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CHAPTER 2

Cross-correlation baroreflex sensitivity and its association with cardiovascular risk in a large multi-ethnic population

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ABSTRACT

Baroreflex sensitivity (BRS) denotes the change in heart beat intervals in response to a blood pressure change and has been established as an important determinant of the sympatho-vagal balance. Potentially it could serve as a integrated cardiovascular risk factor. In this study, we present an automated xBRS analysis method for large datasets. We verify the method and explore the associations between BRS, cardiovascular risk factors and cardio-metabolic risk using baseline data from 13,375 participants of the HELIUS study which is currently performed in the city of Amsterdam.

Cross-correlation BRS was determined in all available 13,375 continuous finger artery blood pressure recordings. All analyses and data selection procedures were performed using purpose build Matlab and Java scripts, available as supplementary materials. 5,926 BRS calculations could be considered reliable.

Automated BRS analysis was successful. Compared to healthy participants at an average age of 44.3 years, BRS is progressively decreased with increasing cardio-metabolic burden up to -7.8 mmHg/ms ($p<0.001$). Thereby corresponding to the average BRS of a 70 year old person. This relation is also present when stratified for 10 year cardiovascular risk.

This study, shows that automated analysis of BRS is feasible and reliable and might be used as a single integrative factor to assess the cardio-metabolic “age” in large populations. Longitudinal studies will have to provide evidence whether BRS is of individual prognostic value, the follow-up of the HELIUS study will provide us with that opportunity.

INTRODUCTION

Baroreflex sensitivity (BRS) denotes the change in heart beat intervals in response to a change in arterial blood pressure. BRS has been established as an important determinant of the sympatho-vagal balance of the cardiovascular system.[1] In a series of studies, BRS has been shown to be a clinically relevant and independent predictor for outcome in subjects with cardiovascular disease, hypertension, metabolic syndrome and obesity.[2-9] This wide range in applicability indicates a potential as an integrative risk factor for patients with cardiovascular disease.[1,10]

Thus far, measurement of BRS in large populations have been complicated by the invasive nature of directs methods and the labor intensive post-processing of acquired data of indirect methods. Of all available measurement techniques, spontaneous BRS computation appears to be the preferred modality for a large-scale population study, as it can be derived from non-invasive continuous arterial blood pressure recordings. One of the available methods of spontaneous BRS measurements is the cross-correlation BRS-algorithm (xBRS). xBRS provides a validated time-domain, cross-correlation baroreflex calculation on spontaneous systolic pressure and R–R interval variability using a 10 second sliding window.[11] Compared to other methods of spontaneous BRS assessment, xBRS shows less scatter within subjects and the algorithm is able to deal with situations in which changes in R–R interval lag behind pressure changes – in the elderly and at high heart rates.[12] The method has also proved its validity in subjects with low interval variability.[11,12] Since its introduction, the xBRS-algorithm has been applied in selected patient groups including fertile women, syncope patients and during exercise in healthy subjects.[13-16]

In this study, we present a novel automated xBRS analysis method and aimed to apply this to a large dataset of continuous non-invasive finger arterial blood pressure recordings. In order to verify the method we aimed to identify associations of xBRS to its known predictors.[17,18] For this purpose, we used baseline continuous non-invasive finger arterial blood pressure recordings from the Healthy Life in an Urban Setting (HELIUS) study, an ongoing large multi-ethnic cohort study among 30,000 participants in Amsterdam, The Netherlands.[19] In addition, we explored the associations between BRS, cardiovascular risk factors and cardiometabolic risk.

METHODS

Participants

The HELIUS study is an ongoing prospective cohort study in subjects aged 18-70 years using a stratification based on ethnicity (Afro-Caribbean Surinamese, South-Asian Surinamese, Turkish, Moroccan, Ghanaian, and ethnic Dutch) who are randomly sampled from the municipality registry of the city of Amsterdam. The primary objective of HELIUS is to assess ethnic inequalities in the risk factors for cardiovascular, psychiatric and infectious diseases. Details on this project have been outlined elsewhere.[19] Inclusion started in January 2011. For each participant, data were collected through questionnaires, standardized physical examination and blood and urine analyses. All blood pressure measurements complied with international standards.[20]

In a subsample of 13,375 participants, a five minute non-invasive continuous finger arterial blood pressure recording (Nexfin, Edwards Life Sciences/BMEYE, Amsterdam, the Netherlands) was taken. Recordings were carried out in supine position, after 10 minutes of supine rest. The finger cuff was placed around the middle phalanx of the middle finger of the left hand, unless scare tissue was present, the finger was deformed or had previously been broken, then the left ring or index finger was chosen before considering the right hand. When the device's internal calibration function reached a stable level (i.e. > 30 beats) the recording was considered suitable for further analysis.

Hypertension was defined as a systolic blood pressure ≥140 mmHg and/or a diastolic blood pressure ≥90 mmHg and/or the use of any anti-hypertensive medication. Diabetes Mellitus was defined as a fasting glucose ≥7 mmol/l and/or the use of any glucose lowering medication. Obesity was defined as a BMI ≥ 25 kg/m^2. The HELIUS study was approved by the local medical ethics committee and informed consent was obtained before study enrolment.

Baroreflex sensitivity

xBRS was determined in all continuous blood pressure recordings using WinXBRS 2 (Edwards Lifesciences/BMEYE, Amsterdam, The Netherlands). All analyses and data selection procedures were performed using purpose build Matlab and Java scripts (MathWorks, Natick, MA, USA, respectively Eclipse Foundation, Ottawa, Ontario, Canada), available as supplementary materials to this paper. Participant characteristics and all output of the data-analysis (including data quality parameters, hemodynamic variables and xBRS results) were stored into a single database that was then merged participant wise to the HELIUS cohort data for further analysis. Afterwards, we selected participants with a reliable xBRS calculation based on the following manufacturer's recommendations: the signal had to be stable signal with calibration signals (physiocal) at least 30 beats apart (physiocal interval) and for a period of at least

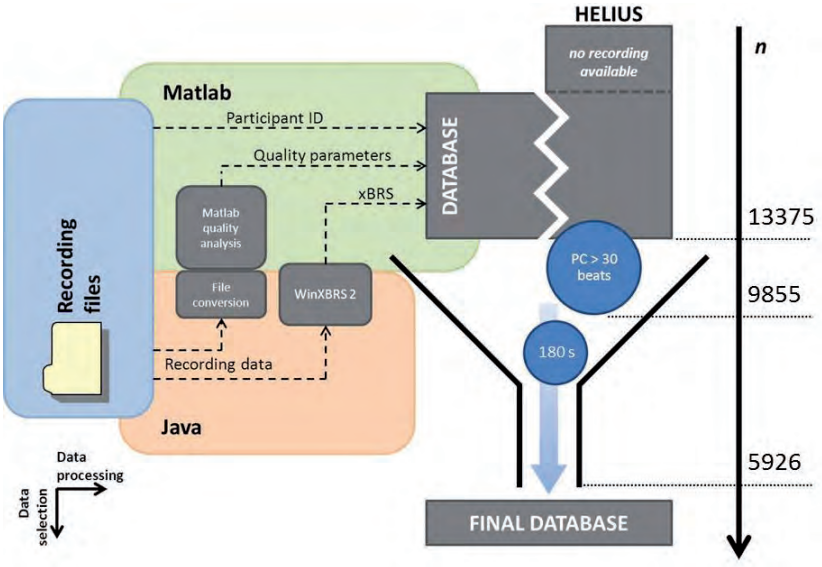

Figure 1. Diagram of the data processing (left to right) and data selection (top to bottom) process leading to a final database of 5,926 participants selected solely on the quality of the continuous blood pressure recording. Abbreviations: xBRS – cross-correlation baroreflex sensitivity; PC – physiocal interval.

180 s.[21] Applying these quality settings excluded 7,449 recordings, resulting in 5,926 eligible records for further analysis. Figure 1 summarizes the data processing and selection process. The algorithm for automated xBRS analysis is freely available as a supplement to this paper, please see http://hyper.ahajournals.org.

Statistical analysis

To verify a random selection, we compared the demographic characteristics of the study population to the complete HELIUS population using chi-squared tests. Secondly, we assessed the differences in xBRS-value and the associations between xBRS and its known determinants, age, gender, body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate (HR),[17] in the complete xBRS cohort and the separate ethnic groups consisting of participants of the various ethnic descents ancestry. We calculated the interclass correlation coefficient (ICC) for xBRS between ethnic groups to determine ethnic variance in xBRS. An ICC >0.15 is considered to indicate between-group variations. Univariate and multivariate linear regression analysis was used to assess the associations of xBRS to its determinants. Finally, we explored the associations between BRS, cardiovascular risk and cardio-metabolic impairment in the multi-ethnic population. Univariate and multivariate linear regression analysis was used to assess the associations of xBRS to cardiovascular risk factors. Also, we stratified xBRS over age for metabolic impairment, cardiovascular risk. The cardio-metabolic strata were: no impairment, obesity, obesity plus hypertension, obesity

plus hypertension and diabetes mellitus. For the CVD risk strata we calculated the Framingham score for each participant and defined groups with a score of 0-10%, 10-20% and >20% risk. The effects of disease burden and CVD risk on xBRS independent of age were analyzed using multiple linear regression analysis with age, separate disease or CVD risk strata and the interactions of the strata with age as predictors. For this analysis age was centered to the mean. Skewed data were normalized by log transformation before statistical testing. Data are presented as mean ± SD unless otherwise denoted. All statistical analyses were performed using SSPS Statistics 23 (IBM, Armonk, NY).

RESULTS

Table 1 lists the baseline characteristics per step in the xBRS data quality selection. Data selection affected several parameters. Participants with valid xBRS results were more frequently male, were more frequently hypertensive and had a higher incidence of diabetes. Overall the differences are minor, suggesting a random sampling of the total cohort. The mean xBRS value was 11.45 ± 6,98 ms/mmHg. The ICC between the groups was 0.0065, within group variance was 112.58, between group variance was 0.89. One-way analysis of variance showed no differences in xBRS values between ethnic groups F=0.18, p = 0.67.

Associations of xBRS its determinants

Univariate linear regression between xBRS and age, sex, BMI, systolic blood pressure (SBP),diastolic blood pressure (DBP) heart rate (HR) and ethnicity are shown in Table 2. In a multivariate linear regression model (Table 3), each variable retained its predictive value except for sex and SBP.

Univariate linear regression analysis of each ethnic subgroup separately revealed similar associations between the xBRS and its predictors across all groups (Table 4). In Dutch, Ghanaian and Moroccans, sex correlated significantly with xBRS (p-values of <0.001, 0004 and 0.002 respectively) while this association was not apparent in subjects of Surinamese and Turkish descent (p-values of 0.52 and 0.17 respectively). Independent of ethnicity, age remained the predictor with the strongest association to xBRS (β -0.54, R^2 0.29, p = <0.001).

Relations between xBRS, risk factors for CVD and metabolic disease

Univariate regression analysis showed that smoking status, Diabetes Mellitus, total cholesterol, HDL cholesterol and eGFR (CKDEPI) are all associated with xBRS (Table 2). In the overall multivariate model, only eGFR, HDL and total cholesterol were independently associated with xBRS (Table 3). This model explained 21% of the variation in xBRS.

Table 1. Baseline characteristics of the HELIUS cohort, participant with and without reliable xBRS calculation compared. Data presented as percentage of total or mean with standard deviation.

	All		**PI ≥30 beats**		**PI ≥30 beats & ≥180 s**		X^2 **test p-value**
	Mean	SD	Mean	SD	Mean	SD	
n	13375		9855		5926		
Age (years)	44	13	44	13	44	13	0.206
Male/female (%)	42/58		45/55		49/51		<0.001
Ethnicity (%)							<0.001
Ethnic Dutch	19.8		18.8		17.1		
South-Asian Surinamese	14.9		15.3		13.6		
Afro-Caribbean Surinamese	20.7		19.1		17.7		
Ghanaian	13.3		12.8		11.4		
Turkish	14.5		16.4		18.8		
Moroccan	15.1		15.9		19.7		
BMI (kg/m^2)	27.1	5.3	27.5	5.3	28.0	5.3	<0.001
SBP (mmHg)	128	18	128	18	129	17	<0.001
DBP (mmHg)	79	11	79	11	80	11	<0.001
HR (bpm)	69	10	69	10	70	10	<0.001
Pack Years	6.1	15.7	6.2	15.7	6.6	16.8	<0.001
Hypertension prevalence (%)	33.9		34.8		35.3		<0.001
Diabetes prevalence (%)	12.9		13.9		14.9		<0.001
CVA self-reported (%)	5.1		5		5		0.063
MI self-reported (%)	11		11.3		11.2		0.46
Total cholesterol (mmol/L)	4.9	1.0	4.9	1.0	4.9	1.0	0.19
Plasma creatinine (µmol/L)	73.6	21.3	73.8	19.3	73.3	18.2	0.068
Diabetes medication (%)	7.4		7.9		8.5		<0.001
Anti lipaemics (%)	10		10.5		11		0.002
Diuretics (%)	3		3.2		3		0.82
B-blockers (%)	6.3		6.3		6.3		0.91
Calcium antagonists (%)	6.7		6.6		6.3		0.175
RAAS inhibition (%)	11		11		10.9		0.76
Framingham score (%)	8.8	5.9	9.05	5.9	9.2	5.9	<0.001

BMI – body mass index; SBP – systolic blood pressure; DBP – diastolic blood pressure; HR – heart rate; CVA – cerebral vascular accident; MI – myocardial infarction; RAAS – renin angiotensin aldosterone system

Figure 2 shows the xBRS decline over age, stratified for cardio-metabolic burden (Fig. 2A) or CVD risk (Fig 2B) in the multi-ethnic cohort. Compared to healthy participants at an average age of 44.3 years, xBRS in obesity is reduced by 2.6 mmHg/ms ($p << 0.001$). When combined

Table 2. Univariate linear regression analysis

	Standardized β	R^2	p-value
Age	-0.50	0.25	<0.001
Sex	0.065	0.004	<0.001
BMI	-0.27	0.071	<0.001
W-H ratio	-0.28	0.076	<0.001
SBP	-0.35	0.12	<0.001
DBP	-0.37	0.14	<0.001
HR	-0.25	0.062	<0.001
Smoking status	-0.048	0.002	<0.001
DM	-0.26	0.068	<0.001
Total Chol	-0.20	0.040	<0.001
HDL	0.11	0.012	<0.001
eGFR (CKDEPI)	0.24	0.059	<0.001
Ethnicity	-0.14	<0.001	0.30

BMI – body mass index; W-H ratio – waist to hip ratio; SBP – systolic blood pressure; DBP – diastolic blood pressure; HR – heart rate; DM – diabetes mellitus; Total chol – total cholesterol; HDL – high density lipoprotein

with hypertension, xBRS is further reduced by -5.3 mmHg/ms (p <<0.001). When obesity, hypertension and diabetes mellitus are combined, xBRS is decreased by 7.8 mmHg/ms (p <<0.001). A similar relation is visible with increasing CVD risk (Fig. 2B). Compared to <10% 10

Table 3 Multivariate linear regression analysis of xBRS

	Coefficient	SE	p-value
Intercept	60.3	1.8	<0.001
Age	-0.34	0.01	<0.001
Sex	0.003	0.25	1.0
BMI	-0.087	0.022	<0.001
W-H ratio	-4.33	1.64	0.008
SBP	0.004	0.009	0.64
DBP	-0.11	0.015	<0.001
HR	-0.20	0.010	<0.001
Smoking status	0.12	0.14	0.40
DM	0.365	0.31	0.24
Total Chol	-0.39	0.10	<0.001
HDL	-0.94	0.26	<0.001
eGFR	-0.039	0.007	<0.001

BMI – body mass index; W-H ratio – waist to hip ratio; SBP – systolic blood pressure; DBP – diastolic blood pressure; HR – heart rate; DM – diabetes mellitus; Total chol – total cholesterol; HDL – high density lipoprotein

Table 4 Univariate linear regression analysis of xBRS per ethnic group

	Ethnic Dutch			South-Asian Surinamese			Afro-Caribbean Surinamese			Ghanaian			Turkish			Moroccan		
	β	R^2	p	β	R^2	p	β	R^2	p	β	R^2	p	β	R^2	p	β	R^2	p
Age	-0.54	0.29	<0.001	-0.45	0.20	<0.001	-0.46	0.21	<0.001	-0.50	0.25	<0.001	-0.57	0.33	<0.001	-0.52	0.27	<0.001
Sex	0.12	0.014	<0.001	0.024	0.001	0.52	0.019	0.001	0.53	0.11	0.011	0.004	0.042	0.001	0.17	0.089	0.007	0.002
BMI	-0.27	0.075	<0.001	-0.20	0.04	<0.001	-0.20	0.038	<0.001	-0.16	0.024	<0.001	-0.37	0.13	<0.001	-0.32	0.099	<0.001
SBP	-0.35	0.12	<0.001	-0.33	0.11	<0.001	-0.33	0.11	<0.001	-0.37	0.14	<0.001	-0.37	0.14	<0.001	-0.37	0.13	<0.001
DBP	-0.37	0.14	<0.001	-0.31	0.097	<0.001	-0.36	0.13	<0.001	-0.42	0.18	<0.001	-0.40	0.16	<0.001	-0.39	0.15	<0.001
HR	-0.29	0.082	<0.001	-0.22	0.047	<0.001	-0.28	0.079	<0.001	-0.25	0.06	<0.001	-0.23	0.052	<0.001	-0.20	0.039	<0.001

BMI – body mass index; W-H ratio – waist to hip ratio; SBP – systolic blood pressure; DBP – diastolic blood pressure; HR – heart rate

year CVD risk, a risk increase to 10 to 20% decreases xBRS by 3.7 mmHg/ms (p <<0.001) on average and a risk increase to >20% reduces xBRS by 5.9 mmHg/ms (p <<0.001).

DISCUSSION

In this study we present BRS analysis in a large-scale multi-ethnic cohort study by introducing an automated xBRS analysis method for large datasets. We applied this method to continuous blood pressure recordings in a population with a wide age range and different ethnic groups. The method provided BRS data showing similar predictive value compared

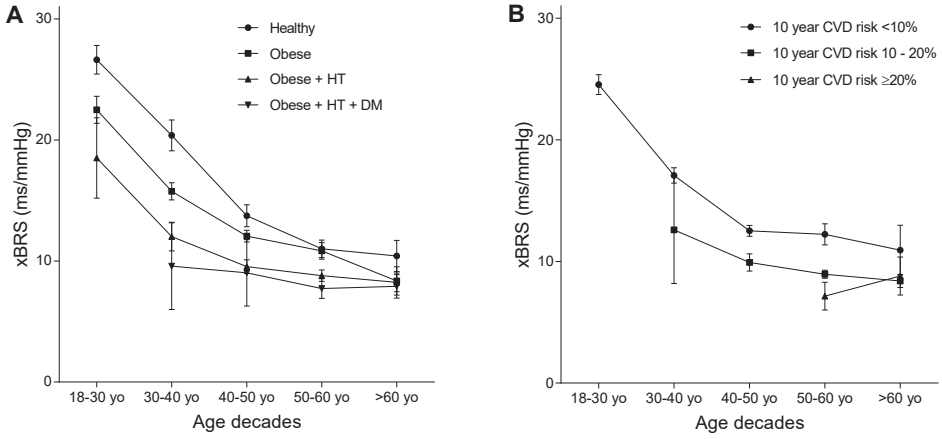

Figure 2. xBRS per age decade stratified to cardio-metabolic burden (A) and cardiovascular risk (B). Data presented as mean xBRS with 95% confidence interval. Abbreviations: HT – hypertension; DM – diabetes mellitus; CVD – cardiovascular disease; yo – years old; xBRS – cross-correlation baroreflex sensitivity

to previously published data and across different ethnic groups. In addition, we found that there is an age-independent association between BRS and cardiovascular risk.

Previously, spontaneous BRS analyses including the xBRS method have been applied in smaller healthy cohorts. Our findings are in line with the findings by Borgers *et al* using the xBRS algorithm in a small random population sample.[17] Using the same determinants they found xBRS to be predicted mainly by age, blood pressure, HR and BMI. The largest study was performed by Kardos et al., involving 1100 healthy Caucasian men and women.[18] The investigators used the sequential BRS (sBRS) method, which correlates closely to xBRS.[11] In this study, BRS showed to follow a decreasing course with increasing age, which was limited to a value between 5 and 10 ms/mmHg in subjects that were over 60 years of age.

We did not find a difference in BRS between ethnic groups nor were there any significant differences in the main determinants of BRS across ethnic groups. This is in contrast to previous studies that showed impaired baroreflex control and decreased BRS in African Americans.[22-24] One British study, comparing BRS in Caucasians and South Asians found no differences between the groups.[25] Even though these were smaller studies including no more than 170 participants – making their generalizability debatable – it surprised us not to find any ethnic predispositions for an increased or decreased BRS. We merely find differences in predictor relations, as sex was not associated to BRS in the Surinamese and Turkish groups for instance. However, there may exist geographical discrepancies in ethnic differences in BRS, making comparisons between the US and European populations difficult. Therefore, we can only conclude the absence of ethnic differences in BRS in The Netherlands and possibly Europe.

The clinical and prognostic value of BRS has been extensively investigated in both cardiovascular and metabolic disease.[3-9] Next to myocardial infarction (MI) and during heart failure, BRS impairment has been associated with impaired left ventricular ejection fraction (LVEF) [26-29]. Moreover, the ATRAMI trial showed an increased 2 year mortality among MI patients (LVEF <35%) with a BRS below 3 ms/mmHg compared to those with a preserved BRS (relative risk 9 vs 2%).[5] However, data in large relatively healthy populations are lacking.[1] Therefore, we investigated the associations between xBRS, cardiovascular risk factors and cardio-metabolic impairment. We found that BRS associated negatively to smoking status, Diabetes Mellitus and total cholesterol levels, while there was a positive association with HDL cholesterol levels and eGFR. In multivariate analysis, only eGFR, HDL and total cholesterol remained significantly associated. Analyses of BRS over age, stratified for cardio-metabolic burden or cardiovascular risk showed that hypertensive and obese diabetics younger than 40 years of age, have an average BRS similar to that of a 60 to 70 year old person. Similarly this is observed in CVD risk, where a 10 year CVD risk of >20% at a young age resulted in an

average BRS as low as that of elderly individuals. This suggests that BRS may be a valuable and easy to measure single integrative variable for cardio-metabolic "age" in large populations. However, its value in individual risk assessment can only be assessed in prognostic studies. Future follow-up data from the HELIUS will provide us with that opportunity.

Limitations

Limitations that merit discussion include, our stringent data quality assessment, which excluded 7,449 out of 13,375 BRS measurements. This was due to the fact that the available blood pressure recordings were relatively short, no longer than six minutes, leaving minimal time to allow the signal to reach adequate stability. In addition, devices for continuous finger artery blood pressure measurements provide a more stable signal when measurements are performed on fingers with larger circumference. Thus, as our quality assessment selected out unstable recordings, it indirectly selected for males and subjects with larger postures. This problem is inherent to the used technique and has been faced by any study using these devices.

Secondly, the HELIUS cohort was set-up to investigate ethnic discrepancies in disease and disease risk. Therefore, the cohort does not reflect the local ethnic distribution. However, as there were no apparent ethnic differences in xBRS and univariate regression analysis showed only negligible shifts in coefficients of proportion to one another, our further analyses considered the complete cohort as a whole.

Lastly, the detailed analyses contain certain highly specified subgroups, which leave relatively small group sizes (e.g. n=19 in the stratum: hypertensive and obese and diabetic between 20 and 30 years of age). However, as all strata were formed adhering to the same stratification rules this does not interfere with the integrity of the data.

On a more general note, researchers are often restricted to the use of software supplied by manufacturers for data analysis and/or conversion of the data files to other formats. More often than not, such software was not designed with research purposes in mind. For this study this was not any different, as for data viewing and conversion Nexfin@PC had to be used and xBRS analysis was run in a separate program WinXBRS 2. Both software packages did not support batch analysis and analysis demanded switching between programs. To circumnavigate these problems, we found a workaround using simulated and timed keypresses programmed in Java scripts, coordinated by a central algorithm in Matlab. Although this is not the most elegant solution, it worked and may be useful for batch-analysis problems in other data. The necessary algorithms for automated xBRS analysis are supplied as supplementary material to this paper, accompanied by set-up instructions.

PERSPECTIVES

In our study, we found that xBRS might be used as a single integrative factor to assess the cardio-metabolic "age" in large populations. Our study showed clear correlations between BRS, traditional cardiovascular risk factors, cardio-metabolic burden and CVD risk. Our findings are in line with previous data and provide additional insight into the BRS distribution in the general population. In contrast to previous studies, we did not find clear ethnic differences in BRS. Thus, longitudinal studies will have to provide evidence whether BRS is of individual prognostic value, the follow-up of the HELIUS study will provide us with that opportunity.

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