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Abstract—The ambulatory arterial stiffness index (AASI) is derived from 24-hour ambulatory blood pressure recordings. We investigated whether the goodness-of-fit of the AASI regression line in individual subjects (r^2) impacts on the association of AASI with established determinants of the relation between diastolic and systolic blood pressures. We constructed the International Database on the Ambulatory Blood Pressure in Relation to Cardiovascular Outcomes (7604 participants from 6 countries). AASI was unity minus the regression slope of diastolic on systolic blood pressure in individual 24-hour ambulatory recordings. AASI correlated positively with age and 24-hour mean arterial pressure and negatively with body height and 24-hour heart rate. The single correlation coefficients and the mutually adjusted partial regression coefficients of AASI with age, height, 24-hour mean pressure, and 24-hour heart rate increased from the lowest to the highest quartile of r^2. These findings were consistent in dippers and nondippers (night:day ratio of systolic pressure $\geq$0.90), women and men, and in Europeans, Asians, and South Americans. The cumulative z score for the association of AASI with these determinants of the relation between diastolic and systolic blood pressures increased curvilinearly with r^2, with most of the improvement in the association occurring above the 20th percentile of r^2 (0.36). In conclusion, a better fit of the AASI regression line enhances the statistical power of analyses involving AASI as marker of arterial stiffness. An r^2 value of 0.36 might be a threshold in sensitivity analyses to improve the stratification of cardiovascular risk. **(*Hypertension*. 2008;52:1038-1044.)**

Key Words: ambulatory arterial stiffness index ■ arterial stiffness ■ blood pressure measurement/monitoring ■ epidemiology ■ population science ■ statistical analysis

In 1914, MacWilliam and Melvin[1] already noticed that loss of elasticity in the arterial system impacted on the relation of diastolic with systolic pressure. We recently defined the ambulatory arterial stiffness index (AASI) as unity minus the regression slope of diastolic on systolic blood pressure in individual 24-hour ambulatory blood pressure recordings.[2,3] The stiffer the arterial tree, the closer the regression slope and AASI are to 0 and 1, respectively. We validated AASI against other markers of arterial stiffness, such as the systolic augmentation index and aortic pulse wave velocity.[2]

In spite of the prognostic accuracy of AASI over and beyond classical risk factors, including pulse pressure[3–5] and pulse wave velocity,[6] some researchers criticized AASI. It would be a surrogate marker of arterial stiffness not different from pulse pressure.[7] Schillaci et al[8] reported that AASI decreased with less nocturnal dipping in blood pressure. Gavish et al[9] suggested that symmetrical regression might provide a better estimate of AASI less affected by the nocturnal blood pressure fall and the goodness-of-fit of the regression slope, as expressed by the coefficient of determi-

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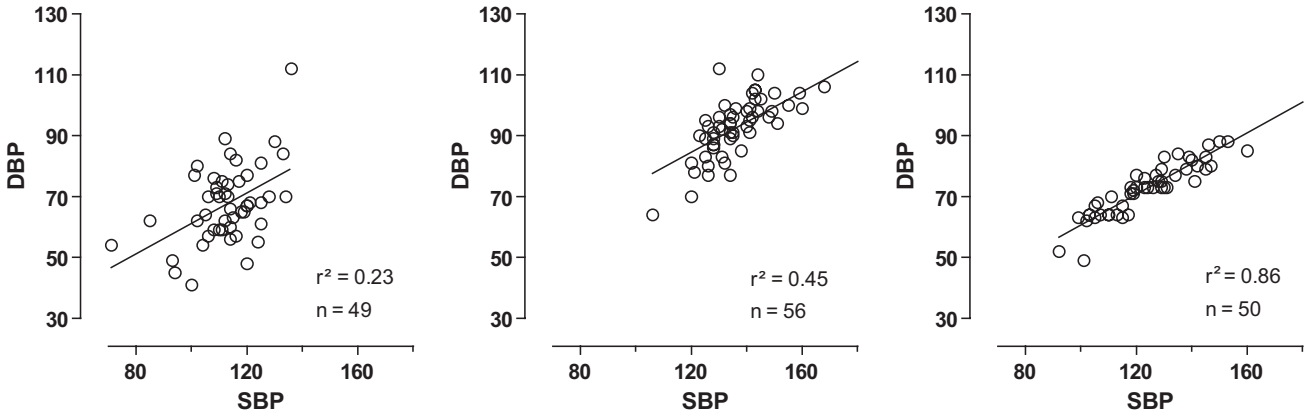

Figure 1. Relation between diastolic (DBP) and systolic blood pressures (SBP) in 3 different subjects with a nearly similar number of ambulatory blood pressure readings (range: 49 to 56), the same regression slope (0.50), and the same value of AASI (0.50). The r^2 expresses the goodness-of-fit of the regression line.

nation (r^2). To clarify these issues, we analyzed the International Database on the Ambulatory Blood Pressure Monitoring in Relation to Cardiovascular Outcomes.[10] We investigated whether r^2 affects the association of AASI with established determinants of the relation between diastolic and systolic blood pressures, including age, body height, heart rate, and mean arterial pressure.[2] We evaluated the consistency of the determinants of AASI in dippers and nondippers, women and men, and across different ethnic groups.

Methods

Study Population

Previous publications (for details, see the expanded Methods in the online data supplement, available at http://hyper.ahajournals.org) described the construction of the International Database on the Ambulatory Blood Pressure Monitoring in Relation to Cardiovascular Outcomes.[10,11] All of the included studies received ethical approval.[12–17] The current analysis incorporates the baseline data of 2138 residents from Copenhagen, Denmark[14]; 1127 subjects from Noorderkempen, Belgium[12]; 1100 older men from Uppsala, Sweden[15]; 1520 inhabitants from Ohasama, Japan[13]; 349 villagers from the JingNing county, China[16]; and 1370 subjects from Montevideo, Uruguay.[17] All 7604 subjects were ≥18 years old, gave informed written consent, and had ≥30 daytime and ≥5 nighttime blood pressure readings.

Blood Pressure Measurement

We programmed portable monitors to obtain ambulatory blood pressure readings at 30-minute intervals throughout the whole day,[13] or at intervals ranging from 15[14] to 30[15] minutes during daytime and from 30[14] to 60[15] minutes at night. The devices implemented an auscultatory algorithm (Accutracker II) in Uppsala[15] or an oscillometric technique (SpaceLabs 90202 and 90207, Nippon Colin, and ABPM-630) in the other cohorts.[12–14,16,17]

We used linear regression, weighted by the time interval between successive readings, to determine the regression slope of diastolic on systolic blood pressure in individual recordings. AASI was unity minus the regression slope. Pulse pressure was systolic minus diastolic blood pressure. Because the oscillometrically measured mean arterial pressure was not available in all of the cohorts, we computed mean arterial pressure as diastolic blood pressure plus one third of pulse pressure. We studied the concordance between the computed and the oscillometrically measured mean arterial pressures in 1144 Belgian[12] and 349 Chinese[2] participants. Ambulatory hypertension was a 24-hour blood pressure of 130 mm Hg systolic or 80 mm Hg diastolic[18] or higher or the use of antihypertensive drugs. While accounting for the daily pattern of activities of the participants, we defined daytime as the interval from 10 AM to 8 PM in Europeans[12,14,15] and South Americans[17] and from 8 AM to 6 PM in Asians.[13,16] The corresponding nighttime intervals ranged from midnight to 6 AM[12,14,15,17] and from 10 PM to 4 AM,[13,16] respectively. In dichotomous analyses, we defined nondipping as a night:day ratio of systolic blood pressure of ≥0.90.[19]

Other Measurements

We used the questionnaires originally administered in each cohort[12–17] to obtain information on each subject's medical history and smoking and drinking habits. Body mass index was body weight in kilograms divided by height in meters squared. We measured serum cholesterol and blood glucose by automated enzymatic methods. Diabetes mellitus was a self-reported diagnosis, a fasting or random blood glucose level of ≥7.0 mmol/L (126 mg/dL) or 11.1 mmol/L (200 mg/dL),[20] respectively, or the use of antidiabetic drugs.

Statistical Analyses

For database management and statistical analyses, we used SAS 9.1.3 (SAS Institute) and its JMP add-on, version 6.0. We checked that the assumption of normality was applicable to the variables under study by normal probability plots. We compared means and proportions by the large sample z test and by the χ^2 statistic, respectively. Statistical significance was a 2-sided P value of 0.05.

In single and multiple regression analyses, the established determinants of the relation of diastolic on systolic blood pressure were age, body height, 24-hour mean arterial pressure, and 24-hour heart rate.[2] In single regression analysis, we also considered the night:day ratio of systolic blood pressure[8,21] and 24-hour pulse pressure.[22] Multivariable-adjusted models included as covariables cohort and/or sex, as appropriate, and age, body height, 24-hour mean arterial pressure, and 24-hour heart rate. In sensitivity analyses, we additionally adjusted for serum cholesterol, smoking, antihypertensive drug treatment, diabetes mellitus, and a history of cardiovascular disease.

We used the coefficient of determination (r^2) as a measure of the goodness-of-fit (Figure 1) of the regression line of diastolic on systolic blood pressure in individual ambulatory recordings. We subdivided the study population in cohort and sex-specific quartiles of r^2. We compared Pearson's correlation coefficients and partial regression coefficients of AASI with its determinants, using Fisher's z transform and interaction terms with binary variables coding for the quartiles of r^2, respectively. In the last step of the analyses, we computed a cumulative z score for the single correlation coefficients of AASI with age, body height, 24-hour mean arterial pressure, and 24-hour heart rate. We plotted the average cumulative z score against the goodness-of-fit of the AASI regression line, going from $r^2=0$ to $r^2=0.80$ (≈90th percentile of r^2) by steps of 0.01.

Table 1. Baseline Characteristics of Participants by Categories of the Goodness-of-Fit of AASI

Characteristic	Low	Medium-Low	Medium-High	High
Limits of goodness-of-fit, r^2	<0.40	≥0.40 to <0.55	≥0.55 to <0.70	≥0.70
Total, n	1901	1906	1896	1901
Auscultatory recordings	492 (25.9)	337 (17.7)	196 (10.3)	75 (3.9)
European	1376 (72.4)	1284 (67.4)	1066 (56.2)	639 (33.6)
Asian	134 (7.0)	248 (13.0)	457 (24.1)	1030 (54.2)
South American	391 (20.6)	374 (19.6)	373 (19.7)	232 (12.2)
Women	759 (39.9)	818 (42.9)	871 (45.9)	1024 (53.9)
Antihypertensive treatment	444 (23.7)	367 (19.3)	375 (19.8)	517 (27.2)
Smokers	503 (26.7)	597 (31.5)	585 (31.0)	518 (27.3)
Using alcohol	1022 (53.8)	1001 (52.5)	879 (46.4)	633 (33.3)
Diabetes mellitus	150 (7.9)	117 (6.1)	120 (6.3)	181 (9.5)
Cardiovascular disorder	266 (14.0)	250 (13.1)	208 (11.0)	162 (8.5)
Nondippers for systolic pressure	952 (50.1)	585 (30.7)	419 (22.1)	287 (15.1)
Age, y	59.8±13.6	57.0±14.0	55.4±13.9	55.5±13.6
Height, cm	168.3±10.3	167.0±10.7	165.4±11.5	159.9±12.0
Weight, kg	74.4±15.1	72.3±15.2	70.0±16.1	63.6±15.2
Body mass index, kg/m^2	26.2±4.3	25.8±4.1	25.4±4.1	24.6±3.8
24-h ambulatory measurements				
Systolic pressure, mm Hg	128.6±15.6	125.2±14.4	123.5±13.6	121.8±13.2
Diastolic pressure, mm Hg	73.5±9.1	73.9±8.5	74.1±8.3	74.2±8.1
Mean arterial pressure, mm Hg	91.9±10.4	91.0±9.8	90.6±9.4	90.1±9.2
Systolic night:day ratio	0.908±0.086	0.867±0.076	0.853±0.076	0.832±0.079
Pulse pressure, mm Hg	55.0±11.1	51.3±9.8	49.4±9.2	47.7±8.5
Heart rate, bpm	71.4±9.5	72.6±9.4	72.3±9.0	71.5±8.7
AASI	0.63±0.15	0.47±0.13	0.39±0.13	0.33±0.14
Serum cholesterol, mmol/L	5.9±1.1	5.8±1.2	5.6±1.1	5.4±1.0
Fasting blood glucose, mmol/L	5.3±1.5	5.2±13	5.1±1.1	5.0±1.0

Data are No. (%) or mean±SD, unless otherwise specified. Nondipping was a night:day ratio of systolic blood pressure ≥0.90. All of the *P* values for the differences between quartiles were significant ($P \leq 0.01$), with the exception of diastolic pressure ($P=0.09$).

Results

Characteristics of Participants

The 7604 participants included 4365 Europeans (57.4%), 1869 Asians (24.6%), and 1370 South Americans (18.0%). Of the 7604 participants, 3472 were women (45.7%), 1703 (22.4%) were taking blood pressure–lowering drugs, and 946 (12.4%) had ambulatory hypertension. Mean±SD age was 56.9±13.9 years. At enrollment, 2203 participants (29.0%) were current smokers, and 3535 (46.5%) reported intake of alcohol. In the whole study population, the 24-hour blood pressure averaged 124.8±14.4 mm Hg systolic and 73.9±9.2 mm Hg diastolic. The systolic and diastolic daytime levels averaged 131.2±15.5 mm Hg and 78.9±9.3 mm Hg, and the nighttime blood pressures were 113.2±15.5 mm Hg and 65.0±9.2 mm Hg. The night:day ratio of systolic blood pressure was 0.87±0.08.

The 24-hour mean arterial pressure averaged 90.0±9.7 mm Hg. In 1493 subjects with available data, the computed compared with the measured mean arterial pressure (SD) was 0.71±2.50 mm Hg higher (88.3±9.1 versus 87.6±9.4 mm Hg; $P<0.0001$). The slope ($P=0.87$) and the intercept ($P=0.54$) of the regression line of the measured on the computed mean arterial pressure ($r=0.98$; $P<0.0001$) did not differ from the parameters of the line of identity (Figure S1).

In all of the subjects, AASI averaged 0.46±0.18 and 24-hour pulse pressure 50.9±10.1 mm Hg. Mean r^2 in 7604 individual recordings was 0.54±0.20. r^2 was lower in the auscultatory recordings in 1100 older Swedish men than in the oscillometric registrations in 6504 other subjects (0.42±0.20 versus 0.56±0.19; $P<0.001$). Table 1 shows the characteristics of the participants by quartiles of r^2. All of the *P* values for the differences between quartiles were significant ($P \leq 0.01$), with the exception of diastolic blood pressure ($P=0.09$).

Unadjusted Analyses

In all of the subjects combined, in single regression analysis, AASI correlated positively with age and 24-hour mean arterial pressure and negatively with height and 24-hour heart rate (Table 2). As shown in Table 2 and Figure 2, the correlation coefficients of AASI with age, height, 24-hour mean arterial pressure, and 24-hour heart rate were significantly tighter in the highest compared with the lowest quartile of r^2. Figure 3 shows the plot of cumulative *z* scores of the

Table 2. Correlates of AASI in the Whole Study Population and by Quartiles of the Goodness-of-Fit of AASI

		Quartiles of the Goodness-of-Fit (r^2) of the AASI Regression Line						
Variable	All Subjects	Low	Medium-Low	Medium-High	High	*P* vs Low Group		
No.	7604	1901	1906	1896	1901			
Mean±SD								
Goodness-of-fit, r^2	0.54±0.20	0.26±0.10	0.48±0.04	0.62±0.04	0.78±0.06	<0.001	<0.001	<0.001
AASI	0.46±0.18	0.63±0.15	0.47±0.13	0.39±0.13	0.33±0.14	<0.001	<0.001	<0.001
Correlation coefficient of AASI with:								
Age	0.37‡	0.20‡	0.32‡	0.46‡	0.56‡	<0.001	<0.001	<0.001
Body height	−0.06‡	0.03	−0.02	−0.14‡	−0.32‡	0.12	<0.001	<0.001
24-h mean arterial pressure	0.14‡	0.06†	0.11‡	0.17‡	0.18‡	0.12	<0.001	<0.001
24-h heart rate	−0.17‡	−0.09‡	−0.23‡	−0.23‡	−0.30‡	<0.001	<0.001	<0.001
24-h pulse pressure	0.49‡	0.35‡	0.42‡	0.47‡	0.53‡	0.01	<0.001	<0.001
Systolic night:day ratio	0.15‡	0.03	−0.24‡	−0.13‡	−0.04	<0.001	<0.001	0.03
Serum cholesterol	0.11‡	0.06*	0.10‡	0.04	0.06*	0.22	0.54	>0.99

Significance of the correlation coefficients: *$P<0.05$; †$P<0.01$; ‡$P<0.001$.

aforementioned 4 covariables against the goodness-of-fit of the AASI regression line in steps of 0.01 of r^2, going from 0 to 0.80. The first, fifth, 10th, 20th, 50th, 75th, and 90th percentile values of r^2 were 0.05, 0.17, 0.25, 0.36, 0.56, 0.69, and 0.79, respectively.

The association between AASI and 24-hour pulse pressure increased across the quartiles of r^2 and was 0.49 ($P<0.0001$) in the whole study population. The correlation between AASI and serum cholesterol did not increase with r^2. In all of the subjects combined, the correlation coefficient between AASI and the night:day ratio in systolic blood pressure was 0.15 ($P<0.001$). This association was inconsistent across the quartiles of r^2 (Table 2). The positive correlation between AASI and the systolic night:day ratio was larger in 1100 auscultatory recordings than in 6504 oscillometric registrations (0.28 versus 0.15; $P<0.0001$). Furthermore, of 7604 participants, 5361 were dippers (70.5%) and 2243 were nondippers (29.5%). The associations of AASI with age, body height, and 24-hour heart rate and mean arterial pressure were similar in dippers and nondippers (Figure 2).

Multivariable Analyses

In all 7604 of the subjects combined, AASI increased independently with age and 24-hour mean arterial pressure and decreased with height and 24-hour heart rate (Table 3). The multivariable-adjusted associations of AASI with age, 24-hour mean arterial pressure, and 24-hour heart rate were significantly closer in the highest compared with the lowest quartile (Table 3). In multiple regression, the variance of AASI explained (R^2) by age, height, 24-hour mean arterial pressure, and 24-hour heart rate increased from 0.04 to 0.37 from the lowest to the highest quartile of r^2.

Sensitivity Analyses

The aforementioned unadjusted (Table S1) and multivariable-adjusted (Table S2) findings were consistent in women and men and in Europeans, Asians, and Americans (see online Data Supplement). Analyses, from which we excluded the 1100 auscultatory recordings, also produced consistent results (Tables S3 and S4 and Figure S2). Our findings also remained consistent after the additional adjustment of the results in

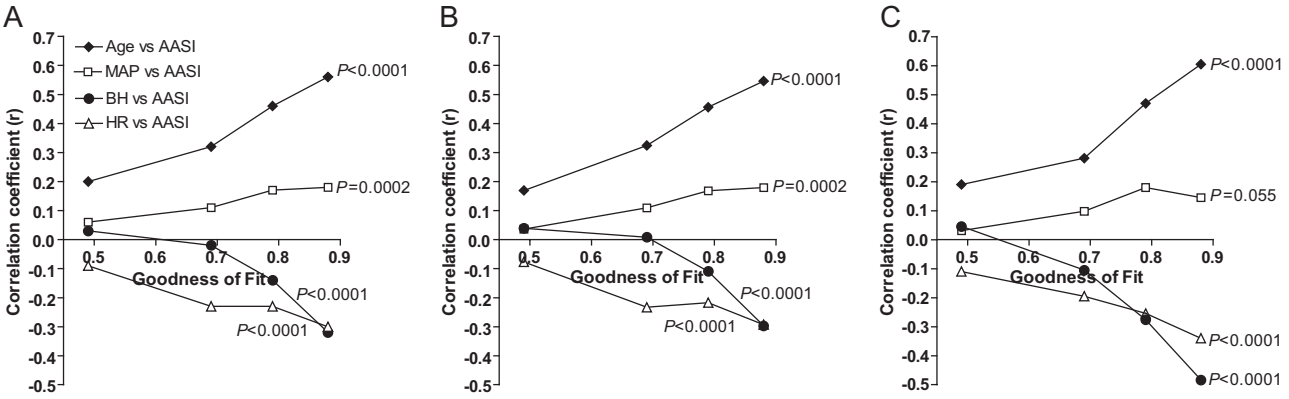

Figure 2. Correlations of AASI with age, height (BH), 24-hour mean arterial pressure (MAP), and 24-hour heart rate (HR) across quartiles of the goodness-of-fit of the AASI regression line (r^2) in all 7604 subjects (A), 5361 dippers (B), and 2243 nondippers (C). *P* values are for the differences between the bottom and top quartiles.

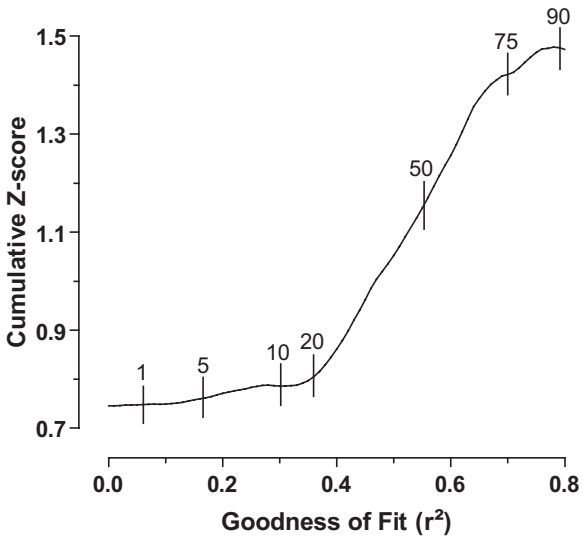

Figure 3. Plot of the average cumulative *z* score against the goodness-of-fit of the AASI regression line, going from $r^2=0$ to $r^2=0.80$ (≈90th percentile of r^2) by steps of 0.01. The cumulative *z* score is the sum of the unsigned Fisher *z* transforms of the single correlations of AASI with age, body height, 24-hour mean arterial pressure, and 24-hour heart rate. Vertical lines denote percentiles of the distribution of the goodness-of-fit (r^2).

Table 3 for serum cholesterol, smoking, antihypertensive drug treatment, diabetes mellitus, and a history of cardiovascular disease (data not shown).

Discussion

We investigated whether r^2 affects the association of AASI with established determinants of the relation between diastolic and systolic blood pressures.[2] We confirmed that the strength of the relation of AASI with age, body height, 24-hour mean arterial pressure, and 24-hour heart rate increased with the goodness-of-fit of the AASI regression line. In fact, in the lowest quartile of the fit, the correlations of AASI with these determinants were weak and at times inconsistent with the expected direction of the associations.

For our current analyses, we used established determinants of AASI.[2] In 348 randomly recruited Chinese subjects, AASI significantly and independently increased with age and mean arterial pressure, decreased with body height, and was higher in women than in men.[2] Most other studies reported differences of these characteristics across quantiles of the distribution of AASI. They showed more advanced age,[3,4,23] a higher proportion of women,[3,4,23] and elevated blood pressure in higher AASI quantiles.[3,23] In keeping with several other studies, in our hands, AASI did not or only weakly correlated with serum cholesterol,[2,5,23,24] body mass index,[3] and smoking.[2,4,5,23] AASI was negatively correlated with heart rate. Although heart rate is not a determinant of static arterial stiffness (pulse wave velocity), it is a determinant of dynamic measures of arterial stiffness, such as AASI or the augmentation index. A faster heart rate reduces the time required for the reflected pressure wave to reach the central arteries and leads to augmentation of systolic blood pressure.[25] As reported by others, there was a positive correlation between AASI and pulse pressure, which increased with r^2. Using 24-hour ambulatory pulse pressure as an index of arterial stiffness assumes that the difference between diastolic and systolic blood pressure is constant throughout the day.[9,22] In contrast, AASI accounts for the dynamic relation between diastolic and systolic blood pressures in individual 24-hour ambulatory recordings. Furthermore, in hypertensive patients[3] and representative population samples,[4–6] AASI predicted cardiovascular mortality and fatal and nonfatal stroke, over and beyond classic risk factors, including pulse pressure[3–5] and even aortic pulse wave velocity.[6] These prospective studies support the use of AASI for risk stratification.

Schillaci et al[8] reported that, in 515 untreated patients, AASI depended on the nocturnal blood pressure fall. We confirmed this observation in our Flemish population study.[12,26] The correlation coefficients were similar to those in the report by Schillaci et al[8]: Flemish population versus Italian patients, −0.24 versus −0.28 for systolic blood pressure (2-sided *P* value for difference computed by Fisher's *z* transformation: 0.42) and −0.39 versus −0.46 for diastolic blood pressure ($P=0.11$). In our current study, the correlation coefficient between AASI and the night:day ratio of systolic blood pressure (n=7604) was significantly weaker ($P=0.0013$) than in the hypertensive patients in the study by Schillaci et al.[8] This association was not significant in the bottom and top quartiles of r^2. At variance with the report by Schillaci et al,[8] we noticed that the associations of AASI with its major determinants across quartiles of r^2 were similar in dippers and nondippers.

Table 3. Adjusted Regression Coefficients of AASI in the Whole Study Population and Across Quartiles of the Goodness-of-Fit of AASI

		Quartiles of the Goodness-of-Fit (r^2) of the AASI Regression Line						
Variable	All Subjects	Low	Medium-Low	Medium-High	High	*P* vs Low Group		
No.	7604	1901	1906	1896	1901			
Partial regression coefficient±SE								
Age, +10 y	25.1±1.7‡	10.4±3.1‡	9.0±2.4‡	20.7±2.4‡	29.3±2.2‡	0.720	0.009	<0.001
Body height, +10 cm	−9.4±2.9‡	−8.9±5.3	−5.6±4.0	−15.6±4.1‡	−12.9±3.8‡	0.620	0.320	0.540
24-h mean pressure, +10 mm Hg	2.2±2.0	1.5±3.4	0.7±2.8	6.5±2.9*	13.3±2.7‡	0.860	0.260	0.007
24-h heart rate, +10 bpm	−12.7±2.1‡	−1.7±3.5‡	−10.6±2.3‡	−8.5±3.0†	−14.3±2.9‡	0.018	0.140	0.006

All of the regression coefficients were mutually adjusted and, in addition, accounted for cohort and sex. The partial regression coefficients were multiplied by 10^3 to remove leading zeros.

Significance of the regression coefficients: *$P\leq0.05$; †$P<0.01$; ‡$P<0.001$.

Li et al[2] measured AASI and aortic pulse wave velocity on the same day in 166 Chinese volunteers. They found a close relation between these indices of arterial stiffness, which was consistent in women ($r=0.58$; $P<0.0001$) and men ($r=0.38$; $P=0.002$) and in young (<40 years; $r=0.26$; $P=0.02$) and older adults ($r=0.25$; $P=0.02$). AASI was also significantly related to aortic pulse wave velocity in 99 diastolic dippers ($r=0.27$; $P=0.007$), as well as in 67 diastolic nondippers ($r=0.41$; $P=0.0005$). Schillaci et al[8] also measured both indices on the same day. In 346 untreated hypertensive patients, they reported a direct correlation between AASI and aortic pulse wave velocity of 0.28 ($P<0.001$). In 1678 subjects randomly recruited from the population of Copenhagen, the correlation coefficient between AASI and aortic pulse wave velocity was only 0.02 ($P=0.47$). In view of our current results, we computed the correlation coefficients between the 2 indices in the lowest and highest quartiles of the distribution of the goodness-of-fit of the AASI regression line in the Danish cohort.[14] These correlation coefficients were −0.007 ($P=0.89$) and 0.22 ($P<0.0001$), respectively (P value for the difference: <0.0001). These unpublished observations, along with the present findings, suggest that a better fit of the AASI regression line in individual subjects might enhance the accuracy of AASI as a measure of arterial stiffness.

The present study has limitations and strengths. First, the 6 populations differed in anthropometric characteristics and lifestyle. However, the correlations of AASI with the determinants of the association between diastolic and systolic blood pressures were adjusted for one another at the level of individual subjects. Sensitivity analyses showed that our findings were consistent in dippers and nondippers, in women and men, in various ethnic groups, and with extensive multivariable adjustments applied. Second, ambulatory blood pressure monitoring was not standardized across the 6 contributing studies in terms of device type and intervals between readings. However, across cohorts, we used the same SAS program to compute blood pressure–derived variables that were time weighted. Sensitivity analyses from which we excluded the auscultatory recordings were also confirmatory. Third, as suggested by experts in the field,[7] AASI is an indirect measure of arterial stiffness and is under the influence of other hemodynamic factors, such as wave reflections originating from peripheral sites, stroke volume, and peripheral resistance. The range of diastolic and systolic blood pressure values, which itself depends on the duration of the awake and asleep periods and on the intensity of physical activity during daytime, might additionally influence AASI. Nevertheless, in collaboration with the Ohasama investigators,[5] we demonstrated recently that random exclusion of readings from ambulatory recordings with measurements programmed at 30-minute intervals did not significantly change the average value of AASI until >7 readings were disregarded. Finally, we chose to use the calculated instead of the measured mean arterial pressure, because in most patients the measured mean arterial pressure was unavailable for analysis. However, the concordance between computed and measured mean arterial pressures was high in 1493 participants with available data.

Perspectives

A higher goodness-of-fit of the AASI regression line in individual subjects strengthens the association with its known determinants and likely enhances the statistical power of analyses involving AASI as a marker of arterial stiffness. Our findings have implications for clinical practice and research. The z score for the association of AASI with the 4 determinants of arterial stiffness combined (age, height, mean arterial pressure, and heart rate) increased curvilinearly with r^2, with most of the increase occurring above the 20th percentile of r^2 (0.36). One might use this threshold in clinical practice as the minimum value of r^2, when AASI is applied for the risk stratification of individual patients. On the other hand, in clinical research, it is not good practice to exclude subjects from statistical analyses based on an arbitrary threshold. We would suggest that future reports of research on AASI might include a sensitivity analysis, excluding subjects with the r^2 value set at a threshold of 0.36. However, primary analyses should always include all of the subjects, because a low r^2 might also reflect disconnection of diastolic from systolic blood pressure because of cardiovascular disease.

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Disclosures

None.

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DATA SUPPLEMENT

Characteristics of the Ambulatory Arterial Stiffness Index in 7604 Subjects from 6 Populations

Short title: Ambulatory Arterial Stiffness Index

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Expanded Methods

Study Population

Previous publications described the construction of the IDACO database.[1,2] After an electronic search of the literature, we included studies if they involved a random population sample. All studies[3-8] included in the IDACO database received ethical approval and have been reported in peer-reviewed publications. For the current analysis, we considered the baseline data of 2311 residents from Copenhagen, Denmark;[5] 2542 subjects from Noorderkempen, Belgium;[3] 1221 older men from Uppsala, Sweden;[6] 1535 inhabitants from Ohasama, Japan;[4] 360 villagers from the JingNing county, China;[7] and 1859 subjects from Montevideo, Uruguay.[8] All participants gave informed written consent. Of the 9828 subjects, we excluded 2224 participants (22.6%), because they were less than 18 years old at enrolment (n=17), or because their 24-h ambulatory recording included less than 30 readings in total (n=563), or less than 5 nighttime readings (n=1644). The number of participants statistically analyzed amounted to 2138 from Copenhagen;[5] 1127 from Noorderkempen;[3] 1100 from Uppsala;[6] 1520 from Ohasama; [4] 349 from JingNing;[7] and 1370 from Montevideo.[8]

Blood Pressure Measurement

We programmed blood pressure monitors to obtain ambulatory readings at 30-minute intervals throughout the whole day,[4] or at intervals ranging from 15[5] to 30[6] minutes during daytime and from 30[5] to 60[6] minutes at night. The devices implemented an auscultatory algorithm (Accutracker II, Suntech Medical Instruments Inc., Morrisville, NC[9]) in Uppsala[6] or an oscillometric technique (SpaceLabs 90202 and 90207, SpaceLabs Inc., Redmond, WA[10]) in Noorderkempen,[3] Montevideo[8] and JingNing.[8] The Takeda TM-2421 recorders (A&D, Tokyo, Japan[11]) and the ABPM-630 devices (Nippon Colin, Komaki, Japan[12]), used in

Copenhagen[5] and Ohasama,[4] respectively, implemented both techniques, but we only analyzed the oscillometric readings. The Ohasama recordings were edited sparsely according to previously published criteria,[13] but all other recordings remained unedited.

We used linear regression, weighted by the time-interval between successive readings, to determine the regression slope of diastolic on systolic pressure in individual recordings. We did not force the regression slope through the origin, because during diastole when blood flow drops to zero, such a phenomenon does not occur for blood pressure.[14] We defined AASI as unity minus the regression slope. Pulse pressure was systolic minus diastolic blood pressure. Mean arterial pressure was diastolic blood pressure plus one third of pulse pressure. Because the oscillometrically measured mean arterial pressure was not available in all cohorts, we computed mean arterial pressure as diastolic blood pressure plus one third of pulse pressure. We studied the concordance between the computed and the oscillometrically measured mean arterial pressure in 1144 Belgian[3] and 349 Chinese[15] participants. Ambulatory hypertension was a 24-h blood pressure of 130 mm Hg systolic or 80 mm Hg diastolic,[16] or higher, or the use of antihypertensive drugs.

While accounting for the daily pattern of activities of the participants, we defined daytime as the interval ranging from 10 AM to 8 PM in Europeans[3,5,6] and South Americans,[8] and from 8 AM to 6 PM in Asians.[4,7] The corresponding nighttime intervals ranged from midnight to 6 AM[3,5,6,8] and from 10 PM to 4 AM,[4,7] respectively. These fixed intervals eliminate the transition periods in the morning and evening when blood pressure changes rapidly, resulting in daytime and night-time blood pressure levels that are within 1–2 mm Hg of the awake and asleep levels.[7,17] In dichotomous analyses, we defined nondipping as a night-to-day ratio of systolic blood pressure of 0.90 or higher.[18]

Other Measurements

We used the questionnaires originally administered in each cohort[3-8] to obtain information on each subject's medical history, and smoking and drinking habits. Body mass index was body weight in kilograms divided by height in meters squared. We measured serum cholesterol and blood glucose by automated enzymatic methods. Diabetes mellitus was a self-reported diagnosis, a fasting or random blood glucose level of at least 7.0 mmol/L (126 mg/dL) or 11.1 mmol/L (200 mg/dL),[19] respectively, or the use of antidiabetic drugs.

Statistical Analyses

For database management and statistical analyses, we used SAS software, version 9.1.3 (SAS Institute, Cary, NC) and its JMP add-on, version 6.0. We checked that the assumption of normality was applicable to the variables under study by normal probability plots. We compared means and proportions by the large sample z-test and by the χ^2 statistic, respectively. Statistical significance was a two-sided *P*-value of 0.05.

In single and multiple regression analyses, the established determinants of the relation of diastolic on systolic blood pressure were age, body height, 24-h mean arterial pressure, and 24-h heart rate.[15] In single regression analysis, we also considered the night-to-day ratio of systolic blood pressure[20,21] and 24-h pulse pressure.[22] Multivariable-adjusted models included as covariables cohort and/or sex, as appropriate, and age, body height, 24-h mean arterial pressure, and 24-h heart rate. In sensitivity analyses, we additionally adjusted for serum total cholesterol, smoking, antihypertensive drug treatment, diabetes mellitus and a history of cardiovascular disease.

We used the coefficient of determination (r^2) as a measure of the goodness of fit of the regression line of diastolic on systolic blood pressure in individual ambulatory recordings. We subdivided the study population in cohort and sex-specific quartiles of the goodness of fit

of the slope of diastolic on systolic blood pressure. We compared Pearson's correlation coefficients across quartiles, using Fisher's z-transform. In multivariable-adjusted analyses, we compared the partial regression coefficients across quartiles, using appropriate interaction terms with 3 design variables coding for the quartiles of r^2. In the last step of the analyses, we computed a cumulative z-score for the single correlation coefficients of AASI with age, body height, 24-h mean arterial pressure, and 24-h heart rate. For each subject, we then computed a cumulative z-score as the sum of the unsigned z-values for the 4 single correlation coefficients of AASI. We plotted the average cumulative z-score against the goodness of fit of the AASI regression line, going from r^2=0 to r^2=0.80 (approximate 90th percentile of r^2) by steps of 0.01.

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Appendix

IDACO Centers and Investigators

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Database Management and Coordination

J Boggia, TW Hansen, M Kikuya, Y Li, JA Staessen (project coordinator), and L Thijs (supervisor database management) constructed the IDACO database at the Studies Coordinating Centre in Leuven, Belgium.

Table S1. Correlates of AASI in the Whole Study Population and in the lowest and highest quartiles of the Goodness of Fit of AASI by Sex and Ethnicity

Variable	All subjects	Low	High	*P*
Women (*n* = 3472)				
Age	0.35‡	0.16‡	0.57‡	<0.001
Body height	–0.06‡	–0.04	–0.49‡	<0.001
24-h mean pressure	0.12‡	0.04	0.24‡	<0.001
24-h heart rate	–0.18‡	–0.15‡	–0.36‡	<0.001
Men (*n* = 4132)				
Age	0.37‡	0..21‡	0.52‡	<0.001
Body height	–0.05‡	–0.02	–0.24‡	<0.001
24-h mean pressure	0.12‡	0.05	0.14‡	0.003
24-h heart rate	–0.13‡	–0.04	–0.22‡	<0.001
Europeans (*n* = 4365)				
Age	0.37‡	0.12‡	0.49‡	<0.001
Body height	–0.06‡	–0.02	–0.13‡	0.020
24-h mean pressure	0.15‡	0.03	0.27‡	<0.001
24-h heart rate	–0.13‡	–0.02	–0.14‡	0.003
Asians (*n* = 1869)				
Age	0.47‡	0.31‡	0.58‡	<0.001
Body height	–0.24‡	–0.18‡	–0.22‡	0.53
24-h mean pressure	0.05*	0.02	0.21‡	0.002
24-h heart rate	–0.12‡	–0.05	–0.24‡	0.002
South Americans (*n* = 1370)				
Age	0.22‡	0.12*	0.33‡	0.002
Body height	–0.06†	–0.03	–0.09	0.44
24-h mean pressure	0.11‡	0.03	0.21‡	0.009
24-h heart rate	–0.17‡	–0.07	–0.23‡	0.016

AASI is the ambulatory arterial stiffness index. The *P*-values are for the differences in the correlation coefficients between the lowest and highest quartiles of the goodness of fit of AASI.
Significance of the correlation coefficients: * $P \leq 0.05$; † $P < 0.01$; ‡ $P < 0.001$.

Table S2. Adjusted Regression Coefficients in the Whole Study Population and in the Lowest and Highest Quartiles of the Goodness of Fit of AASI by Sex and by Ethnicity

Variable	All subjects	Low	High	*P*
Women (*n* = 3472)				
Age (+10 years)	32.1±2.4 ‡	11.4±4.2 †	27.7±3.4 ‡	0.003
Body height (+10 cm)	–8.9±4.3*	–15.2±7.4 *	–13.8±5.7 *	0.88
24-h mean pressure (+10 mmHg)	–1.4±2.9	–0.5±4.9	14.1±3.8 ‡	0.019
24-h heart rate (+10 bpm)	–12.8±3.2 ‡	–8.2±5.5	–16.3±4.4 ‡	0.250
Men (*n* = 4132)				
Age (+10 years)	18.4±2.4 ‡	10.9±4.7 *	28.1±3.1 ‡	0.002
Body height (+10 cm)	–11.1±3.8 †	–3.2±7.4	–13.8±5.2 †	0.24
24-h mean pressure (+10 mmHg)	4.4±2.6	–2.1±4.6	11.7±3.9 †	0.022
24-h heart rate (+10 bpm)	–11.5±2.7 ‡	0.1±4.8	–11.3±3.9 †	0.065
Europeans (*n* = 4365)				
Age (+10 years)	23.6±2.5 ‡	9.3±4.7 *	26.2±3.4 ‡	<0.001
Body height (+10 cm)	–5.9±3.8	–0.8±6.6	–12.4±5.5 *	0.18
24-h mean pressure (+10 mmHg)	0.2±2.7	–2.8±4.3	9.7±4.3 *	0.026
24-h heart rate (+10 bpm)	–12.1±2.7 ‡	–2.7±4.4	–7.6±4.2	0.420
Asians (*n* = 1869)				
Age (+10 years)	34.5±2.6 ‡	20.3±5.2 ‡	24.3±3.6 ‡	<0.001
Body height (+10 cm)	–7.4±4.5 ‡	–10.1±9.0	–7.8±5.5	0.82
24-h mean pressure (+10 mmHg)	4.2±2.8	10.9±4.7 *	14.3±3.7 ‡	0.57
24-h heart rate (+10 bpm)	–1.6±3.4	–3.0±6.2	–12.7±4.4 †	0.20
South Americans (*n* = 1370)				
Age (+10 years)	18.0±3.8 ‡	10.4±6.4	24.8±6.7 ‡	<0.001
Body height (+10 cm)	–23.6±7.8 †	–9.9±14.2	–19.2±12.0	0.62
24-h mean pressure (+10 mmHg)	5.1±5.3	–3.8±8.6	–20.7±9.1 *	0.18
24-h heart rate (+10 bpm)	–25.7±5.8 ‡	–6.1±9.9	–33.0±9.0 ‡	0.039

AASI is the ambulatory arterial stiffness index. All regression coefficients were mutually adjusted and in addition accounted for cohort (except in South Americans). The associations in different ethnic groups were also adjusted for sex. The partial regression coefficients were multiplied by 10^3 to remove leading zeros. The *P*-values are for the differences in the regression coefficients between the lowest and highest quartiles.
Significance of associations: * $P \leq 0.05$; † $P<0.01$; ‡ $P<0.001$.

Table S3. Correlation Coefficients of AASI in the All Subjects and by Quartiles of the Goodness of Fit of AASI — Sensitivity Analysis Excluding 1100 Auscultatory Recordings

Variable	All subjects	Quartiles of the goodness of fit (r^2) of the AASI regression line						
		Low	Medium-low	Medium-high	High	*P*-value versus low group		
Number	6504	1580	1667	1616	1641			
Mean ± SD								
Goodness of fit (r^2)	0.73±0.15	0.52±0.12	0.71±0.03	0.80±0.02	0.89±0.03	<0.001	<0.001	<0.001
AASI	0.44±0.17	0.60±0.15	0.45±0.13	0.37±0.13	0.33±0.13	<0.001	<0.001	<0.001
Correlation coefficient of AASI with								
Age	0.32‡	0.18‡	0.32‡	0.45‡	0.54‡	<0.001	<0.001	<0.001
Body height	–0.05‡	–0.02	–0.12‡	–0.24‡	–0.40‡	0.04	<0.001	<0.001
24-h mean arterial pressure	0.15‡	0.06*	0.12‡	0.18‡	0.17‡	0.09	<0.001	<0.001
24-h heart rate	–0.17‡	–0.13‡	–0.21‡	–0.20‡	–0.30‡	0.02	0.04	<0.001
24-h pulse pressure	0.47‡	0.32‡	0.42‡	0.47‡	0.53‡	0.001	<0.001	<0.001
Systolic nigh-to-day ratio	0.15‡	–0.05	–0.22‡	–0.09†	0.01			
Serum total cholesterol	0.11‡	0.09‡	0.09‡	0.03	0.09‡	>0.99	0.09	<0.001

AASI is the ambulatory arterial stiffness index. Significance of the correlation coefficients: * $P \leq 0.05$; † $P<0.01$; ‡ $P<0.001$.

Table S4 Mutually Adjusted Associations of AASI with Established Determinants of Arterial Stiffness in the Whole Study Population and Across Quartiles of the Goodness of Fit of AASI— Sensitivity analysis excluding 1100 auscultatory recordings

Variable	All subjects	Quartiles of the goodness of fit (r^2) of the AASI regression line						
		Low	Medium-low	Medium-high	High	*P*-value versus low group		
Number	6504	1580	1667	1616	1641			
Partial regression coefficient (±SE)								
Age (+10 years)	28.1±1.7‡	9.9±3.0‡	13.5±2.5‡	23.7±2.6‡	28.1±2.4‡	0.36	<0.001	<0.001
Body height (+10 cm)	–4.3±2.5	–13.1±4.8†	–19.9±3.7	–31.5±3.6‡	–38.1±3.2‡	0.86	0.002	<0.001
24-h mean pressure (+10 mmHg)	9.0±2.2‡	3.5±3.6	6.1±3.1*	14.8±3.3‡	20.1±2.9‡	0.57	0.02	<0.001
24-h heart rate (+10 bpm)	–10.5±2.3‡	–7.0±3.9	–7.5±3.3*	–11.4±3.4‡	–16.9±3.2‡	0.92	0.39	0.05

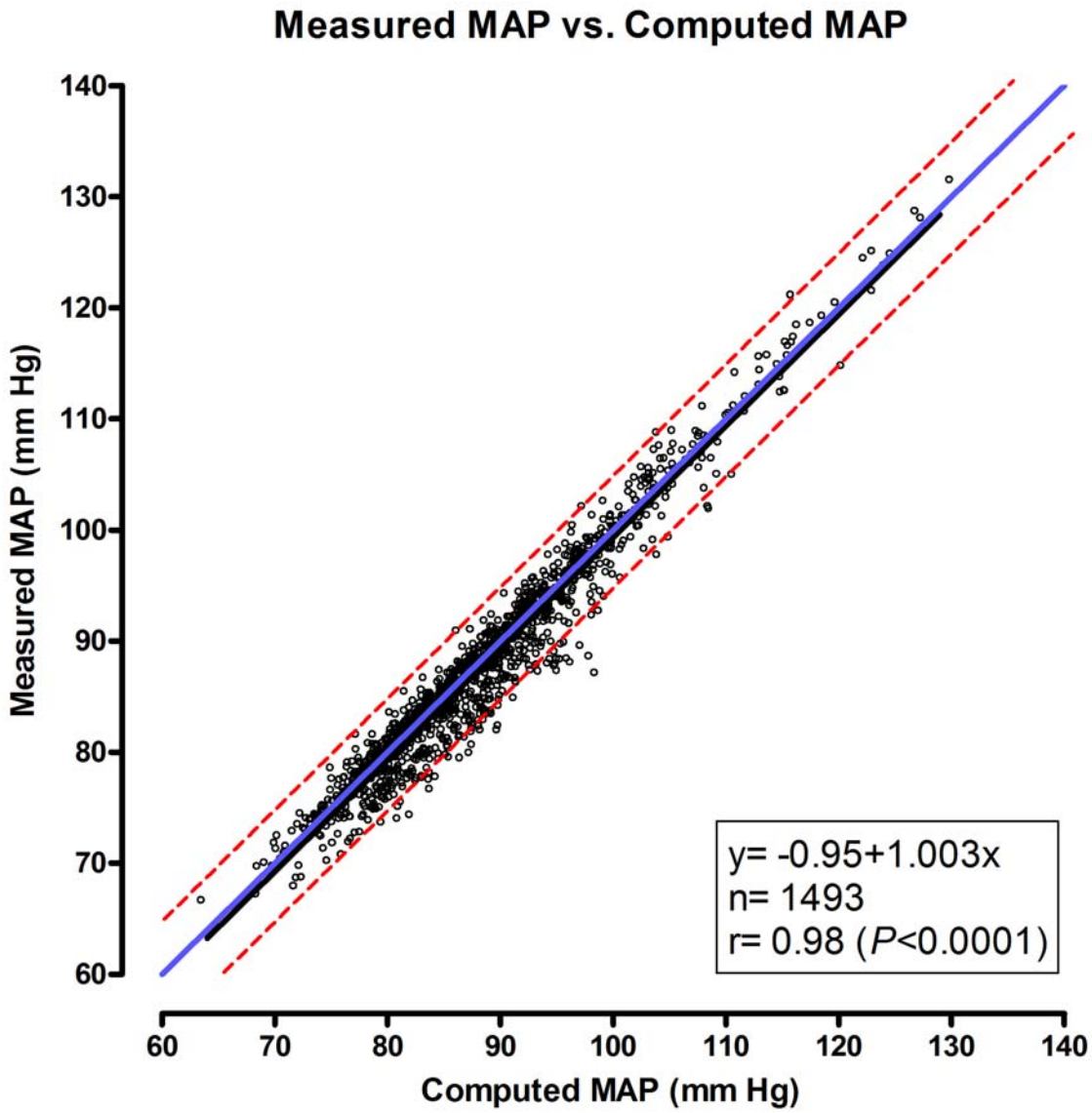
AASI is the ambulatory arterial stiffness index. All regression coefficients were mutually adjusted and were in addition adjusted for cohort and sex. The partial regression coefficients were multiplied by 10^3 to remove leading zeros. Significance of the associations: * $P \leq 0.05$; † $P<0.01$; ‡ $P<0.001$.

Legends to Figures

Figure S1. Scatter plot of the measured on the computed mean arterial pressure (MAP) in 1493 subjects. The slope (P=0.87) and the intercept (P=0.54) of the regression line (blue; r=0.98; P<0.0001) did not differ from the parameters of the line of identity (black). The dotted lines delineate a 5 mm Hg interval above and below the regression line.

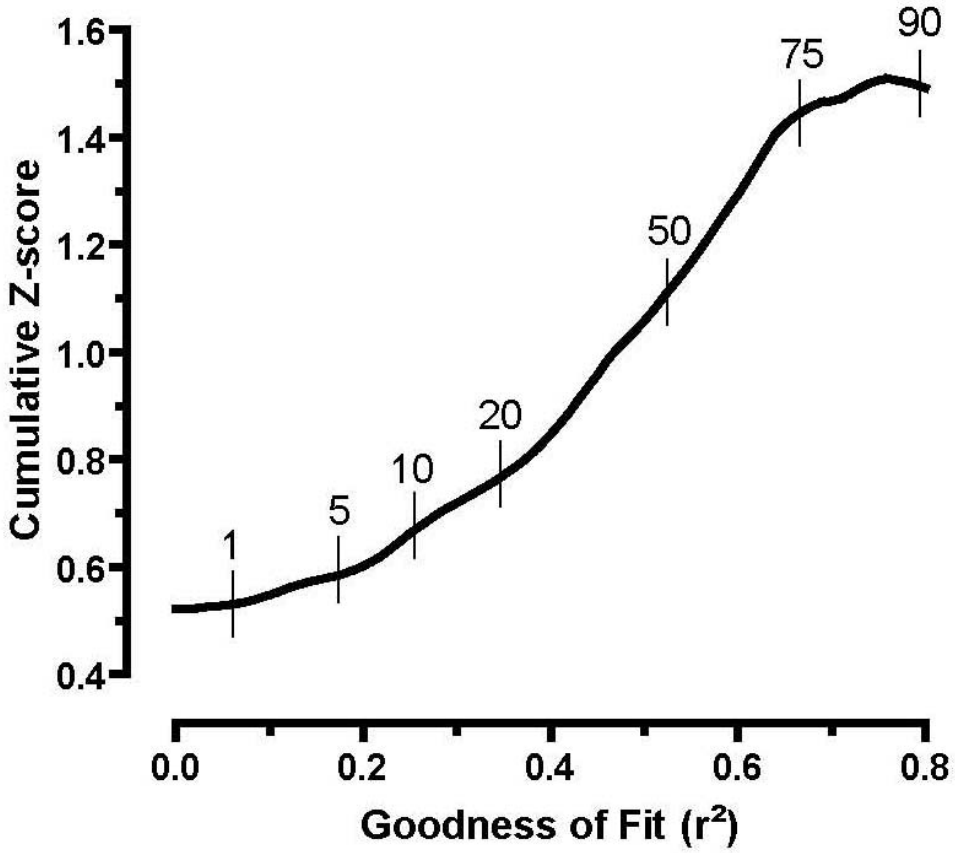
Figure S2. Plot of the average cumulative z-score against the goodness of fit of the AASI regression line, going from r^2=0 to r^2=0.80 (approximate 90th percentile of $r2$) by steps of 0.01. The cumulative z-score is the sum of the unsigned Fisher z-transforms of the single correlations of AASI with age, body height, 24-h mean arterial pressure, and 24-h heart rate. Vertical lines denote percentiles of the distribution of the goodness of fit (r^2). This sensitivity analysis excludes 1100 auscultatory recordings.

Figure S1



Scatterplot of the measured on the computed mean arterial pressure (MAP) in 1493 subjects. The slope (P=0.87) and the intercept (P=0.54) of the regression line (blue; r=0.98; P<0.0001) did not differ from the parameters of the line of identity (black). The dotted lines delineate a 5 mm Hg interval above and below the regression line.

Figure S2



Plot of the average cumulative z-score against the goodness of fit of the AASI regression line, going from r^2=0 to r^2=0.80 (approximate 90th percentile of r^2) by steps of 0.01. The cumulative z-score is the sum of the unsigned Fisher z-transforms of the single correlations of AASI with age, body height, 24-h mean arterial pressure, and 24-h heart rate. Vertical lines denote percentiles of the distribution of the goodness of fit (r^2). This sensitivity analysis excludes 1100 auscultatory recordings.