DATA SUPPLEMENT

Longitudinal changes of input impedance, pulse wave velocity, and wave reflection in a middle-aged population: the Asklepios Study

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Expanded Methods

Study population

Between 2002 and 2004, we non-invasively measured carotid blood pressure (applanation tonometry) and aortic flow (ultrasound) in 2524 apparently healthy, middle-aged subjects aged 35-55 years. Baseline cross-sectional data from this cohort were previously reported in 2026 subjects (1052 women and 974 men; visit 1) [1], who met the requirements to be included into the analysis. The same individuals, now aged 45-65 years old, were invited from 2013 to 2017 for a follow-up exam (visit 2; same single operator). To this call, 2252 returning volunteers (91% of the surviving subjects) had their second visit. On average, subjects were 10.15 ± 1.40 years older upon the second visit. The primary analyses in this study were performed on a sample of 2026 subjects included in the 2007 analysis [1]. Basic analyses were limited to subjects included in the previous cross-sectional study and with analyzable datasets on both occasions, yielding N=1757 (920 women and 837 men).

Exclusion criteria at baseline included antihypertensive and/or lipid lowering drug treatment, and incomplete data sets because of missing flow data, left ventricular outflow tract dimensions or non-invasive pressure measurements [1]. Of the 2026 subjects that formed the baseline cohort for our study on arterial hemodynamics and impedance, 33 died before follow-up, 94 were lost to follow-up, moved or withdrew from follow-up, and 83 declined re-exam because of loss of interest, illness or logistical difficulties; an additional 59 presented incomplete data sets (n=54 inability and/or technical failure to accurately assess carotid tonometry, and n=5 missing flow data). Figure S1 shows a detailed flowchart of participants with available data at baseline and follow-up.

Measured and derived variables

The data acquisition protocol and methods for data processing have been previously described [1]. Briefly, anthropometric measurements of height, weight, distances from sternal notch to carotid, radial and femoral arteries were performed, and body mass index (BMI) and body surface area (BSA) were derived. Before examinations, subjects were allowed 10-15 minutes of rest in a temperature-controlled environment. Blood pressure waveforms were acquired noninvasively at the left brachial artery by using applanation tonometry (SPT 301, Millar Instruments, Houston, Texas, USA), and the signal was calibrated based on oscillometric brachial systolic (SBP) and diastolic (DBP) blood pressure. Mean arterial pressure (MAP) was derived as the numerical average of the calibrated brachial pressure waveform. Tonometry was also performed at the left common carotid artery. Further calibration was based on brachial pressure, assuming that DBP and MAP remain approximately constant in the whole body.

Aortic flow velocity waveforms and left ventricular outflow tract (LVOT) were assessed using ultrasound (Vivid 7 for the baseline visit; Vivid E9 for the follow-up visit, GE Vingmed Ultrasound, Horten, Norway). LVOT area was calculated assuming circularity. Flow velocity images were processed off-line within a dedicated software interface written in Matlab (Mathworks, Natick, MA, USA), and were combined with the LVOT cross-sectional areas to obtain the aortic flow waveforms (Q). Stroke volume (SV) was derived by integration of Q, and cardiac output (CO) as the product of SV and HR. Signals of pressure (P) and Q were carefully time-aligned.

Input impedance (Z_{in}) was derived from the time-aligned pressure and flow waveforms after decomposing in harmonics, with the modulus being estimated as the ratio of both signals harmonics and the phase angle as their difference. Characteristic impedance (Z_{c}) was then assessed by averaging the modulus of harmonics 3 to 10, with exclusion of values higher than 3 times the median value of Z_{in} over that range of harmonics. The modulus of Z_{in} at 0 Hz equals SVR. Total arterial compliance was estimated using the pulse pressure method (C_{PPM}) [2]. The reflection coefficient was calculated as $\Gamma=\frac{Z_{\mathrm{in}}-Z_{\mathrm{c}}}{Z_{\mathrm{in}}+Z_{\mathrm{c}}}$ and reported as the amplitude at the heart frequency ($|\Gamma_1|$). The pressure signal was separated into its forward and backward components ($\mathrm{P_f} = (\mathrm{P} + Z_{\mathrm{c}}Q)/2$ and $\mathrm{P_b} = (\mathrm{P} - Z_{\mathrm{c}}Q)/2$, respectively), and the reflection magnitude was derived from the ratio of the amplitudes of $\mathrm{P_b}$ and $\mathrm{P_f}$ ($|\mathrm{P_b}|/|\mathrm{P_f}|$). Reflected wave transit time (RWTT) was derived from wave separation analysis, as the time delay between the zero crossings of the reflected and forward pressure waves.

To allow for direct comparison with the round 1 data and values published earlier, carotid-femoral PWV was estimated using the subtracted distance method as $(\Delta L_{\text{S-F}} - \Delta L_{\text{S-C}})/(\Delta T_{\text{Q-F}} - \Delta T_{\text{Q-C}})$, with $\Delta L_{\text{S-F}}$ and $\Delta L_{\text{S-C}}$ the distance measured from sternum to femoral and carotid measuring sites, respectively, and $\Delta T_{\text{Q-F}}$ and $\Delta T_{\text{Q-C}}$, the time delay between the start of the QRS complex and the upstroke of flow measured with Doppler echography in the femoral and carotid artery, respectively.

Statistical methods

General characteristics of the study population are presented as mean ± standard deviation (SD) for normally-distributed variables, median (interquartile range) for non-normally distributed variables and counts (percentages) for categorical variables. In the figures with observed data, standard errors of the mean (SEM) are displayed. Subjects were classified into half-decades of age (35-40, 41-45, 46-50, and 51-56 years) based upon age at baseline. Differences between sex and examination visits were tested from t-tests in the basic analysis. Moreover, analyses of variance and covariance were performed for all the variables of interest, accounting for the repeated measures by subjects. The categorical variables age, sex, visit, and their interaction terms were included in the models. Height, weight and mean arterial pressure were considered as covariates when applicable.

For a better comprehension of the longitudinal relationships among variables, linear mixed-effects (LME) analyses were performed [3]. Data were assumed to be missing at random (MAR), and consequently the analyses also included those participants with only baseline observations. Mixed-effects models in combination with the MAR assumption have been shown to provide robust estimates, even when data are actually missing not at random [3]. A comparison of baseline characteristics between the group with complete dataset and the group with missing data at follow-up can be seen in Table S10. Models describing the effects on PWV, blood pressure variables, impedance and wave reflection parameters were constructed. Age at baseline (Entry-Age) and follow-up time (Time), are considered as fixed effects in all models [4], and as random effects, we had random intercepts for subjects in simpler models, as well as bysubject random slopes for the effect of time in more complex models. In these models, baseline and follow-up measurements were used for the dependent as well as the independent variables. Time and its interaction terms in mixed-effects models, account for the longitudinal changes on the response variable. Correlation analysis was used to identify significant relationship among variables of interest that were further considered as potential covariates in the mixed-effects models (see the correlation matrix in Figure S8). Sex, HR, height, weight, and the previously mentioned dependent variables (when applicable), were included as potential covariates. Age-squared terms were also added to models to better capture the observed differences associated with older age, with age terms centered to reduce collinearity. The estimated variance inflation factor was lower than 10. Selection of significant independent factors was obtained by likelihood ratio test. Sex-specific models were considered when the factor sex was found significant. Residual plots were visually inspected to check for deviations from homoscedasticity or normality. The correlation between predicted and observed data was used as a measure of model quality (e.g. Figures S2-S4). An estimation of the conditional explained variance (R^2) for mixed-effects models was derived as described in [5]. As an alternative to assuming a normal distribution of the dependent variable, generalized linear mixed-effect (GLME) models were also considered assuming a gamma distribution and the logarithmic function as the link function. P-values < 0.05 were considered statistically significant. All analyses were done using Matlab (Mathworks, Natick, MA, USA). Tables and figures with the overview of the mixed-effects models are presented in the main text or in this Data Supplement (Tables S1-S9 and Figures S2-S7).

Basic analysis of the complete dataset

Basic clinical data and hemodynamic parameters of the study cohort at baseline and follow-up, stratified by sex and age group, are shown in Table 1. Females exhibited lower height, weight, body mass index (BMI) and body surface area (BSA) than males. Body mass index increased from one examination visit to the other, both in men and in women. Stroke volume (SV) and cardiac output (CO) were also significantly lower in women (P<0.001), whereas heart rate (HR) was higher in women than in men. None of these three hemodynamic variables varied with age over the studied ranges (cross-sectional observations), but CO and SV increased or tended to increase, comparing baseline data with measurements at follow-up (10-year period). LVOT cross-sectional area increased significantly between examination visits for both females and males; the area was lower for females compared to males and showed a decrease from younger to older groups, as observed from the cross-sectional studies.

SVR, adjusted for height and weight, was significantly different for men and women (P<0.001), with women presenting higher values per visit (Figure 3A). In males, and females in the oldest category, there was a longitudinal decrease in SVR rather than an increase. C_{PPM} showed an unexpected increase from baseline to follow-up (Figure 3B), with significant differences of visit by age and sex (P<0.01). Z_c on the other hand, decreased significantly between examination visits, with less pronounced changes and even a slight increase for the oldest (Figure 3C), but the changes between visit were not different by sex. The reflection coefficient and RWTT decreased between examination visits (Figures 4A and S5A, respectively), with women displaying shorter transit times (P<0.01), and changes in $|\Gamma_1|$ being steeper in men and in the oldest group for men and women. The amplitude of the forward wave (Figure 4B) differed by sex and age (P<0.001), with women showing higher values than men only for the oldest subjects, but the changes between visits were overall not found significant, except when depending on the age group (P<0.001). The amplitude of the reflected wave on the other hand, decreased between visits for men and women (Figure 4C), and there were significant differences by age category. Although the overall effect of sex was not significant, values of $|\mathrm{P_b}|$ differed between men and women by age (P<0.001) and by visit (P<0.01) as seen from the ANOVA, with men in age groups A_1 and A_2 having higher values than women, and the opposite happening for A_3 and A_4.

Results of input impedance

Comparing between visits, women that entered the study at a younger age (35 to 45 years), had a significant decrease in the modulus of Z_{in} in the high-frequency range (harmonics 4 and 5 for A_1 and 4 to 7 for A_2). Men had also a significant decrease in the modulus of Z_{in} for the youngest group, in the low and high frequency range (harmonics 1, 3-5 and 7), and for subjects that entered the study in their forties, in harmonics 4-5 for both groups and 9-10 only for A_2. In the oldest group of males and females, differences between examination visits were mostly non-significant. After correcting for height and weight, the age and sex effects had significant effects on the modulus of Z_{in} for harmonics 1 to 7, while visit and the interaction term between age and sex were significant for harmonics 1 to 5. The phase angle also showed higher differences between examination visits mainly for high frequencies (Figure 2B and 2D).

Results obtained for total arterial compliance can be gleaned from the input impedance plots (Figure 2). The modulus of the first two harmonics of Z_{in} in men decreased from visit 1 to visit 2, this decrease between visits being more evident from the younger to the older group. This indicates an increase in total arterial compliance as it is confirmed from the C_{PPM} data. The change in women is less apparent and does not have a constant behavior with age, which again reflects the results of C_{PPM}. In contrast, within the same visit, the modulus of the first two harmonics of Z_{in} systematically increases with age. This is consistent with the continuous cross-sectional decrease of C_{PPM} with increasing age.

Association of impedance parameters with cardiovascular risk factors

At the end of the second round of measurements, there were 82 diabetic subjects (84.1% diagnosed during follow-up). We performed extra analyses testing for the association between PWV, impedance or wave reflection parameters and traditional cardiovascular risk factors. Diabetes, smoking, obesity, weekly alcohol intake, lipid-lowering medications use, hypertension, entry-age, time, HR and education, were considered as potential covariates in the models (see Table S7-S9 and Figures S6-S7). Hypertension was defined as SBP ≥ 140 mmHg, or DBP ≥ 90 mmHg, or use of antihypertensive medications. Compared to normal weight subjects, obese and overweight subjects had higher C_{PPM} and lower SVR and Z_{c}, but there were no longitudinal associations. In women, the use of lipid-lowering treatment had a decreasing effect on Z_{c} that was lower over time. In men, subjects that never smoked and ex-smokers over time had higher C_{PPM} and lower $|\Gamma_1|$ than active smokers. Diabetic women had lower SVR and lower compliance for the older than nondiabetic women, whereas diabetic men had lower C_{PPM}, and higher characteristic impedance depending on the entry age, but none of these associations were longitudinal. Interestingly, men with lower education level showed lower SVR, $|\Gamma_1|$, and PWV compared to men with higher education level.

Comparison of subjects of the same age but distinct generation controlling for lifestyle factors

For some of the studied parameters, statistically significant differences were observed when comparing subjects of a certain age at baseline with subjects that reached the same age during follow-up. E.g. women that were about 50 years old at the beginning of the study, had on average a volume compliance 9% lower than women that were about the same age 10 years later. An extra analysis was performed to test whether the observed differences between two groups of subjects in the same age range but a decade apart, were associated with lifestyle and social factors. In a subsample of subjects (n=1427, 48.5% second-generation) with age between 44 and 57 years old, we first fitted regression models using a group indicator variable and controlling for age, sex, obesity, smoking status, education level and weekly alcohol intake. Then, we tested the null hypothesis that the effects of these factors were not different across both groups. We found statistically significant differences of the effects of education, obesity and smoking status on the reflection coefficient across the first- and second-generation groups. Subjects with an education level beyond secondary school had higher $|\Gamma_1|$ in the first generation group, while the opposite occurred for the second group. The effect of smoking status on $|\Gamma_1|$ differed between the two groups, with higher values for active smokers in the group 2, in comparison to ex-smokers and subjects that never smoked. Subjects with normal weight showed higher mean values in group 1 but lower mean values in group 2, while overweight or obese subjects presented similar characteristics. Table S11 shows other group interaction effects that resulted statistically significant for parameters that differed between the two groups. For other parameters that also showed statistically significant differences when comparing both generation groups (e.g. C_{PPM}, SVR, LVOT area or SV), we did not find enough evidence to support the hypothesis that these differences may be also influenced by lifestyle or socio-economic factors.

Supplemental References

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Supplemental Tables

Table S1. Generalized linear mixed-effect model of the longitudinal effects on PWV for the entire cohort. The correlation coefficient between observed and predicted values and the conditional R^2 are reported.

Variables	Estimate	SE	P-value
Intercept	1.8431	0.0074	0.0000
Sex (Men)	0.0059	0.0086	0.4933
Time	0.0140	0.0009	2.32E-51
Entry-Age	0.0115	0.0007	7.85E-54
$(\text{Entry-Age})^2$	0.0001	0.0001	0.2685
Sex (Men)×Time	-0.0028	0.0013	0.0256
Entry-Age×Time	-6.87E-05	0.0001	0.5177
$(\text{Entry-Age})^2$×Time	2.85E-05	1.78E-05	0.1092
Sex (Men)×Entry-Age×Time	0.0001	0.0001	0.3761
Sex (Men)×$(\text{Entry-Age})^2$×Time	-6.79E-05	2.42E-05	0.0050
R (Obs. vs. Pred.)		0.826	
R^2		0.880	

Table S2. Generalized linear mixed-effects model of the longitudinal effects on PWV for groups of men and women.

	Men			**Women**		
Variables	Estimate	SE	P-value	Estimate	SE	P-value
Intercept	1.8555	0.0060	0.0000	1.8448	0.0061	0.0000
Time	0.0098	0.0007	2.88E-46	0.0150	0.0007	4.06E-91
Entry-Age	0.0120	0.0009	7.40E-41	0.0111	0.0009	3.82E-36
Entry-Age×Time	-	-	-	-	-	-
R (Obs. vs. Pred.)		0.844			0.812	
R^2		0.865			0.886	

Table S3. Generalized linear mixed-effects models of the longitudinal effects on PWV for men and women, including HR, height, weight, and BP variables as covariates.

Covariate: SBP_{CA}	**Men**			**Women**		
Variables	Estimate	SE	P-value	Estimate	SE	P-value
Intercept	0.9766	0.0502	1.30E-76	0.9422	0.0507	4.18E-71
Weight	0.0005	0.0004	0.2821	0.0008	0.0004	0.0188
SBP_{CA}	0.0040	0.0003	8.44E-51	0.0050	0.0002	3.35E-97
HR	0.0052	0.0004	3.00E-32	0.0031	0.0006	2.45E-07
Time	-0.0011	0.0043	0.8053	-0.0032	0.0053	0.5412
Entry-Age	-0.0015	0.0056	0.7916	0.0069	0.0009	3.25E-14
SBP_{CA} × Entry-Age	8.67E-05	4.24E-05	0.0412	-	-	-
Weight ×Time	0.0001	5.16E-05	0.0438	-	-	-
HR ×Time	-	-	-	0.0002	8.02E-05	0.0036
Entry Age×Time	-	-	-	0.0002	0.0001	0.0467
R (Obs. vs. Pred.)		0.836			0.806	
R^2		0.928			0.941	

Covariate: DBP	**Men**			**Women**		
Variables	Estimate	SE	P-value	Estimate	SE	P-value
Intercept	1.1419	0.0469	2.71E-113	1.1630	0.0468	2.19E-118
Weight	0.0002	0.0005	0.6863	-	-	-
DBP	0.0057	0.0004	3.12E-42	0.0077	0.0004	5.40E-72
HR	0.0041	0.0005	3.08E-19	0.0015	0.0006	0.0215
Time	-0.0019	0.0043	0.6676	-0.0024	0.0054	0.6562
Entry-Age	0.0096	0.0009	5.41E-25	0.0093	0.0009	9.01E-23
$(\text{Entry-Age})^2$	-	-	-	0.0001	0.0002	0.3568
Entry Age × Time	0.0003	0.0001	0.0078	0.0003	0.0001	0.0130
$(\text{Entry Age})^2$ × Time	-	-	-	3.19E-05	1.90E-05	0.0927
HR × Time	-	-	-	0.0002	8.18E-05	0.0121
Weight × Time	0.0001	0.0001	0.0376	-	-	-
R (Obs. vs. Pred.)		0.836			0.810	
R^2		0.922			0.932	

Covariate: PP_{CA}	**Men**			**Women**		
Variables	Estimate	SE	P-value	Estimate	SE	P-value
Intercept	1.1483	0.0446	1.92E-124	1.2188	0.0554	6.09E-96
Weight	0.0017	0.0004	4.09E-06	0.0019	0.0004	7.33E-07
PP_{CA}	0.0033	0.0004	1.64E-18	0.0040	0.0005	2.47E-18
HR	0.0064	0.0005	2.25E-43	0.0045	0.0006	4.43E-12
Time	0.0088	0.0007	1.43E-39	-0.0092	0.0067	0.1693
Entry-Age	0.0009	0.0034	0.8019	0.0085	0.0008	8.75E-26
PP_{CA} × Entry-Age	0.0002	6.23E-05	0.0034	-	-	-
PP_{CA} × Time	-	-	-	0.0002	5.46E-05	0.0053
HR × Time	-	-	-	0.0002	8.47E-05	0.0069

R (Obs. vs. Pred.)		0.835			0.803	
R^2		0.914			0.930	
Covariate: MAP		**Men**			**Women**	
Variables	Estimate	SE	P-value	Estimate	SE	P-value
Intercept	0.9700	0.0437	1.46E-96	1.0018	0.0475	3.13E-89
Weight	0.0007	0.0004	0.0657	-	-	-
MAP	0.0059	0.0004	8.08E-55	0.0076	0.0003	1.13E-98
HR	0.0039	0.0004	4.16E-18	0.0014	0.0006	0.0219
Time	0.0075	0.0006	1.43E-30	-0.0013	0.0052	0.7971
Entry-Age	0.0092	0.0009	1.58E-23	-0.0014	0.0055	0.8007
Entry-Age × Time	0.0003	0.0001	0.0178	0.0002	0.0001	0.0296
HR × Time	-	-	-	0.0002	7.97E-05	0.0083
MAP × Entry-Age	-	-	-	9.38E-05	5.41E-05	0.0830
R (Obs. vs. Pred.)		0.837			0.814	
R^2		0.928			0.940	

Table S4. Linear mixed-effects models of the longitudinal effects on BP variables for groups of men and women, with PWV, HR, weight and height as covariates.

SBP_{CA}		**Men**			**Women**	
Variables	Estimate	SE	P-value	Estimate	SE	P-value
Intercept	153.442	10.9147	1.24E-42	133.752	12.5086	5.73E-26
Height	-0.4048	0.0648	5.16E-10	-0.3170	0.0740	1.90E-05
Weight	0.2310	0.0339	1.23E-11	0.1986	0.0352	1.85E-08
PWV	4.5068	0.3291	1.22E-40	5.6991	0.3333	3.72E-61
HR	-	-	-	-0.0421	0.0508	0.4076
Time	0.8875	0.2988	0.0030	2.0918	0.4823	1.52E-05
Entry-Age	0.0628	0.0748	0.4010	0.3483	0.0813	1.92E-05
$(\text{Entry-Age})^2$	0.0034	0.0120	0.7786	-	-	-
Entry-Age × Time	-0.0105	0.0099	0.2894	-0.0276	0.0098	0.0050
$(\text{Entry-Age})^2$ × Time	-0.0032	0.0016	0.0489	-	-	-
PWV × Time	-0.0933	0.0418	0.0257	-0.1371	0.0379	0.0003
HR × Time	-	-	-	-0.0163	0.0070	0.0189
R (Obs. vs. Pred.)		0.938			0.927	
R^2		0.672			0.668	
DBP		**Men**			**Women**	
Variables	Estimate	SE	P-value	Estimate	SE	P-value
Intercept	72.1116	7.5564	4.42E-21	64.9088	7.0789	1.18E-19
Height	-0.2476	0.0433	1.29E-08	-0.2163	0.0421	3.05E-07
Weight	0.1957	0.0224	4.86E-18	0.2131	0.0199	3.86E-26
PWV	3.3439	0.2438	9.42E-41	3.3234	0.2073	1.99E-54
HR	0.1920	0.0250	2.59E-14	0.1682	0.0251	2.75E-11
Time	1.2637	0.1868	1.81E-11	1.1286	0.1530	2.39E-13
Entry-Age	0.6096	0.1724	0.0004	0.3456	0.1395	0.0133
Entry-Age × Time	-0.0215	0.0064	0.0007	-0.0163	0.0059	0.0058
PWV × Time	-0.1547	0.0270	1.13E-08	-0.1421	0.0218	8.56E-11
PWV × Entry-Age	-0.0950	0.0257	0.0002	-0.0642	0.0203	0.0016
R (Obs. vs. Pred.)		0.963			0.970	
R^2		0.747			0.770	
PP_{CA}		**Men**			**Women**	
Variables	Estimate	SE	P-value	Estimate	SE	P-value
Intercept	80.6319	8.0216	3.72E-23	58.4179	11.1176	1.65E-07
Height	-0.1490	0.0430	0.0005	-0.0439	0.0635	0.4891
PWV	1.8778	0.1991	1.22E-20	2.6654	0.1831	1.16E-45
HR	-0.2274	0.0289	5.71E-15	-0.2438	0.0427	1.30E-08
Time	-0.0732	0.0441	0.0975	3.7871	1.3272	0.0044
Entry-Age	0.0296	0.0600	0.6211	0.3591	0.0555	1.19E-10
$(\text{Entry-Age})^2$	-	-	-	0.0193	0.0087	0.0264
Entry-Age × Time	0.0180	0.0073	0.0142	-	-	-

Height × Time	-	-	-	-0.0185	0.0076	0.0143
HR × Time	-	-	-	-0.0132	0.0056	0.0178
R (Obs. vs. Pred.)		0.756			0.786	
R^2		0.332			0.430	
MAP		**Men**			**Women**	
Variables	Estimate	SE	P-value	Estimate	SE	P-value
Intercept	101.881	8.2611	1.39E-33	92.1053	8.2579	4.80E-28
Height	-0.3024	0.0476	2.60E-10	-0.2717	0.0493	4.00E-08
Weight	0.2208	0.0246	7.07E-19	0.2233	0.0232	1.67E-21
PWV	3.5366	0.2436	3.38E-45	3.9987	0.2204	4.43E-68
HR	0.1893	0.0271	4.17E-12	0.1657	0.0288	1.03E-08
Time	0.8710	0.2005	1.48E-05	1.0480	0.1691	6.98E-10
Entry-Age	0.0332	0.0549	0.5451	0.0642	0.0548	0.2418
$(\text{Entry-Age})^2$	-0.0170	0.0080	0.0333	-	-	-
Entry-Age × Time	-0.0243	0.0067	0.0003	-0.0221	0.0061	0.0003
PWV × Time	-0.1164	0.0287	5.17E-05	-0.1456	0.0238	1.10E-09
R (Obs. vs. Pred.)		0.931			0.916	
R^2		0.690			0.670	

Table S5. Generalized linear mixed-effects models of the longitudinal effects on impedance indices for men and women, including covariates.

SVR	**Men**			**Women**		
Variables	Estimate	SE	P-value	Estimate	SE	P-value
Intercept	1.7469	0.1745	5.30E-23	2.1644	0.1720	5.38E-35
Height	-0.0061	0.0010	2.38E-09	-0.0074	0.0010	1.18E-12
Weight	-0.0020	0.0005	0.0001	-0.0031	0.0006	4.88E-08
HR	-0.0056	0.0006	9.96E-24	-0.0073	0.0006	2.52E-33
Time	-0.0019	0.0008	0.0101	-0.0075	0.0042	0.0723
Entry-Age	0.0150	0.0059	0.0107	0.0042	0.0011	0.0002
(Entry-Age)^2	-	-	-	0.0003	0.0002	0.1220
Entry-Age ×Time	-	-	-	-0.0003	0.0001	0.0165
(Entry-Age)^2 ×Time	-	-	-	-5.13E-05	2.09E-05	0.0142
Weight ×Time	-	-	-	0.0002	6.07E-05	0.0076
HR × Entry-Age	-0.0002	9.41E-05	0.0152	-	-	-
R (Obs. vs. Pred.)		0.887			0.892	
R^2		0.360			0.406	
C_{PPM}	**Men**			**Women**		
Variables	Estimate	SE	P-value	Estimate	SE	P-value
Height	0.0036	0.0004	6.64E-17	0.0031	0.0004	3.85E-13
Weight	0.0062	0.0006	5.73E-25	0.0080	0.0005	3.64E-46
MAP	-0.0061	0.0006	5.69E-21	-0.0089	0.0006	1.62E-47
HR	-0.0065	0.0007	4.43E-22	-0.0040	0.0007	3.31E-09
Time	0.0396	0.0086	4.83E-06	0.0449	0.0079	1.38E-08
Entry-Age	-0.0149	0.0075	0.0475	0.0094	0.0078	0.2299
(Entry-Age)^2	-	-	-	-0.0005	0.0002	0.0096
Entry-Age × Time	-0.0007	0.0002	8.96E-06	-	-	-
MAP × Time	-0.0003	8.40E-05	5.96E-05	-0.0004	7.73E-05	4.19E-08
MAP × Entry-Age	-	-	-	-0.0002	7.66E-05	0.0172
Weight × Entry-Age	0.0002	9.20E-05	0.0573	-	-	-
R (Obs. vs. Pred.)		0.872			0.815	
R^2		0.400			0.314	
Z_c	**Men**			**Women**		
Variables	Estimate	SE	P-value	Estimate	SE	P-value
Intercept	-2.0366	0.1041	1.87E-77	-1.7509	0.1031	1.84E-60
Weight	-0.0041	0.0007	4.29E-08	-0.0055	0.0007	6.69E-14
MAP	0.0001	0.0009	0.9134	0.0006	0.0009	0.5028
HR	-	-	-	-0.0024	0.0010	0.0141
Time	-0.0549	0.0123	8.31E-06	-0.0640	0.0117	5.35E-08
Entry-Age	-0.0101	0.0019	5.40E-08	-0.0330	0.0110	0.0028
(Entry-Age)^2	0.0009	0.0003	0.0005	0.0007	0.0002	0.0075
Entry-Age × Time	0.0008	0.0002	0.0005	0.0005	0.0002	0.0229

MAP × Time	0.0005	0.0001	5.81E-05	0.0006	0.0001	7.72E-07
MAP × Entry-Age	-	-	-	0.0003	0.0001	0.0093
R (Obs. vs. Pred.)		0.843			0.805	
R^2		0.249			0.209	

Table S6. Linear mixed-effects models of the longitudinal effects on the reflection coefficient ($|\Gamma_1|$), RWTT, and the amplitudes of the forward ($|P_f|$) and reflected ($|P_b|$) pressure waves for men and women, including HR, height, weight and MAP as covariates.

$\|\Gamma_1\|$	Men			Women		
Variables	Estimate	SE	P-value	Estimate	SE	P-value
Intercept	0.7319	0.0865	5.25E-17	0.8479	0.0753	1.64E-28
Height	-0.0009	0.0005	0.0684	-0.0016	0.0004	0.0003
Weight	-0.0006	0.0003	0.0244	-0.0007	0.0003	0.0088
MAP	0.0017	0.0003	1.18E-10	0.0017	0.0002	1.62E-18
HR	-0.0040	0.0002	1.27E-63	-0.0042	0.0003	1.65E-34
Time	0.0254	0.0113	0.0241	-0.0198	0.0035	2.06E-08
Entry-Age	0.0017	0.0004	1.06E-05	0.0019	0.0004	4.89E-06
$(\text{Entry-Age})^2$	-0.0002	6.32E-05	0.0018	-	-	-
Height × Time	-0.0002	6.35E-05	0.0021	-	-	-
MAP × Time	-0.0001	3.30E-05	0.0393	-	-	-
Weight × Time	0.0001	3.41E-05	5.17E-05	0.0001	3.05E-05	0.0037
HR × Time	-	-	-	0.0002	4.52E-05	0.0002
R (Obs. vs. Pred.)		0.704			0.699	
R^2		0.361			0.310	
RWTT	**Men**			**Women**		
Variables	Estimate	SE	P-value	Estimate	SE	P-value
Intercept	0.0509	0.0166	0.0022	0.1219	0.0047	9.14E-127
Height	0.0004	9.15E-05	1.42E-05	-	-	-
Weight	0.0001	4.93E-05	0.1040	0.0001	3.36E-05	4.55E-05
MAP	-0.0004	4.63E-05	1.66E-17	-0.0005	4.06E-05	5.12E-32
HR	-0.0003	6.39E-05	8.54E-08	-0.0003	4.54E-05	3.33E-14
Time	-0.0018	0.0006	0.0036	-0.0022	0.0006	9.07E-05
Entry-Age	-0.0026	0.0006	1.44E-05	-0.0039	0.0006	1.17E-09
$(\text{Entry-Age})^2$	5.76E-05	1.50E-05	0.0001	-	-	-
HR × Entry-Age	1.85E-05	7.81E-06	0.0178	-	-	-
HR × Time	2.26E-05	9.85E-06	0.0218	-	-	-
MAP × Time	-	-	-	1.53E-05	5.44E-06	0.0050
MAP × Entry-Age	-	-	-	1.91E-05	5.14E-06	0.0002
Weight × Entry-Age	1.94E-05	7.18E-06	0.0070	-	-	-
R (Obs. vs. Pred.)		0.856			0.800	
R^2		0.494			0.455	
$\|P_f\|$	**Men**			**Women**		
Variables	Estimate	SE	P-value	Estimate	SE	P-value
Intercept	20.5095	8.1615	0.0121	15.1044	7.2268	0.0367
Height	0.0881	0.0442	0.0463	0.0821	0.0407	0.0439
Weight	0.0444	0.0289	0.1248	-0.0261	0.0251	0.2980
MAP	0.0714	0.0289	0.0135	0.2132	0.0239	9.03E-19

HR	-0.0696	0.0261	0.0078	-0.1118	0.0321	0.0005
Time	-1.7437	0.4030	1.59E-05	-1.1839	0.3919	0.0026
Entry-Age	-1.1478	0.3511	0.0011	-0.9551	0.2855	0.0008
$(\text{Entry-Age})^2$	0.0256	0.0073	0.0005	0.0128	0.0079	0.1053
Entry-Age ×Time	0.0291	0.0069	2.29E-05	0.0152	0.0061	0.0128
$(\text{Entry-Age})^2$ × Time	-	-	-	0.0022	0.0010	0.0276
Weight ×Time	-0.0097	0.0032	0.0029	-0.0060	0.0029	0.0394
HR ×Time	-	-	-	-0.0115	0.0043	0.0072
MAP × Time	0.0238	0.0036	3.28E-11	0.0214	0.0031	7.38E-12
MAP × Entry-Age	0.0092	0.0035	0.0083	0.0100	0.0028	0.0004
R (Obs. vs. Pred.)		0.740			0.741	
R^2		0.302			0.379	
$\lvert \mathbf{P_b} \rvert$		**Men**			**Women**	
Variables	Estimate	SE	P-value	Estimate	SE	P-value
Intercept	21.1319	4.6381	5.56E-06	15.6762	1.3687	1.91E-29
Height	-0.0201	0.0238	0.3982	-	-	-
Weight	-	-	-	-0.0493	0.0089	3.37E-08
MAP	0.1146	0.0140	5.16E-16	0.1825	0.0121	8.78E-49
HR	-0.1456	0.0122	1.06E-31	-0.1659	0.0123	6.18E-40
Time	0.2100	0.5631	0.7093	-1.1234	0.1551	6.31E-13
Entry-Age	-0.3501	0.1644	0.0333	-0.0696	0.1886	0.7121
Height × Time	-0.0069	0.0029	0.0191	-	-	-
MAP × Time	0.0076	0.0017	7.74E-06	0.0093	0.0015	1.14E-09
MAP × Entry-Age	0.0039	0.0016	0.0142	0.0089	0.0014	5.71E-10
HR × Entry-Age	-	-	-	-0.0067	0.0021	0.0015
Weight × Entry-Age	-	-	-	-0.0036	0.0015	0.0153
R (Obs. vs. Pred.)		0.910			0.921	
R^2		0.554			0.643	

Table S7. Generalized linear mixed-effects models examining the associations between PWV and traditional cardiovascular risk factors for men and women.

PWV	**Men**			**Women**		
Variables	Estimate	SE	P-value	Estimate	SE	P-value
Intercept	1.5197	0.0286	0.0000	1.5855	0.0388	1.97E-264
Time	0.0065	0.0008	1.33E-15	-0.0033	0.0056	0.5583
Entry-Age	0.0098	0.0008	7.05E-32	0.0095	0.0008	9.46E-34
HR	0.0049	0.0005	4.87E-25	0.0034	0.0006	6.26E-09
HR × Time	-	-	-	0.0002	0.0001	0.0079
Obesity	0.0498	0.0142	0.0005	0.0373	0.0139	0.0073
Overweight	0.0147	0.0093	0.1141	0.0117	0.0093	0.2072
Diabetes (Yes)	-	-	-	-0.0374	0.0366	0.3071
Diabetes (Yes) × Entry-Age	-	-	-	0.0181	0.0069	0.0086
Hypertension (Yes)	0.1010	0.0092	4.18E-27	0.1334	0.0092	2.12E-45
Lipid-lowering drugs (Yes)	-0.4882	0.0902	7.17E-08	-0.4961	0.1039	1.94E-06
Lipid-lowering drugs (Yes) × Time	0.0471	0.0089	1.31E-07	0.0476	0.0103	4.04E-06
Lipid-lowering drugs (Yes) × Entry-Age	0.0045	0.0022	0.0364	-	-	-
Weekly alcohol intake	0.0006	0.0003	0.0270	-	-	-
Education (not beyond secondary school)	-0.0200	0.0092	0.0290	-	-	-
R (Obs. vs. Pred.)		0.897			0.887	
R^2		0.938			0.943	

Table S8. Generalized linear mixed-effects models examining the associations between impedance parameters and traditional cardiovascular risk factors for men and women.

SVR		**Men**			**Women**	
Variables	Estimate	SE	P-value	Estimate	SE	P-value
Intercept	0.4872	0.0410	2.03E-31	0.7013	0.0387	6.77E-68
Time	0.0065	0.0051	0.2050	0.0012	0.0010	0.2278
Entry-Age	0.0149	0.0059	0.0112	0.0030	0.0010	0.0020
HR	-0.0051	0.0007	1.84E-14	-0.0068	0.0006	2.78E-30
HR × Time	-0.0002	0.0001	0.0363	-	-	-
HR × Entry-Age	-0.0002	0.0001	0.0187	-	-	-
Obesity	-0.0666	0.0172	0.0001	-0.0499	0.0167	2.82E-03
Overweight	-0.0411	0.0112	0.0003	-0.0265	0.0110	0.0156
Diabetes (Yes)	-	-	-	-0.1048	0.0383	0.0063
Hypertension (Yes)	0.1198	0.0108	1.68E-27	0.1649	0.0141	1.54E-30
Hypertension (Yes) × Time	-	-	-	-0.0056	0.0017	0.0012
Education (not beyond secondary school)	-0.0327	0.0120	0.0063	-	-	-
R (Obs. vs. Pred.)		0.881			0.897	
R^2		0.194			0.419	
C_{PPM}		**Men**			**Women**	
Variables	Estimate	SE	P-value	Estimate	SE	P-value
Intercept	0.6022	0.0464	5.91E-37	0.3637	0.0478	4.43E-14
Time	0.0011	0.0028	0.6913	0.0025	0.0010	0.0128
Entry-Age	-0.0020	0.0014	0.1474	-0.0081	0.0014	3.14E-09
Entry-Age ×Time	-0.0006	0.0002	0.0018	-	-	-
HR	-0.0083	0.0007	1.12E-32	-0.0073	0.0007	3.01E-23
Obesity	0.1367	0.0212	1.40E-10	0.1584	0.0205	1.63E-14
Overweight	0.0646	0.0140	4.14E-06	0.0771	0.0136	1.79E-08
Diabetes (Yes)	-0.0854	0.0346	0.0137	0.1017	0.0504	0.0439
Diabetes (Yes) × Entry-Age	-	-	-	-0.0170	0.0096	0.0771
Smoker (Ex-smoker)	0.0095	0.0213	0.6565	-	-	-
Smoker (Never smoked)	0.0431	0.0204	0.0351	-	-	-
Smoker (Ex-smoker) × Time	0.0063	0.0033	0.0617	-	-	-
Smoker (Never smoked) × Time	0.0061	0.0032	0.0539	-	-	-
Hypertension (Yes)	-0.1612	0.0138	2.89E-30	-0.2495	0.0134	1.64E-71
Hypertension (Yes) × Entry-Age	-	-	-	-0.0066	0.0021	0.0019
R (Obs. vs. Pred.)		0.870			0.867	
R^2		0.371			0.320	
Z_c		**Men**			**Women**	
Variables	Estimate	SE	P-value	Estimate	SE	P-value
Intercept	-2.4293	0.0571	1.32E-274	-2.1993	0.0151	0.0000
Time	-0.0100	0.0018	1.52E-08	-0.0072	0.0015	1.82E-06
Entry-Age	-0.0104	0.0019	2.46E-08	-0.0083	0.0019	2.36E-05

$(Entry-Age)^2$	0.0008	0.0003	0.0022	0.0005	0.0003	0.0365
Entry-Age × Time	0.0007	0.0002	0.0049	0.0007	0.0002	0.0038
HR	0.0017	0.0009	0.0624	-	-	-
Obesity	-0.1179	0.0277	2.24E-05	-0.1185	0.0268	1.04E-05
Overweight	-0.0401	0.0185	0.0302	-0.0799	0.0182	1.20E-05
Diabetes (Yes)	0.0515	0.0488	0.2912	-	-	-
Diabetes (Yes) × Entry-Age	0.0191	0.0081	0.0184	-	-	-
Hypertension (Yes)	0.0197	0.0247	0.4248	0.1206	0.0180	3.03E-11
Hypertension (Yes) × Time	0.0087	0.0031	0.0052	-	-	-
Hypertension (Yes) × Entry-Age	-	-	-	0.0100	0.0030	0.0008
Lipid-lowering drugs (Yes)	-	-	-	-0.5348	0.1928	0.0056
Lipid-lowering drugs (Yes) × Time	-	-	-	0.0490	0.0189	0.0096
R (Obs. vs. Pred.)		0.841			0.801	
R^2		0.247			0.208	

Table S9. Linear mixed-effects models examining the associations between wave reflection parameters and traditional cardiovascular risk factors for men and women.

$\lvert\Gamma_1\rvert$	Men			Women		
Variables	Estimate	SE	P-value	Estimate	SE	P-value
Intercept	0.6668	0.0155	1.59E-278	0.6703	0.0212	4.69E-177
Time	-0.0021	0.0012	0.0717	-0.0104	0.0032	0.0014
Entry-Age	0.0036	0.0006	4.05E-10	0.0025	0.0004	2.62E-09
$(\text{Entry-Age})^2$	-0.0002	0.0001	0.0007	-	-	-
HR	-0.0036	0.0002	4.22E-55	-0.0035	0.0003	6.17E-29
HR × Time	-	-	-	0.0001	4.70E-05	0.0024
Obesity	-0.0027	0.0084	0.7466	-0.0131	0.0096	0.1745
Overweight	-0.0088	0.0053	0.0980	-0.0073	0.0062	0.2424
Obesity × Time	0.0030	0.0012	0.0120	0.0032	0.0012	0.0112
Overweight × Time	0.0013	0.0009	0.1241	0.0024	0.0009	0.0098
Diabetes (Yes)	-0.0024	0.0131	0.8534	-	-	-
Diabetes (Yes) × Entry-Age	-0.0047	0.0021	0.0253	-	-	-
Smoker (Ex-smoker)	0.0001	0.0069	0.9860	-0.0008	0.0085	0.9219
Smoker (Never smoked)	0.0068	0.0065	0.2995	-0.0092	0.0072	0.2029
Smoker (Ex-smoker) × Time	-0.0026	0.0012	0.0313	-0.0029	0.0014	0.0349
Smoker (Never smoked) × Time	-0.0036	0.0012	0.0018	-0.0011	0.0012	0.3749
Hypertension (Yes)	0.0303	0.0059	3.73E-07	0.0304	0.0065	3.23E-06
Hypertension (Yes) × Time	-0.0020	0.0008	0.0178	-0.0021	0.0009	0.0170
Lipid-lowering drugs (Yes)	-	-	-	0.1315	0.0582	0.0240
Lipid-lowering drugs (Yes) × Time	-	-	-	-0.0136	0.0058	0.0189
Education (not beyond secondary school)	-0.0031	0.0044	0.4827	-	-	-
Education (not beyond secondary school) × Time	-0.0020	0.0007	0.0071	-	-	-
R (Obs. vs. Pred.)		0.868			0.879	
R^2		0.519			0.471	

$\lvert P_f\rvert$	Men			Women		
Variables	Estimate	SE	P-value	Estimate	SE	P-value
Intercept	44.4901	1.6067	1.28E-140	44.0198	1.5827	8.33E-144
Time	-0.1748	0.0681	0.0103	-0.2053	0.0472	1.44E-05
Entry-Age	-0.2809	0.0525	9.88E-08	-0.0905	0.0476	0.0574
$(\text{Entry-Age})^2$	0.0323	0.0089	0.0003	0.0150	0.0062	0.0151
Entry-Age ×Time	0.0270	0.0072	0.0002	0.0159	0.0063	0.0125
$(\text{Entry-Age})^2$ ×Time	-0.0022	0.0012	0.0612	-	-	-
HR	-0.0545	0.0250	0.0296	-0.0810	0.0238	0.0007
Diabetes (Yes)	2.6433	1.3918	0.0577	-	-	-
Diabetes (Yes) × Entry-Age	0.5372	0.2281	0.0186	-	-	-
Hypertension (Yes)	3.7852	0.7046	0.0000	7.7663	0.6228	2.11E-34
Hypertension (Yes) × Time	0.2518	0.0919	0.0062	0.2363	0.0818	0.0039

Hypertension (Yes) × Entry-Age	-	-	-	0.3333	0.0757	1.12E-05
Lipid-lowering drugs (Yes)	10.0653	4.9305	0.0414	-2.4072	0.7726	0.0019
Lipid-lowering drugs (Yes) × Time	0.9069	0.4854	0.0619	-	-	-
Education (not beyond secondary school)	0.4946	0.5001	0.3228	-	-	-
R (Obs. vs. Pred.)		0.770			0.811	
R^2		0.312			0.451	
$\lvert P_b \rvert$		**Men**			**Women**	
Variables	Estimate	SE	P-value	Estimate	SE	P-value
Intercept	27.1468	0.7945	1.16E-197	25.7834	0.8803	9.57E-157
Time	-0.2374	0.0222	7.81E-26	-0.2467	0.0535	4.23E-06
Entry-Age	0.0303	0.0206	0.1413	0.0851	0.0231	0.0002
HR	-0.1167	0.0119	2.84E-22	-0.1035	0.0125	2.14E-16
Diabetes (Yes)	0.8516	0.6313	0.1775	-	-	-
Diabetes (Yes) × Entry-Age	0.2321	0.1028	0.0241	-	-	-
Smoker (Ex-smoker)	-0.5598	0.3304	0.0903	-0.4195	0.4404	0.3410
Smoker (Never smoked)	-0.9376	0.3234	0.0038	-0.7357	0.3716	0.0479
Smoker (Ex-smoker) × Time	-	-	-	0.0154	0.0655	0.8141
Smoker (Never smoked) × Time	-	-	-	0.1040	0.0581	0.0738
Hypertension (Yes)	3.5643	0.2415	1.27E-46	5.2166	0.2368	2.79E-96
Hypertension (Yes) × Entry-Age	-	-	-	0.1649	0.0379	1.39E-05
Lipid-lowering drugs (Yes)	-6.6480	2.2426	0.0031	-1.0349	0.3898	0.0080
Lipid-lowering drugs (Yes) × Time	0.6239	0.2216	0.0049	-	-	-
R (Obs. vs. Pred.)		0.837			0.700	
R^2		0.432			0.387	

Table S10. Baseline characteristics of subjects with complete dataset and subjects with missing data at follow-up.

	Complete dataset (N=1757)	Missing data (N=269)	P-value
Women, %	52.36	49.07	0.3143
Age, years	45.13 (40.6-49.8)	45.06 (40.1-50.8)	0.6043
Height, cm	169.47 ± 8.75	169.21 ± 9.15	0.6489
Weight, kg	71.1 (62.1-81.4)	72.9 (63.7-84.2)	0.0144
BMI, kg/m^2	24.7 (22.5-27.1)	25.5 (22.8-28.3)	0.0005
BSA, m^2	1.83 ± 0.20	1.85 ± 0.21	0.1252
SBP_{CA}, mmHg	129.19 ± 16.07	131.55 ± 15.43	0.0244
DBP, mmHg	76.36 ± 10.73	78.66 ± 10.16	0.0010
MAP, mmHg	99.40 ± 11.82	101.71 ± 11.41	0.0027
PP_{CA}, mmHg	52.83 ± 11.30	52.89 ± 10.87	0.9325
HR, bpm	63.28 ± 9.07	66.13 ± 10.47	2.94E-06
SV, mL	78.21 ± 18.09	78.85 ± 19.33	0.5923
CO, L/min	4.89 ± 1.10	5.15 ± 1.22	0.0006
LVOT area, cm^2	3.27 ± 0.69	3.28 ± 0.71	0.7426
Diabetes, %	0.74	1.49	0.2110
Obesity, %	9.39	17.84	2.56E-05
Overweight, %	36.99	36.06	0.7671
Active smoker, %	18.33	31.23	8.56E-07
Ex-smoker, %	27.26	24.54	0.3476
Weekly alcohol intake, u/week	10 (5-21)*	12 (6-24)*	0.0189
Education beyond secondary school, %	39.61*	30.86*	0.0226

Data are expressed as mean ± SD, median (interquartile range) or percent. BMI: body mass index; BSA: body surface area; DBP: diastolic blood pressure; MAP: mean arterial pressure; SBP_{CA} and PP_{CA}: carotid systolic and pulse pressure; HR: heart rate; SV: stroke volume; CO: cardiac output; LVOT: left ventricular outflow tract. P<0.05 significant differences comparing groups by using Student t-test for continuous variables and a chi-square test for categorical variables. *Missing values.

Table S11. Differences between two groups of subjects with the same mean age but from distinct decade, explained by lifestyle- and social-related factors.

Variables	F	P-value
$\|\Gamma_1\|$:		**<0.001***
Group × Education	5.09	0.02
Group × Obesity	3.38	0.03
Group × Smoker	3.10	0.04
RWTT:		**0.001***
Group × Obesity	3.23	0.04
$\|P_b\|$:		**<0.001***
Group × Education	3.79	0.05

*****P<0.05 t-unpaired test determining whether the difference between the mean of both groups was statistically significant. Regression models included terms shown, sex, age, and weekly alcohol intake (units/week); all group interaction terms were evaluated. Only significant (P<0.05) group interaction terms in the hypothesis tests are reported.

Supplemental Figures

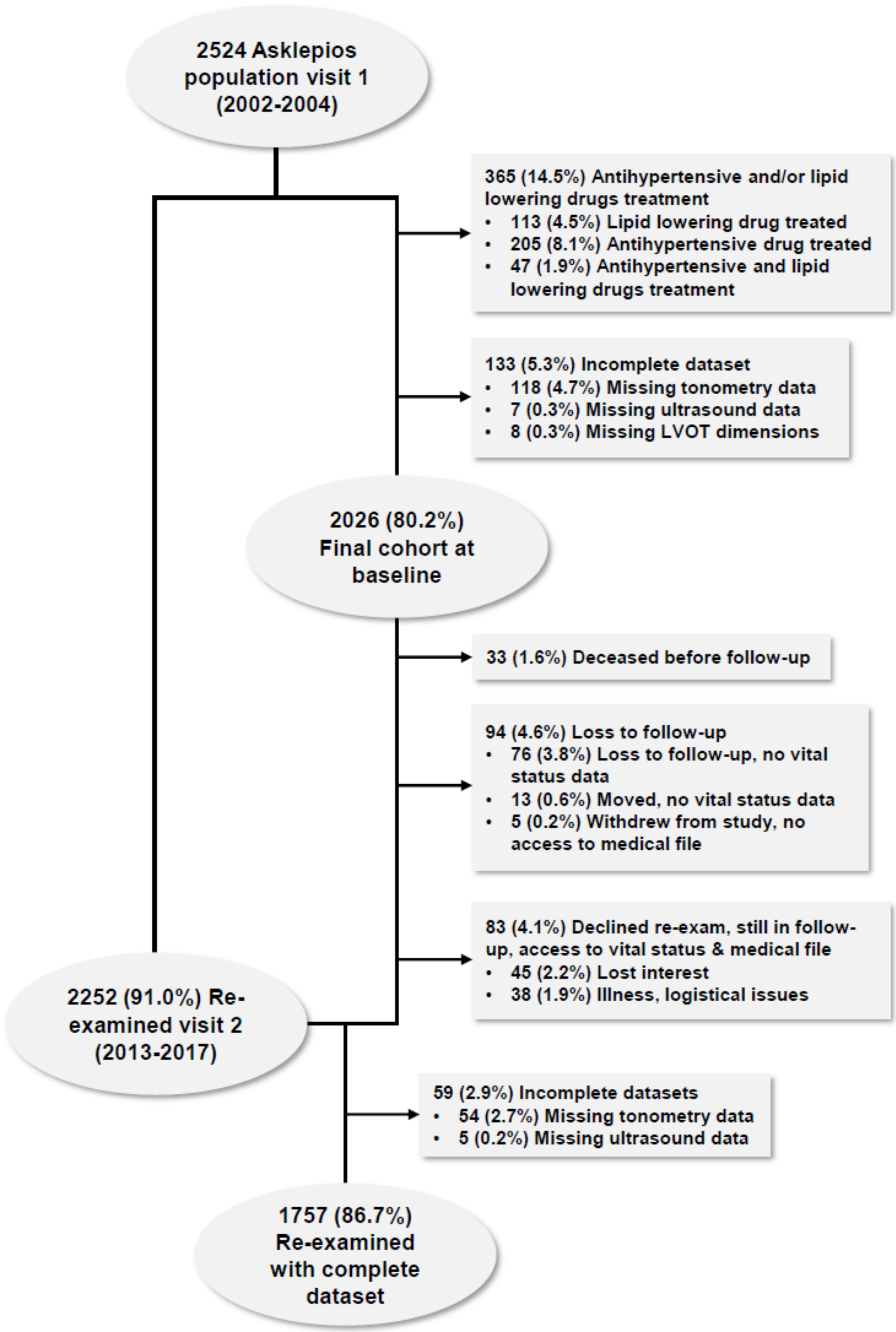


Figure S1. Flow chart of the Asklepios study – baseline and follow-up.

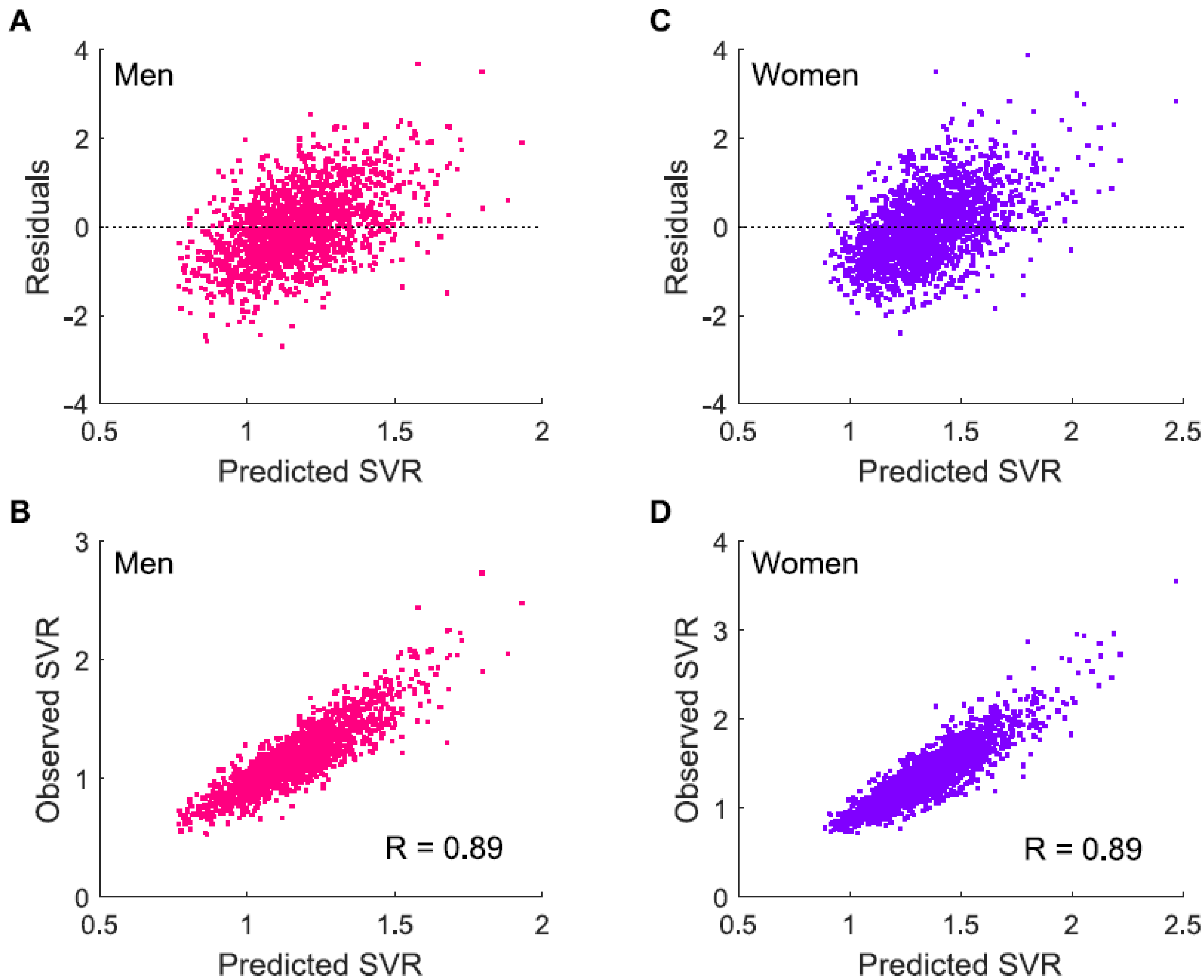


Figure S2. Residuals vs. predicted values of SVR for men and women (A and C). Correlation between observed and predicted values of SVR for men and women (B and D). The plots refer to models in Table S5.

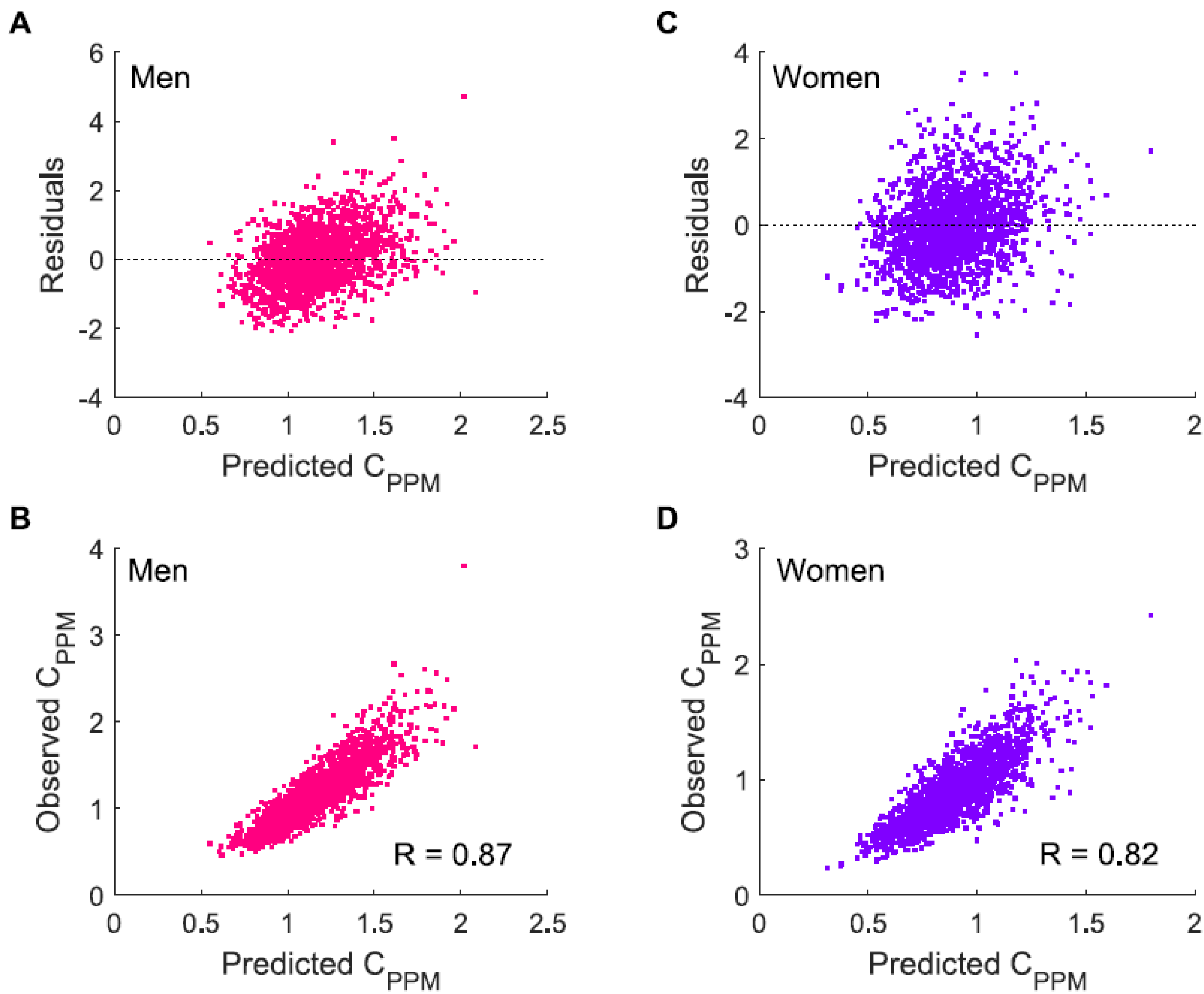


Figure S3. Residuals vs. predicted values of C_{PPM} for men and women (A and C). Correlation between observed and predicted values of C_{PPM} for men and women (B and D). The plots refer to models in Table S5.

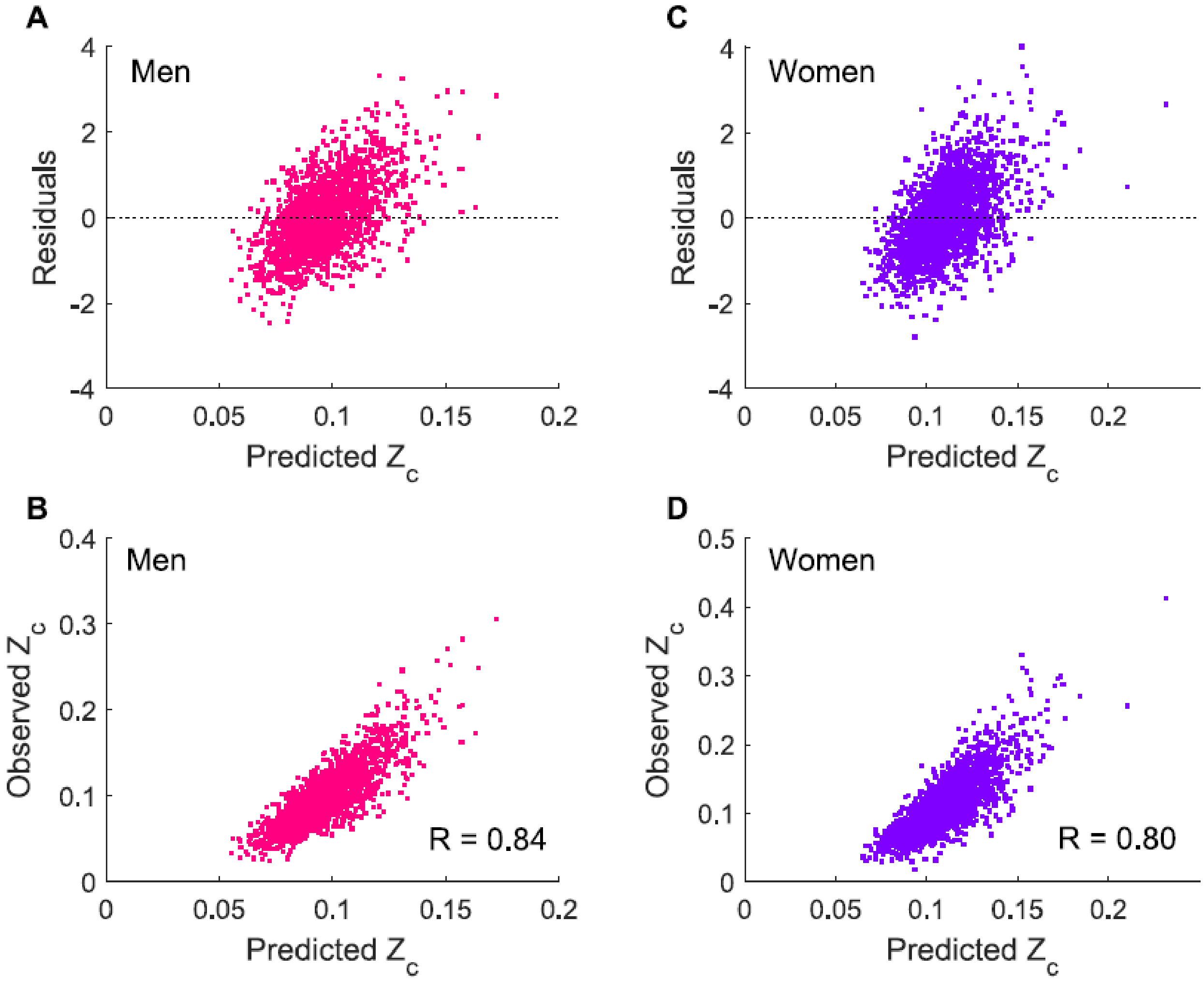
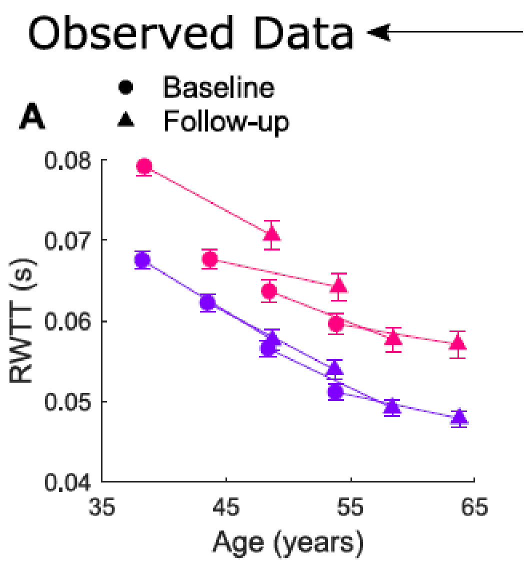


Figure S4. Residuals vs. predicted values of Z_c for men and women (A and C). Correlation between observed and predicted values of Z_c for men and women (B and D). The plots refer to the models in Table S5.



	F	P
Age	71.59	6.33E-45
Sex	149.97	8.61E-34
Visit	125.15	1.44E-28
Age x Sex	1.96	0.1182
Age x Visit	3.90	0.0086
Sex x Visit	3.00	0.0834

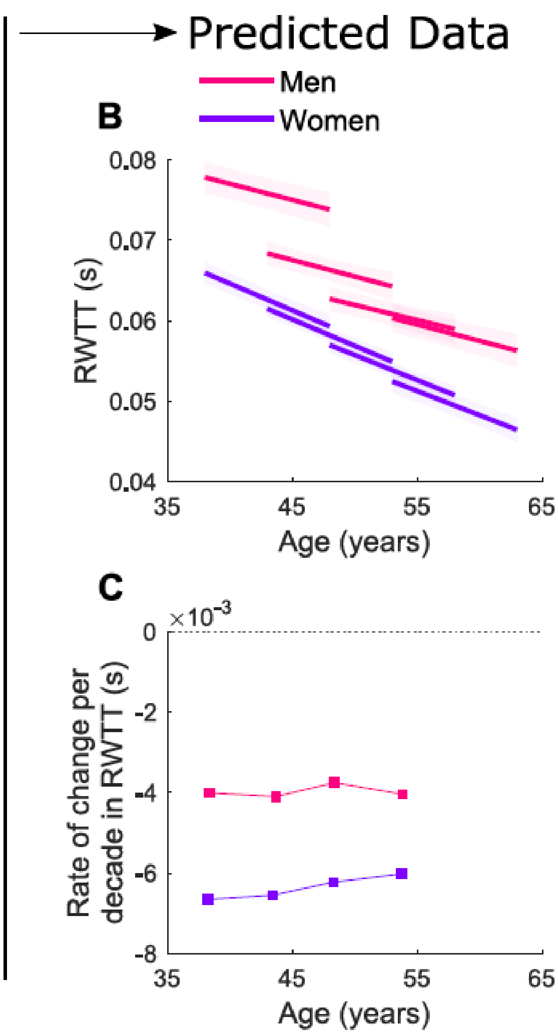


Figure S5. Observed (A) and predicted (B) longitudinal trajectories in RWTT per sex and age strata. Shaded area represents the non-simultaneous 95% confidence intervals. (C) Model-predicted rate of change per decade in RWTT for men and women. The plots of the predictions refer to models in Table S6. The P and F values in the table indicate the statistical significance of the factors age, sex, visit, and their interaction in the ANOVA. Values of the observations are mean ± SEM.

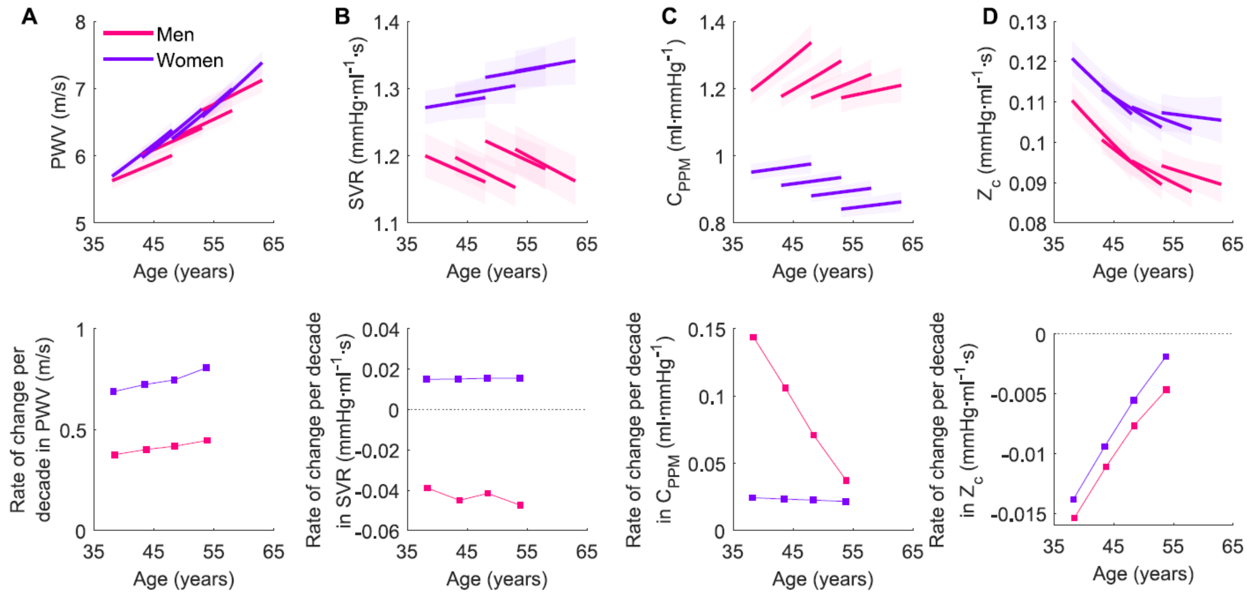


Figure S6. Model-predicted longitudinal trajectories (top) and rate of change per decade (bottom) in PWV (A), SVR (B), C_{PPM} (C), and Z_c (D) for average subjects (men and women) without cardiovascular risk factors and per age group. Shaded area represents the non-simultaneous 95% confidence intervals. The plots refer to models in Table S7 and S8.

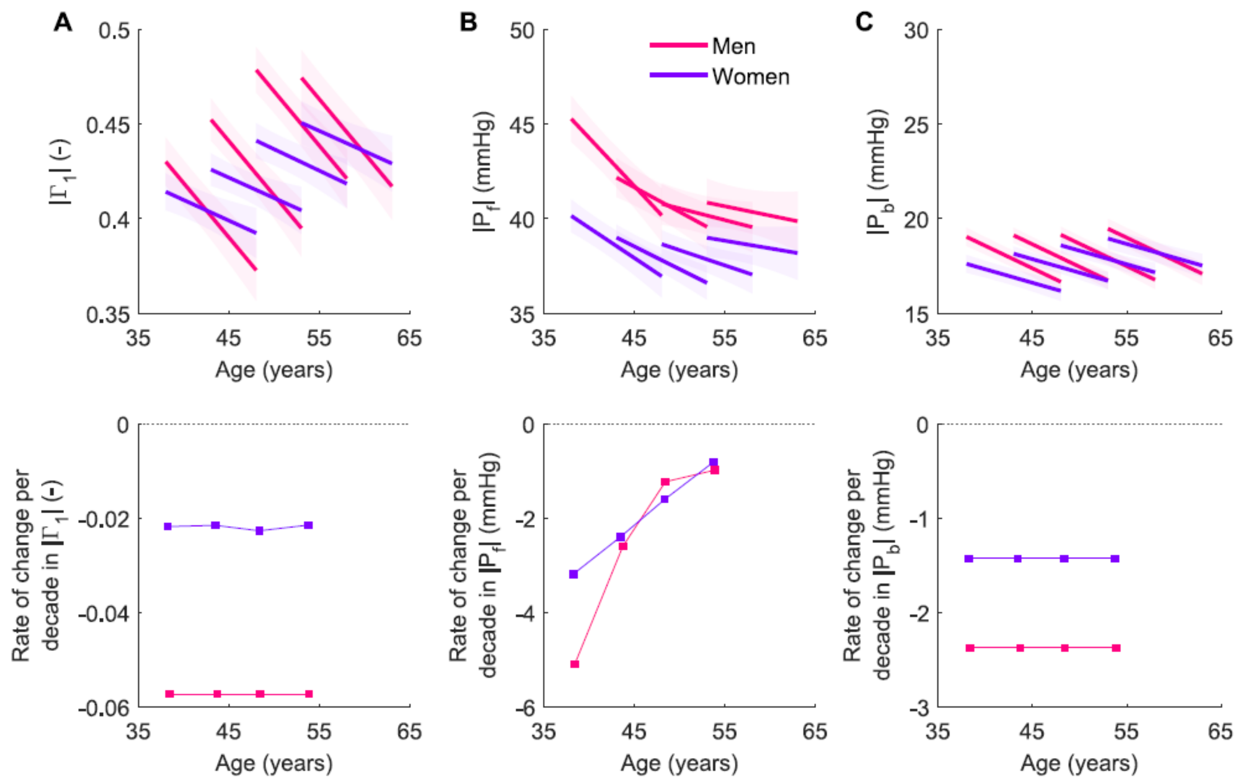


Figure S7. Model-predicted longitudinal trajectories (top) and rate of change per decade (bottom) in $|\Gamma_1|$ (A), $|P_f|$ (B), and $|P_b|$ (C) for average subjects (men and women) without cardiovascular risk factors and per age group. Shaded area represents the non-simultaneous 95% confidence intervals. The plots refer to models in Table S9.

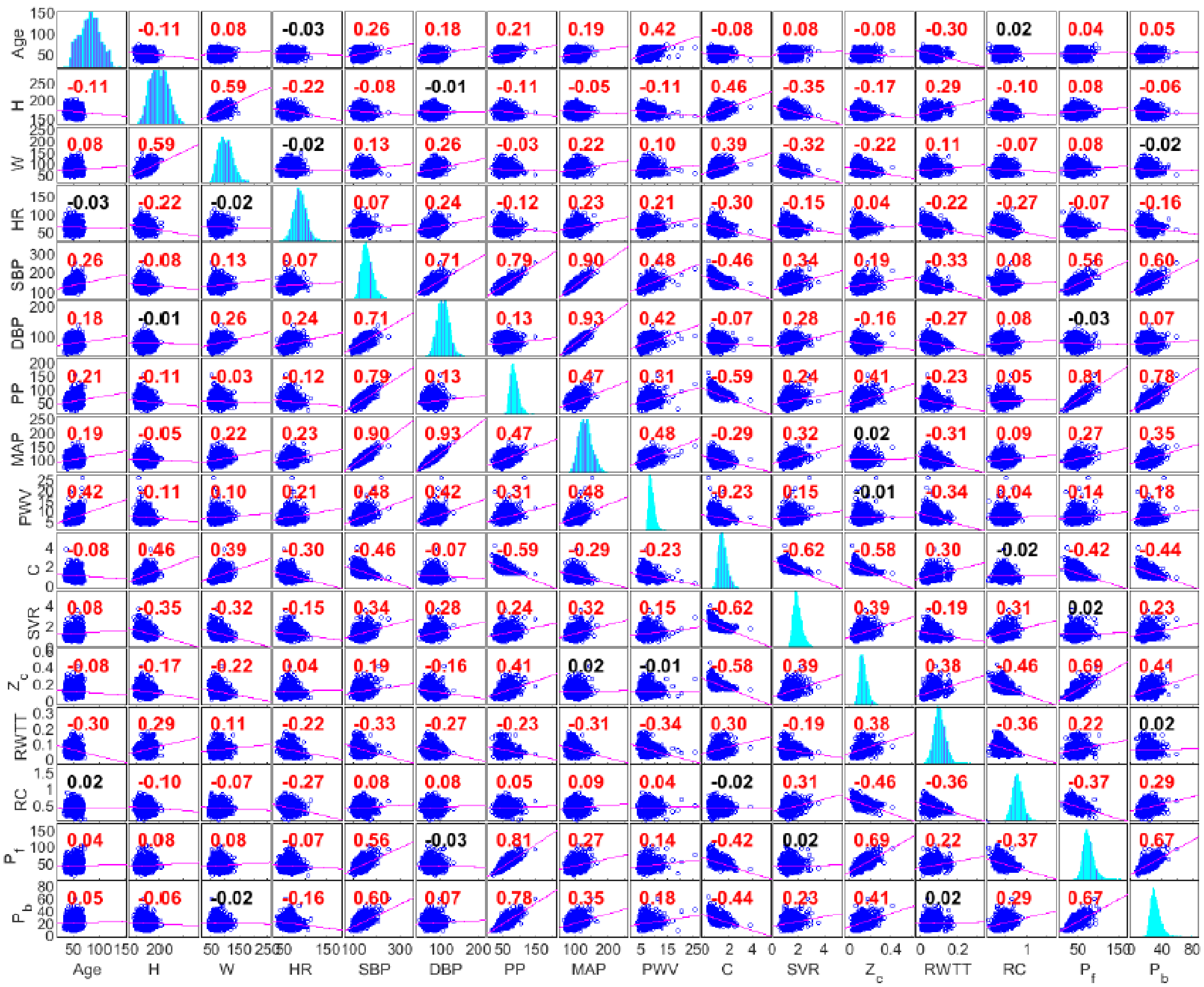


Figure S8. Correlation matrix of key variables in the analyses. Values in red indicate significant correlation. H: height; W: weight; SBP: carotid systolic blood pressure; PP: carotid pulse pressure; C: volume compliance (C_{PPM}); RC: amplitude of the reflection coefficient at the heart frequency ($|\Gamma_1|$).