflex sensitivity; %BF, percentage body fat; CI, confidence interval; WHR, waist-to-hip ratio. n.s., nonsignificant (P > 0.05).

[a]Men had higher BRS than women.

[b]Persons with hypertension had lower BRS than persons withouthypertension.

Multivariable analysis of log-transformed BRS

In all models, age, sex, %BF, and hypertension were independently associated with BRS irrespective of adjustment for other covariates (Table 3). None of the lifestyle variables contributed significantly. In addition, there was no evidence of association with the interactions, except age^2 × sex. The significant age^2 × sex interaction indicated that the BRS decrease with age was different between men and women; with a more linear decrease over the entire age range in men and a leveling off in women after age 70 years. This can also be seen when conducting regression analysis in men and women separately, which revealed the effect of age^2 with BRS in women (β = 0.0011, 95% CI: 0.0007 to 0.0015) but not in men (β = 0.0003, 95% CI: −0.0001 to 0.0007; further

details were given in Supplementary Tables 2 and 3). According to model 4 (including sex, age, age^2, their interactions, %BF, and hypertension), BRS decreased with −0.10 (95% CI: −0.15 to −0.06) ms/mm Hg with each year of increase in age, women had on average a −1.55 (95% CI: −2.28 to −0.73) ms/mm Hg lower mean BRS than men and the effects of %BF (per 10% increase) and hypertension were −0.55 (95% CI: −0.97 to −0.13) ms/mm Hg and −1.23 (95% CI: −1.92 to −0.46) ms/mm Hg, respectively.

Regarding the contributions to the percentage of variance explained in BRS, age, age^2, sex, and their interactions explained 15.2% of the individual differences in BRS. The inclusion of %BF, hypertension (also their interactions with age, age^2, and sex) and lifestyle factors explained only additional 0.1–0.9% of the BRS variance. However, no evidence of association to BRS was observed for those interactions and lifestyle factors.

DISCUSSION

Previous findings of experimental, clinical, and epidemiological studies reported on the association between low BRS and cardiovascular diseases and outlined potential determinants of BRS level[3–5]. However, most of these earlier studies suffered from small sample sizes, limited age ranges, and only investigated BMI representing obesity. In our large general population-based sample with a wide age range and sophisticated obesity indices, we extended on previous studies by characterizing associations of BRS with demographical, lifestyle, and clinical factors. We confirmed earlier reported negative correlations between BRS and age, sex, hypertension status, and obesity. Age and sex were the major factors associated with BRS. Even though %BF and hypertensive status were both independently associated with BRS, their contributions to the explained variance in BRS were quite small after adjusting for age and sex effects. For none of the lifestyle variables, which included smoking, alcohol consumption and physical exercise, evidence for association with BRS was found.

Age and sex together contributed most (15.2%) of the total explained variance of BRS. This finding was in line with earlier findings of Kardos and colleagues obtained in a cross-sectional study in a working population sample (18– 60 years, n = 1,134), where age contributed 21.3% and sex 1% to the explained variance of BRS[3]. The authors suggested that loss of arterial distensibility with age[18] and age-dependent reduction in M_2 muscarinic receptor density and function[19] might be responsible for reduction in BRS in older subjects.

Table 3: *Multivariable regression analysis predicting log-transformed BRS with age, sex, hypertension, %BF, and lifestyle variables*

Model	Determinant factors	β (SE)	95% CI of β	*P*-value of β	R^2 (%)	ΔR^2	*P*-value of the ΔR^2
1	Age Age^2	−0.0173 (0.0027)	(−0.0227, −0.0120)	<0.001			
	Sex (women)Age × Sex	0.0003 (0.0002)	(−0.0001, 0.0008)	n.s.			
	Age^2 × Sex	−0.2808 (0.0551)	(−0.3889, −0.1727)	<0.05			
		−0.0071 (0.0037)	(−0.0145, 0.0002)	n.s.	15.2	—	—
		0.0008 (0.0003)	(0.0002, 0.0014)	<0.05			
2	%BF	−0.0078 (0.0026)	(−0.0128, −0.0027)	<0.05	16.1	0.9	<0.01
3	Age × %BF	0.0003 (0.0002)	(−0.0001, 0.0007)	n.s.			
	Age^2 × %BFSex × %BF	0.0000 (0.0000)	(0.0000, 0.0000)	n.s.	16.3	0.2	n.s.
		0.0044 (0.0056)	(−0.0066, 0.0154)	n.s.			
4	Hypertension	−0.1586 (0.0519)	(−0.2605, −0.0567)	<0.05	16.9	0.8	<0.01
5	Age × Hypertension Age^2 ×	0.0071 (0.0060)	(−0.0046, 0.0188)	n.s.			
	Hypertension	0.0002 (0.0004)	(−0.0006, 0.0009)	n.s.	17.4	0.5	n.s.
	Sex × Hypertension	0.1153 (0.1030)	(−0.0868, 0.3175)	n.s.			
6	Current smoking	0.0265 (0.0274)	(−0.0273, 0.0803)	n.s.			
	Alcohol drinking	0.0069 (0.0511)	(−0.0935, 0.1073)	n.s.	17.0	0.1	n.s.
	Physical exercise	−0.0036 (0.0312)	(−0.0648, 0.0576)	n.s.			

The variables of age and %BF were centered by subtracting the mean from their original values before being included into the regressionmodel.
Model 2 = Model 1 + %BF.
Model 3 = Model 2 + interactions of age, age^2, and sex with %BF.
Model 4 = Model 2 + hypertension, because the interactions from model 3 were not significant.
Model 5 = Model 4 + interactions of age, age2, and sex with hypertension.
Model 6 = Model 4 + lifestyle factors, because the interactions from model 5 were not significant.
Model 2 was compared with Model 1; Model 3 was compared with Model 2; Model 4 was compared with Model 2; Model 5 was compared with Model 4; Model 6 was compared with Model 4.
ΔR^2 is the difference in R^2 compared with the reference models as indicated above. Abbreviations: BRS, baroreflex sensitivity; %BF, percentage body fat; n.s., nonsignificant ($P > 0.05$).

In addition, aging might contribute to reducing BRS through nominal changes in peripheral nervous pathways, central nervous control of the baroreflex system, and sinus node function[20]. In our study, we observed that BRS values decreased with older age and that BRS values were higher in men compared with women after the age of 40 years. For men, the observed pattern with age was similar to the earlier findings from Kardos *et al*. who reported a linearly decreasing course with age. In women, BRS seemed to decrease more steeply with age until 70 years of age and became flat afterwards. The outlined reasons above could also explain the tendency of BRS being lower at older ages. The mechanism responsible for the lower BRS in women and the flattening at higher age was not known, potentially sex hormones play a role[15].

We investigated the correlations of BRS with various obesity indices, including %BF, BMI, WHR, and waist circumference. We found that except for WHR, other obesity indices, including BMI (r = −0.17, 95% CI: −0.23 to −0.11), waist circumference (r = −0.14, 95% CI: −0.20 to −0.08), and %BF (r = −0.26, 95% CI: −0.32 to −0.20), were all correlated with BRS. Among these, the latter effect of %BF was notably higher. These findings were in line with those reported before (18–40 years, n = 223)[4] where the association of BRS with body fat mass index (BFMI = body fat/height^2, r = −0.239) was higher than waist circumference (r = −0.137) or WHR (r = −0.150) in pre-obese subjects[4]. Although BMI was a widely used obesity index, it lacked the capability of discriminating between body fat and lean mass[21]. %BF, on the contrary, was a specific measure of a person's amount of adipose tissue unconfounded by lean muscle mass. This was important as body fat may directly affect baroreceptor reflex regulation through activation of the renin–angiotensin–aldosterone system and sympathetic nervous system eventually leading to hypertension[22]. However, we must acknowledge that even though we used %BF as the variable representing obesity, its additional contribution to the explained variance of BRS was fairly small (<1%), which was in line with previous reports[3]. Hypertension was another factor that was proved to be negatively associated with BRS in our study, replicating the results of earlier studies[6,23]. However, like %BF, its contribution to explain the total variance of BRS was very small (<1%). In our study, we did not find any significant associations between BRS and lifestyle variables. Similar to us, Kardos *et al*. also did not find any associations of BRS with physical activity or alcohol consumption. However, they did report that BRS was significantly associated with smoking, but its contribution was negligible (r^2 = 0.4%)[3].

Our study had several strengths: (i) our data were collected from a representative population-based study with large sample size and a wide age range (33–77 years old), which yielded robust and generalizable results; (ii) to get accurate estimations/ interpretations, we designed a stepwise analysis strategy, in which we included valid obesity indices, considered interaction effects with age, age^2, and sex, and for interpretation back-transformed the results to raw BRS values. However, a limitation of our study was the cross-sectional design. Such a design did not allow interpretation of the results in a life-course context, which should be acknowledged when interpreting the role of factors contributing to explanation of the variance of the BRS. A longitudinal design, with repeated BRS assessments over the life course, would have been superior. Another limitation was that the supine continuous BP and IBI measurements in our study may make our findings less comparable to other studies where BRS was assessed in sitting posture. Third,

the majority of the subjects in our study were Caucasian; therefore, our results cannot be generalized to other ethnic groups.

To conclude, our findings from a representative population-based study with large sample size and a wide age range confirmed prior findings of associations between lower BRS and cardiovascular risk factors, such as obesity, and hypertension, which supported the physiological fundamental mechanism underlying them. However, the stronger relationships between age and sex with BRS pointed to the importance of taking into account the contributions of demographic factors to BRS when considering its relationships with cardiovascular risk.

Supplementary materials

Supplementary data are available at American Journal of Hypertension online.

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