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ORIGINAL RESEARCH

Impact of Blood Pressure in the Early 40s on Left Atrial Volumes in the Mid-60s: Data From the ACE 1950 Study

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BACKGROUND: Echocardiographic measures of left atrial volumes are powerful predictors of cardiovascular events and important for assessing diastolic dysfunction. Despite this, there is limited knowledge of factors influencing left atrial remodeling. In particular, the impact of blood pressure in those in their early 40s on left atrial volumes later in life has not been sufficiently elucidated.

METHODS AND RESULTS: We linked data from individuals born in 1950 who participated in the Age 40 Program, and the ACE (Akershus Cardiac Examination) 1950 Study. We divided the study population into quartiles of systolic blood pressure in their early 40s and assessed the proportion of individuals with an enlarged left atrium in their mid-60s. The associations between blood pressure and left atrial volumes were assessed in linear regression analyses. Of the 2591 individuals included in this study, 1302 (50.3%) were women, and the mean age in the Age 40 Program was 40.1±0.3 years. Systolic blood pressure was 128.1±13.6 mm Hg and diastolic blood pressure was 78.3±9.5 mm Hg. Mean age in the ACE 1950 Study was 64.0±0.6 years. The proportion of individuals with an enlarged left atrium increased across the quartiles of systolic blood pressure (P=0.001). Systolic blood pressure was independently associated with left atrial volumes; the end-systolic volume was 0.09 mL (95% CI, 0.04–0.14 mL) larger per 1-mm Hg higher systolic blood pressure.

CONCLUSIONS: Our findings suggest that increased blood pressure in those in their early 40s is relevant for left atrial remodeling later in life.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT01555411.

Key Words: echocardiography ■ high blood pressure ■ hypertension ■ left atrium ■ remodeling

Left atrial (LA) enlargement is associated with cardiovascular morbidity and mortality.[1,2] In the Framingham Heart Study, LA volumetric measures were the echocardiographic parameters most strongly associated with cardiovascular events.[3] They are particularly recognized as predictors of atrial fibrillation.[4,5] Despite the compelling evidence of these parameters being important risk predictors, knowledge of factors upstream of LA remodeling is limited.

To predict cardiovascular events, echocardiographic measurement of LA volume is superior to measurement of the area and diameter.[6] The American Society

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CLINICAL PERSPECTIVE

What Is New?

- Systolic blood pressure at ages 40 to 43 years was independently associated with left atrial volumes at ages 62 to 65 years, most strongly with left atrial maximum volume; diastolic blood pressure had a weaker association with left atrial volumes.
- The association was similar in men and women.
- Blood pressure at ages 40 to 43 years was not associated with left atrial emptying fraction at ages 62 to 65 years.

What Are the Clinical Implications?

- Increased blood pressure in those in their early 40s may induce left atrial remodeling later in life, which may be relevant for the development of atrial fibrillation and heart failure.

Nonstandard Abbreviations and Acronyms

ACE 1950 Study	Akershus Cardiac Examination 1950 Study
E	early transmitral peak velocity inflow
e′	early mitral annular peak velocity
LAEF	left atrial emptying fraction
$LAVi_{max}$	left atrial maximum volume indexed to body surface area
LAV_{max}	left atrial maximum volume (end-systolic)
LAV_{min}	left atrial minimum volume (end-diastolic)

of Echocardiography and the European Association of Cardiovascular Imaging recommend assessing LA maximum (end-systolic) volume indexed to body surface area ($LAVi_{max}$).[7] $LAVi_{max}$ is also part of the diagnostic criteria for diastolic dysfunction[8] representing the burden of increased left ventricular filling pressure over time.[9] However, data suggest that body surface area indexed LA minimum (end-diastolic) volume, and LA emptying fraction (LAEF) may add important prognostic information, including that these indices may be superior to $LAVi_{max}$ in terms of risk assessment.[10–12]

Several risk factors contributing to the development of left ventricular remodeling have been established, but less is known about LA remodeling. An association between increased blood pressure and LA enlargement is well established.[13] LA volume has been demonstrated to be associated with antecedent blood pressure.[14] However, long-term data on the impact of blood pressure in those in their early 40s on LA volumetric measures are limited, particularly on LA minimum volume indexed to body surface area and LAEF.

In a longitudinal population-based study including the 1950 birth cohort, we aimed to investigate the association between measured blood pressure of those in their early 40s and LA volumes and LAEF measured in those in their mid-60s. Our hypothesis was that increased blood pressure would be associated with both LA volumes and inversely associated with LAEF.

METHODS

The data set used in this study is not publicly available; the Data Protection Authority approval and patient consent do not allow for such publication. However, the study group welcomes initiatives for cooperation, and data access may be granted on application. More information is available on the study website (http://www.ace1950.no).

Study Population

The ACE (Akershus Cardiac Examination) 1950 Study is a cohort study designed to investigate the development of cardiovascular disease and its precursors in a general population. All residents of Akershus County, Norway as of 2011, born in 1950, were invited to participate.[15] Baseline examinations were performed from 2012 to 2015, and hence, the participants were aged 62 to 65 years. The ACE 1950 Study was linked to a nationwide cardiovascular health screening survey, the Age 40 Program, conducted by the National Health Screening Services. Participants of the ACE 1950 Study had been examined in 1990 to 1993 at the ages of 40 to 43 years.[16]

Variables From the Age 40 Program

Participants in the Age 40 Program received a questionnaire to fill out at home. This form included questions about history of angina, myocardial infarction, stroke, diabetes, current treatment for hypertension, and current daily smoking. A nurse checked the questionnaire at the study site and measured height and weight. Systolic and diastolic blood pressure in millimeters of mercury and heart rate were measured with an automatic device using an oscillometric method (DINAMAP; Criticon, Tampa, FL). The size of the cuff (small, medium, or large) was chosen according to measurement of the right arm circumference 10 cm above the cubital fossa. After 2 minutes of seated rest, 3 recordings with 1-minute intervals were made. The mean of the second and third blood pressure measurement was used in the analyses. Hypertension was defined as antihypertensive medication use, systolic blood pressure above 140 mm Hg, and/or diastolic blood pressure above 90 mm Hg. We used the first heart rate measurement, because this was the lowest reading and therefore assumed to be the closest representing resting heart rate.

Echocardiography in the ACE 1950 Study

In the ACE 1950 Study, all participants underwent transthoracic echocardiography using a Vivid E9 scanner with M5S probe (GE Healthcare, Horten, Norway). After all recordings were done, images were analyzed using custom software (EchoPAC; GE Vingmed, Horten, Norway). Four trained fellows and 2 ultrasonographers performed recordings and analyses.

Chamber quantifications of the left atrium and left ventricle were performed as recommended by the American Society of Echocardiography and the European Association of Cardiovascular Imaging.[7] If the left atrium was foreshortened in the standard apical 4- and 2-chamber views, examiners were instructed to record left atrium–focused images. We used the summation of discs method to calculate LA volumes. We obtained the end-systolic volume, when the left atrium was at its maximum size (LAV_{max}), by measuring at the frame just before mitral valve opening. By measuring at the frame just before mitral valve closure, we obtained the end-diastolic volume, when the left atrium was at its minimum size (LAV_{min}). When tracing the LAV_{min}, we started and ended at the basal part of the mitral leaflet. LA volumes were indexed to body surface area according to the Mosteller formula.[17] LA enlargement was defined as $LAVi_{max}$ >34 mL/m^2 according to the recommendations of chamber quantifications.[7] We calculated LAEF using the following formula: $LAEF=(LAV_{max-}LAV_{min}/LAV_{max})\times100\%$.

Left ventricular systolic function was assessed with biplane ejection fraction according to the modified Simpson method and with global longitudinal strain using speckle tracking analyses.[18] Left ventricular diastolic function was assessed with pulsed Doppler imaging of transmitral inflow, thereby obtaining early (E) and late (A) peak velocity flow measures. Tissue Doppler imaging of the mitral annular lateral and septal velocity was performed, and the average of the lateral and septal early mitral annular peak velocity (e′) was calculated. E/e′ was then calculated as a measure reflecting left ventricular filling pressure. Doppler imaging was used to measure tricuspid regurgitation peak velocity. We calculated left ventricular mass from measurements obtained in M-mode. The relative wall thickness was calculated as 2 times the left ventricular posterior wall thickness divided by the left ventricular diastolic diameter.

Other Variables From the ACE 1950 Study

Participants filled out a questionnaire at the ACE 1950 Study visit and went through clinical examination, blood sampling, 12-lead ECG, and seated measurement of systolic and diastolic blood pressure. Blood pressure was measured 3 times, and the mean from the second and third reading was calculated. Hypertension was defined as antihypertensive medication use, systolic blood pressure above 140 mm Hg, and/or diastolic blood pressure above 90 mm Hg. Participants filled out a questionnaire including information on medical history of atrial fibrillation, stroke, heart failure, vascular disease, and diabetes. Information was crosschecked against hospital records in case of uncertainty. Coronary artery disease was defined as having a history of myocardial infarction, coronary artery bypass grafting surgery, or percutaneous coronary intervention. All self-reported history of atrial fibrillation was validated through either ECG documentation or hospital records. Additional details about the study design, conduct, and variables have been reported previously.[15,19]

Statistical Analysis

Continuous data are reported as mean±standard deviation, and comparisons were made with the Student *t* test. Categorical data are reported as number and percentage and were compared with the χ^2 test. We divided our study population into quartiles, based on their systolic blood pressure at ages 40 to 43 years, and assessed variables at ages 40 to 43 years and 62 to 65 years across the quartiles. Comparisons were made with 1-way ANOVA for continuous variables and χ^2 test for categorical variables. In an unadjusted logistic regression model, we assessed the risk of having LA enlargement ($LAVi_{max}$>34 mL/m^2)[7] across the quartiles of blood pressure.

The associations between systolic and diastolic blood pressure at ages 40 to 43 years, and LA volumes and LAEF at ages 62 to 65 years were assessed in linear regression analyses. In the regression models, we used blood pressure as a continuous variable. Nonlinear associations were assessed by restricted cubic splines with knots placed at the 5, 27.5, 50, 72.5, and 95 sample percentiles. We present the unadjusted regression coefficient in Model 1. We adjusted for the available clinically meaningful confounders assessed at ages 40 to 43 years. The following covariates were included in Model 2: sex, body mass index, smoking, heart rate, and treatment with antihypertensive medication. Correlation analyses did not reveal any highly correlated independent variables, and collinearity statistics did not indicate any multicollinearity. We evaluated the normal probability plot of regression standardized residuals and the scatterplot of standardized residuals to meet the assumptions about normality, outliers, and homoscedasticity. Although it is recommended to index LA volume to body surface area in a clinical setting,[7] we used nonindexed volumes as a dependent variable in these analyses. Instead of indexing to contemporary body surface area, we adjusted for sex and body mass index at ages 40 to 43 years in the multivariable analyses. With this approach, we avoided overadjustment for height and weight, and were to a larger extent able to account for the longitudinal impact of weight, because this could have changed during the observation period. The same linear regression models were used to explore the association between systolic blood pressure and other echocardiographic parameters. We had missing covariate data for BMI (n=110) and heart rate (n=111), and a total of 111 subjects with missing covariate data were excluded from the multivariable regression analyses. As a sensitivity analysis, we used multiple imputation with predictive mean matching to generate an imputed complete case data set. As an additional sensitivity analysis, we excluded individuals who were using antihypertensive medication at ages 62 to 65 years. We assessed receiver operating characteristic area under the curve analysis to evaluate the ability of systolic blood pressure at ages 40 to 43 years to predict development of LA enlargement at ages 62 to 65 years. The optimal cutoff value for systolic blood pressure was calculated by Youden's J statistic with accompanying receiver operating characteristic area under the curve, sensitivity, specificity, positive predictive value, and negative predictive value. A *P* value of <0.05 was considered statistically significant. Data were analyzed with IBM SPSS Statistics version 27 (IBM, Armonk, NY) and with Stata 16 (StataCorp, College Station, TX).

Ethics

Informed consent was obtained from all participants in the ACE 1950 Study. The study was approved by the Regional Committee for Medical and Health Research Ethics in Norway (ref: 2011/1475), and it conforms to the ethical guidelines of the Helsinki Declaration.

RESULTS

Among 5827 eligible individuals invited to the ACE 1950 Study, 3706 (64%) participated. Out of these, 2733 (74%) also had available data from the Age 40 Program. We excluded 136 individuals because of missing measurements of the left atrium at the ACE 1950 visit, and 6 individuals because of missing blood pressure measurement at the Age 40 Program. This left 2591 individuals for the current analyses (Figure 1). A comparison of participants of the ACE 1950 Study that did or did not participate in the Age 40 Program is provided in Table S1. Nonparticipants of the Age 40 Program included more men, reported more cardiovascular diseases, and had poorer levels for most clinical and echocardiographic measures, except for systolic blood pressure levels.

Table 1 shows study population characteristics at ages 40 to 43 years and 62 to 65 years. The participants were aged 40.1±0.3 years (range, 40–43 years) at the Age 40 Program and 64.0±0.6 years (range, 62–65 years) at the ACE 1950 Study. There were 1302 (50.3%) women. At ages 40 to 43 years, systolic blood pressure was 128.1±13.6 mm Hg, and diastolic blood pressure was 78.3±9.5 mm Hg. At ages 40 to 43 years, 20.7% of the participants had hypertension, and 1.3% were using antihypertensive medication, whereas at ages 62 to 65 years, 60.7% had hypertension, and 34.7% were using antihypertensive treatment. Echocardiographic characteristics at ages 62 to 65 years are provided in Table 2. The average $LAVi_{max}$ was 26.5±7.3 mL/m^2, the average LA minimum volume indexed to body surface area was 14.6±5.6 mL/m^2, and the average LAEF was 45.5%±9.6%. Systolic dysfunction with left ventricular ejection fraction below 40% was present in 32 individuals (1.2%). For echocardiographic indices indicating left ventricular diastolic dysfunction,[8] 332 (12.8%) had $LAVi_{max}$>34 mL/m^2, 116 (4.6%) had E/e′>14, 2196 (86%) had septal e′<7 cm/s or lateral e′<10 cm/s, and 32 (1.6%) had tricuspid regurgitation maximum velocity>2.8 m/s.

Table 3 shows an increasing proportion of LA enlargement at ages 62 to 65 years across the quartiles of blood pressure at ages 40 to 43 years. We found almost twice as high risk of having LA enlargement for the individuals in quartile 4 compared with quartile 1 (odds ratio, 1.93 [95% CI, 1.37–2.73]). The proportion of participants with atrial fibrillation at ages 62 to 65 years also increased across the quartiles. At ages 40 to 43 years, 945 individuals (38.1%) had a body mass index above 25 kg/m^2, and among them, the proportion with LA enlargement ($LAVi_{max}$>34 mL/m^2) at ages 62 to 65 years was 17.6% (166 individuals). Furthermore, 138 individuals (5.6%) had a body mass index above 30 kg/m^2. Among them, the proportion with LA enlargement was 18.1% (25 individuals).

In Figure 2, the association between systolic blood pressure at ages 40 to 43 years and LAV_{max} at ages 62 to 65 years by sex is illustrated with a scatter plot. In unadjusted linear regression analyses, systolic blood pressure as a continuous variable was associated with LAV_{max} and LAV_{min} but not with LAEF (Table 4). There was no effect modification by sex for either LAV_{max} (*P* for interaction=0.123) or LAV_{min} (*P* for interaction=0.089). The associations persisted when adjusting for covariates in Model 2 (Table 4). Linear models were appropriate for LAV_{max} and LAV_{min} (*P* for

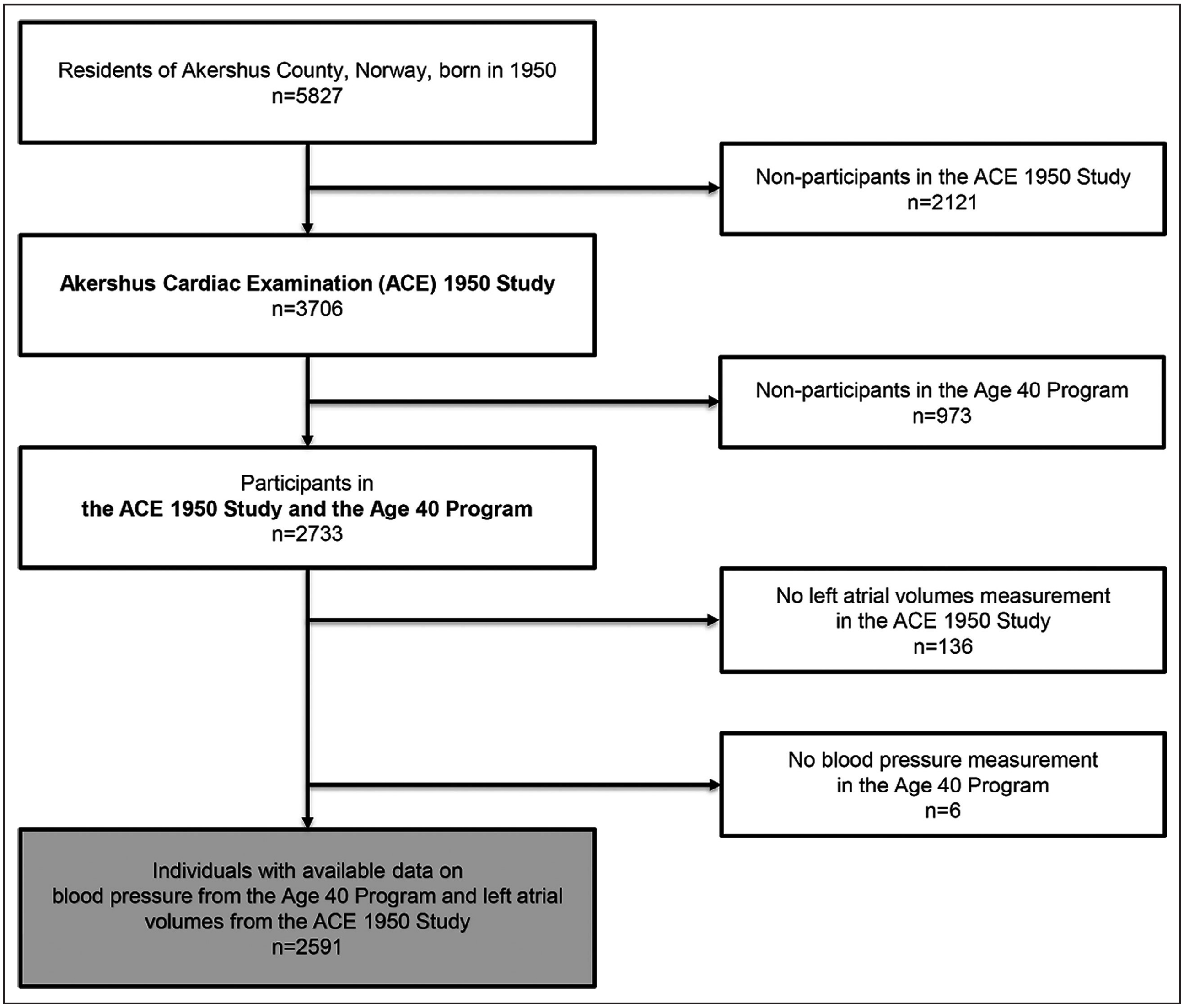

Figure 1. Flowchart of the study population.
ACE 1950 Study indicates Akershus Cardiac Examination 1950 Study.

nonlinearity>0.05, Figures S1 and S2); for LAEF the associations were more nonlinear in nature (*P* for nonlinearity=0.035, Figure S3). The results were not different using an imputed complete case data set (Table S2). Figure 3 shows a receiver operating characteristic curve with an area under the curve of 0.58 (95% CI, 0.54–0.61; *P*<0.001) for the ability of systolic blood pressure at ages 40 to 43 years to predict LA enlargement ($LAVi_{max}$>34 mL/m^2) at ages 62 to 65 years. The optimal cutoff value for systolic blood pressure in predicting LA enlargement was 132 mm Hg (Youden's J=0.121), with receiver operating characteristic area under the curve 0.56 (95% CI, 0.53–0.59; *P* < 0.001), sensitivity 47.0% (95% CI, 41.5%–52.5%), specificity 65.1% (95% CI, 63.1%–67.1%), positive predictive value 16.5% (95% CI, 14.2%–19.1%), and negative predictive value 89.3% (95% CI, 87.7%–90.8%).

The impact of diastolic blood pressure on LA volumes was weaker, and not statistically significant in multivariable analyses (Table S3). In Table S4 we show study population characteristics for women and men, and in Table S5 we conducted linear regression analyses stratified by sex.

At ages 62 to 65 years, 899 (35%) of the participants received treatment with antihypertensive medication. In a sensitivity analysis that excluded these participants, systolic blood pressure was associated with LAV_{max} and LAEF, but the association with LAV_{min} was attenuated (Table S6). Table S6 also shows a sensitivity analysis excluding individuals with atrial fibrillation and heart failure diagnosis at ages 62 to 65 years, which yielded similar results. Moreover, we performed a sensitivity analysis with LA volumes indexed to body surface area as the dependent variable. This yielded similar associations as the nonindexed volumes (Table S7).

Table 1. Study Population Characteristics at Ages 40 to 43 Years and at Ages 62 to 65 Years

Characteristic	At ages 40–43 years	At ages 62–65 years
Age, y	40.1±0.3	64.0±0.6
Heart rate, beats/min	71.2±12.6	62.8±10.3
BSA, m^2	1.87±0.20	1.95±0.22
BMI, kg/m^2	24.4±3.3	26.9±4.3
Systolic blood pressure, mm Hg	128.1±13.6	137.8±18.6
Diastolic blood pressure, mm Hg	78.3±9.5	76.7±10.0
Daily smokers	888 (34.3%)	379 (14.7%)
Atrial fibrillation	N/A	108 (4.2%)
Myocardial infarction	4 (0.2%)	102 (3.9%)
Coronary artery disease	N/A	174 (6.7%)
Angina pectoris	9 (0.3%)	N/A
Stroke	2 (0.1%)	92 (3.6%)
Diabetes	7 (0.3%)	203 (7.8%)
Antihypertensive medication	34 (1.3%)	899 (34.7%)
Hypertension	536 (20.7%)	1573 (60.7%)
Heart failure	N/A	35 (1.4%)

The total number of women in the study was 1302 (50.3%). Values are mean±SD for continuous data and n (percent) for categorical data. Coronary artery disease was defined as myocardial infarction, coronary artery bypass graft surgery, and/or percutaneous coronary intervention. Hypertension was defined as antihypertensive medication use, systolic blood pressure above 140 mm Hg, and/or diastolic blood pressure above 90 mm Hg. BMI indicates body mass index; BSA, body surface area; and N/A, not available because this variable was not assessed in the current health examination.

Table 2. Echocardiographic Characteristics at Ages 62 to 65 Years

Characteristic	Value
LAV_{max}, mL	52.0±16.5
$LAVi_{max}$, mL/m^2	26.5±7.3
LAV_{min}, mL	28.7±12.4
$LAVi_{min}$, mL/m^2	14.6±5.6
LAEF, %	45.5±9.6
LV septal wall thickness, mm	8.0±1.2
LV posterior wall thickness, mm	8.0±1.1
LV end-diastolic volume, mL	135.9±36.9
LV end-systolic volume, mL	60.5±20.4
LV mass, g	150.2±43.7
LV mass index, g/m^2	76.4±18.1
LV relative wall thickness	0.31±0.05
LVEF, %	55.8±5.7
E/A	1.1±0.3
E/e′	9.0±2.6
Global longitudinal strain, %	−20.1±2.6
Tricuspid annular plane systolic excursion, cm	2.4±0.4
Tricuspid regurgitation maximum velocity, m/s	2.2±0.3

Values are mean±SD. A indicates peak velocity of late mitral flow; E, peak velocity of early mitral flow; e′, early peak velocity of the mitral annulus; $LAVi_{max}$, left atrial maximum volume indexed to body surface area; $LAVi_{min}$, left atrial minimum volume indexed to body surface area; LAV_{max}, left atrial maximum volume (end-systolic); LAV_{min}, left atrial minimum volume (end-diastolic); LV, left ventricular; and LVEF, left ventricular ejection fraction.

On the impact of systolic blood pressure on other echocardiographic parameters, a significant, although weak association persisted when adjusting for covariates for maximal tricuspid regurgitation velocity, E/e′, and left ventricular mass (Table S8). The left ventricular relative wall thickness was unaffected by blood pressure. An association between systolic blood pressure and right atrial and ventricular volumes was present, albeit not significant in the multivariable models.

DISCUSSION

In this study, blood pressure at ages 40 to 43 years was significantly associated with LA volumes at ages 62 to 65 years. The strongest independent association was observed between systolic blood pressure and LAV_{max}. There was no impact of either diastolic or systolic blood pressure on LAEF.

In accordance with the present study, Vasconcellos et al reported that cumulative blood pressure over 30 years in 1033 individuals with a mean age 55.4±3.5 years, was associated with both LA maximum and minimum volume, measured with 3-dimensional echocardiography. Similar to the present study, the effect was greater for systolic than for diastolic blood pressure.[20] Moreover, in a British cohort study of 1417 individuals, the authors reported significant associations between systolic blood pressure at ages 36, 43, and 53 years, and $LAVi_{max}$ at ages between 60 and 64 years.[14] Our longitudinal analyses in a larger sample confirm these findings, and we added data on LAV_{min} and LAEF. A possible explanation for the absent association between blood pressure and LAEF is that LAV_{max} and LAV_{min} dilate approximately to the same degree, nullifying the effect on LAEF.

It has been shown previously in a hypertensive population that LA dilatation is associated with female sex.[21] In our population-based study we did not detect an interaction with sex, but blood pressures were measured at an earlier age. Men had higher systolic blood pressure at ages 40 to 43 years compared with women, but at ages 62 to 65 years there was no longer a difference. This is in line with the expected trajectories of blood pressure, because women start with a lower blood pressure but are subjected to a steeper increase compared with men.[22] We have previously shown that in a healthy subgroup of this general population at ages 62 to 65 years, men had larger LA volumes indexed for body surface area compared with women.[23] However, most studies of normal LA volumes have not identified clinically significant differences between the sexes, and sex-specific cutoffs have not been endorsed.[24]

Table 3. Characteristics Across Quartiles of Systolic Blood Pressure at Ages 40 to 43 Years

Characteristic	Q1, n=648	Q2, n=663	Q3, n=663	Q4, n=617	*P* value
Female sex	504 (77.8%)	367 (55.4%)	265 (40.0%)	166 (26.9%)	<0.001
At ages 40–43 y					
Body mass index, kg/m^2	23.0±2.8	24.1±3.1	24.9±3.4	25.6±3.3	<0.001
Heart rate, beats/min	70±10	70±12	70±12	75±15	<0.001
Antihypertensive medication	3 (0.5%)	3 (0.5%)	3 (0.5%)	25 (4.1%)	<0.001
Smoking	243 (37.5%)	214 (32.3%)	225 (33.9%)	206 (33.4%)	0.220
At ages 62–65 y					
$LAVi_{max}$, mL/m^2	25.5±6.5	26.5±7.2	26.6±7.2	27.6±8.3	<0.001
LAV_{max}, mL	47.2±14.0	51.5±15.8	53.0±16.0	56.6±18.6	<0.001
Left atrial enlargement	59 (9.1%)	78 (11.8%)	95 (14.3%)	100 (16.2%)	0.001
$LAVi_{min}$, mL/m^2	14.0±4.6	14.5±5.3	14.7±5.3	15.3±6.9	0.001
LAV_{min}, mL	26.0±10.0	28.2±11.4	29.3±11.8	31.5±15.3	<0.001
LAEF, %	45.3±9.1	45.8±9.1	45.3±9.5	45.5±10.6	0.811
Atrial fibrillation	12 (1.9%)	26 (3.9%)	27 (4.1%)	43 (7.0%)	<0.001
Heart failure	7 (1.1%)	7 (1.1%)	12 (1.8%)	9 (1.5%)	0.595
Hypertension	226 (34.9%)	372 (56.1%)	453 (68.3%)	522 (84.6%)	<0.001
Antihypertensive medication	95 (14.7%)	189 (28.5%)	253 (38.2%)	362 (58.7%)	<0.001
E/e′	8.7±2.3	8.8±2.5	9.1±2.7	9.4±2.9	<0.001
LV mass index, g/m^2	71.9±16.7	75.2±17.0	78.1±18.2	80.7±19.5	<0.001
LV relative wall thickness	0.31±0.05	0.31±0.05	0.31±0.05	0.31±0.05	0.569
TRV_{max}, m/s	2.2±0.3	2.2±0.3	2.2±0.3	2.3±0.3	0.002

Values are mean±SD for continuous data and n (percent) for categorical data. Quartiles of systolic blood pressure: Q1: <119 mm Hg, Q2: 119–127 mm Hg, Q3: 127.5–136.5 mm Hg, Q4: ≥137 mm Hg. Left atrial enlargement: $LAVi_{max}$>34 mL/m^2. E/e′ indicates ratio of early peak velocity of mitral flow and of the mitral annulus; LAEF, left atrial emptying fraction; $LAVi_{max}$, left atrial end-systolic volume indexed to body surface area; $LAVi_{min}$ indicates left atrial end-diastolic volume indexed to body surface area; LAV_{max}, left atrial maximum volume (end-systolic); LAV_{min}, left atrial minimum volume (end-diastolic); LV, left ventricular; and TRV_{max}, tricuspid regurgitation maximum velocity.

Long-term LA dilatation is attributable to increased left ventricular filling pressure caused by increased arterial blood pressure, even in the mild range.[25,26] Correspondingly, and similar to Ghosh et al,[14] we found a significant association between systolic blood pressure and the echocardiograhic index reflecting increased filling pressure of the left ventricle (the E/e' ratio). The hemodynamic consequence of a passive backward propagation of the high pressure on the left side of the heart can be increased pulmonary blood pressure. This was also observed in patients with heart failure with preserved ejection fraction in the Olmsted study.[27] The present study demonstrated an association between systolic blood pressure and tricuspid regurgitation peak velocity, reflecting increased pulmonary pressure, and also with increased right ventricular and atrial size. Although these associations were weak, they imply that increased arterial blood pressure over a long time span may also impact the pulmonary circulation and the right side of the heart.

The total time with elevated blood pressure is already regarded as important in developing cardiovascular disease, mainly left ventricular diastolic dysfunction. Our data are only observational, but they add to the body of evidence that early onset of increased blood pressure is relevant for LA remodeling. The physiological explanation for $LAVi_{max}$ being a predictor of clinical outcomes is not fully understood. Still, it has been suggested that it may be a marker of underlying diastolic dysfunction, which is the actual clinical determinant of poor outcome.[28] One study from the general population found that $LAVi_{max}$ lost its prognostic abilities of all-cause mortality when also adjusting for other diastolic dysfunction parameters.[29] In the ARIC (Atherosclerosis Risk in Communities) Study, Teramoto et al studied the effect of cumulative blood pressure on cardiac structure and heart failure as clinical end points. The study demonstrated an effect on $LAVi_{max}$ from cumulative systolic blood pressure, which was also associated with incident heart failure, particularly heart failure with preserved ejection fraction.[30] Furthermore, in the CARDIA (Coronary Artery Risk Development in Young Adults) Study with a similar number of participants as in our study, the effects of cumulative blood pressure over 25 years on left ventricular systolic and diastolic dysfunction were investigated.[31] The authors found an effect on diastolic dysfunction evaluated as E/e′ ratio >15, notably a more prominent effect from diastolic blood pressure. However, $LAVi_{max}$ was more affected by systolic blood pressure. In a recent pooled population study, hypertension was associated with a greater attributable risk of heart failure in young individuals.[32] Earlier age of onset of hypertension

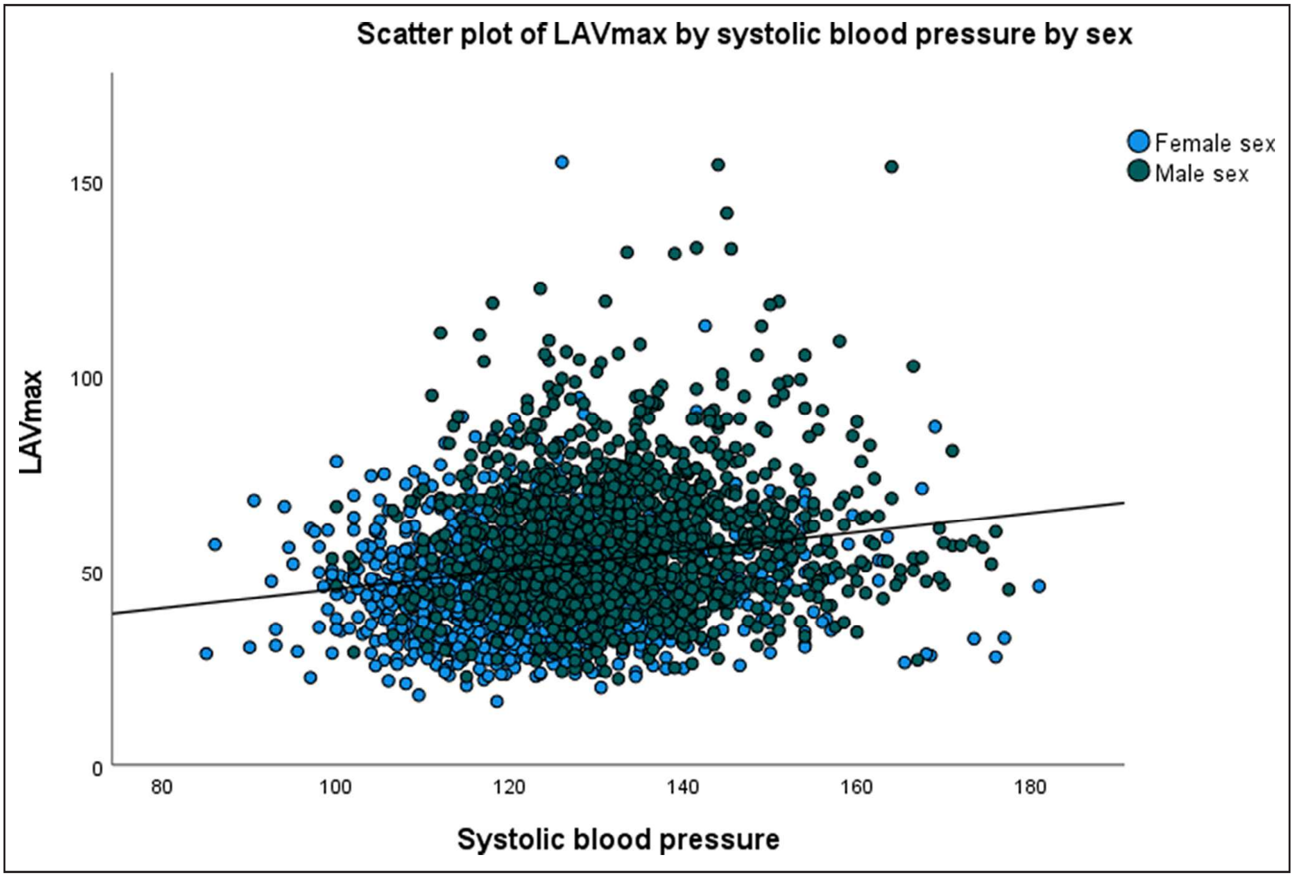

Figure 2. Scatterplot of systolic blood pressure at ages 40 to 43 years (*x* axis) and left atrial maximum volume (LAVmax) at ages 62 to 65 years (*y* axis), by sex.
Fitted linear regression line: y=20.85+0.24 x, with R^2=0.04.

has been demonstrated to be associated with increased cardiovascular morbidity and mortality,[33] and Mendelian randomization studies support this notion.[34,35]

Another study using genetically predicted blood pressure strengthened the hypothesis of increased blood pressure being causative in the development of atrial fibrillation.[36] Even blood pressure in the upper normal range has been associated with an increased risk of atrial fibrillation.[37] In our data, the proportion of individuals with LA enlargement was increased also in the upper normal quartile of systolic blood pressure. In a pooled analysis of the SPRINT (Systolic Blood Pressure Intervention Trial), SHEP (Systolic Hypertension in the Elderly Program), and the ACCORD (Action to Control Cardiovascular Risk in Diabetes) studies, intensive antihypertensive treatment was significantly associated with reduced risk of new-onset atrial fibrillation.[38] This favorable effect could partly be mediated through less atrial dilatation, as suggested in the the LIFE (Losartan Intervention For Endpoint Reduction) Study.[39]

Strengths of this study include the population-based large sample size with long-term follow-up data.

Table 4. Association Between Systolic Blood Pressure at Ages 40 to 43 Years and Left Atrial Volumes and Emptying Fraction at Ages 62 to 65 Years

Dependent variable at ages 62–65 y	Model 1		Model 2	
	Systolic blood pressure at ages 40–43 y, β (95% CI)	*P* value	Systolic blood pressure at ages 40–43 y, β (95% CI)	*P* value
LAV_{max}, mL	0.24 (0.20, 0.29)	<0.001	0.09 (0.04, 0.14)	<0.001
LAV_{min}, mL	0.15 (0.11, 0.18)	<0.001	0.05 (0.01, 0.09)	0.011
LAEF, %	0.00 (−0.02, 0.03)	0.842	0.02 (−0.02, 0.05)	0.311

Model 1: Unadjusted. Model 2: Adjusted for sex, body mass index, smoking, heart rate, and antihypertensive treatment, all assessed at ages 40–43 y. β (95% CI): regression coefficient per 1-mm Hg systolic blood pressure at ages 40–43 y with 95% CI. LAEF indicates left atrial emptying fraction; LAV_{max}, left atrial end-systolic volume; and LAV_{min}, left atrial end-diastolic volume.

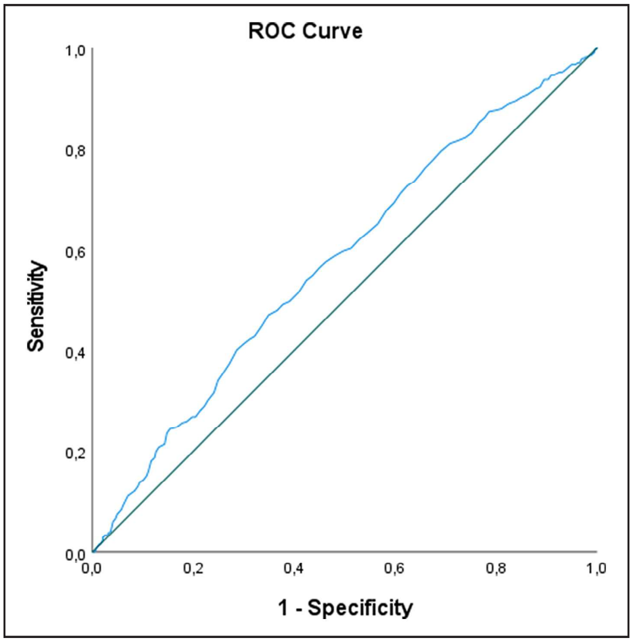

Figure 3. Receiver operating characteristic (ROC) curve indicating the ability of systolic blood pressure as a continuous variable at ages 40 to 43 years to predict participants that developed left atrial enlargement ($LAVi_{max}$>34 mL/m^2) at ages 62 to 65 years.
Area under the curve, 0.58 (95% CI, 0.54–0.61; *P*<0.001). $LAVi_{max}$ indicates left atrial end-systolic volume indexed to body surface area.

All individuals underwent comprehensive echocardiographic examination in the ACE 1950 Study. However, not all participants in the ACE 1950 Study had data from the Age 40 Program, and thus, selection bias might have influenced our results. The Age 40 Program was conducted with less phenotyping than the ACE 1950 Study. Participants did not undergo echocardiography, and they were not questioned about history of heart failure or atrial fibrillation. Therefore, we could not explore changes in LA volumes. The lack of baseline heart failure and atrial fibrillation data could potentially limit our results. However, it is likely that only a minor proportion of the participants had these conditions at ages 40 to 43 years. Some survival bias may also be present in the case of any deceased participants between the 2 study visits. However, considering the large sample size, we assume that this would have a limited impact. The study is nevertheless limited by the lack of data from the period between the 2 study visits. The study population is mainly White, and this limits the generalizability of our findings.

CONCLUSIONS

Systolic blood pressure in those in their early 40s was independently associated with LA volumes in their mid-60s, more strongly with LA maximum volume. Our findings suggest that increased blood pressure in those in their early 40s is relevant for LA remodeling later in life.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Tables S1–S8
Figures S1–S3

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SUPPLEMENTAL MATERIAL

Table S1. Comparison of characteristics at age 62-65 according to participation or not at age 40-43

	Participant at age 40-43 n=2733	Non-participant at age 40-43 n=973	p-value
Female sex	1377 (50.4%)	430 (44.2%)	0.001
Body mass index (kg/m^2)	27.0 ± 4.4	27.5 ± 4.5	0.004
Systolic blood pressure (mm Hg)	138 ± 18	138 ± 20	0.369
Diastolic blood pressure (mm Hg)	77 ± 10	78 ± 10	0.020
Atrial fibrillation	111 (4.1%)	54 (5.5%)	0.053
Hypertension	1664 (60.9%)	633 (65.1%)	0.022
Coronary artery disease	180 (6.6%)	83 (8.5%)	0.043
$LAVi_{max}$ (ml/m^2)	26.5 ± 7.3	27.5 ± 8.3	0.001
$LAVi_{min}$ (ml/m^2)	14.6 ± 5.6	15.1 ± 6.5	0.036
LV mass index (g/m^2)	76.1 ± 18.1	78.0 ± 19.4	0.007
LV relative wall thickness	0.31 ± 0.05	0.31 ± 0.06	0.141
E/e'	9.0 ± 2.6	9.2 ± 2.7	0.045
TRVmax (m/s)	2.2 ± 0.3	2.2 ± 0.3	0.082

Values are mean ± SD for continuous data and n (percentages) for categorical data. *$LAVi_{max}$:* left atrial end-systolic volume – indexed to body surface area, *$LAVi_{min}$:* left atrial end-diastolic volume – indexed to body surface area, *LV:* left ventricular, *E/e':* ratio of early peak velocity of mitral flow and of the mitral annulus, *TRVmax:* Tricuspid regurgitation maximum velocity

Table S2. Association between systolic blood pressure at age 40-43 and left atrial volumes and emptying fraction at age 62-65, using an imputed complete case data set

	Model 1		Model 2	
Dependent variable at age 62-65	β (95% CI) systolic blood pressure at age 40-43	p-value	β (95% CI) systolic blood pressure at age 40-43	p-value
LAV_{max} (ml)	0.24 (0.20, 0.29)	<0.001	0.08 (0.03, 0.13)	0.001
LAV_{min} (ml)	0.15 (0.11, 0.18)	<0.001	0.04 (0.002, 0.08)	0.038
LAEF (%)	0.00 (-0.02, 0.03)	0.842	0.02 (-0.01, 0.05)	0.173

Model 1: Unadjusted. Model 2: Adjusted for sex, body mass index, smoking, heart rate, and antihypertensive treatment, all assessed at age 40-43. *β (95% CI):* regression coefficient per 1 mm Hg systolic blood pressure at age 40-43 with 95% confidence interval, *LAVmax:* left atrial end-systolic volume, *LAVmin:* left atrial end-diastolic volume, *LAEF:* left atrial emptying fraction

Table S3. Association between diastolic blood pressure at age 40-43 and left atrial volumes and emptying fraction at age 62-65

	Model 1		Model 2	
Dependent variable at age 62-65	β (95% CI) diastolic blood pressure at age 40-43	p-value	β (95% CI) diastolic blood pressure at age 40-43	p-value
LAV_{max} (ml)	0.17 (0.11, 0.24)	<0.001	0.01 (-0.06, 0.08)	0.803
LAV_{min} (ml)	0.11 (0.06, 0.16)	<0.001	0.01 (-0.04, 0.07)	0.678
LAEF (%)	0.00 (-0.04, 0.04)	0.860	0.01 (-0.04, 0.05)	0.752

Model 1: Unadjusted. Model 2: Adjusted for sex, body mass index, smoking, heart rate and antihypertensive treatment, all assessed at age 40-43. *β (95% CI):* regression coefficient per 1 mm Hg diastolic blood pressure at age 40-43 with 95% confidence interval, *LAVmax:* left atrial end-systolic volume, *LAVmin:* left atrial end-diastolic volume, *LAEF:* left atrial emptying fraction

Table S4. Study population characteristics in men and women, at age 40-43 and 62-65

	Women		Men	
Participants	1302 (50.3%)		1289 (49.7%)	
Health examination	At age 40-43	At age 62-65	At age 40-43	At age 62-65
Age (years)	40.1 ± 0.3	64.0 ± 0.6	40.1 ± 0.4	64.0 ± 0.6
Heart rate (beats/minute)	73.6 ± 12.3	64.4 ± 9.4	68.7 ± 12.4	61.1 ± 10.8
BSA (m2)	1.7 ± 0.1	1.8 ± 0.2	2.0 ± 0.2	2.1 ± 0.2
BMI (kg/m2)	23.6 ± 3.5	26.4 ± 4.8	25.3 ± 2.8	27.4 ± 3.7
Systolic blood pressure (mm Hg)	123.1 ± 12.8	137.1 ± 19.5	133.2 ± 12.5	138.5 ± 17.6
Diastolic blood pressure (mm Hg)	75.9 ± 9.0	73.7 ± 9.4	80.7 ± 9.4	79.8 ± 9.6
Daily smokers	461 (35.4%)	199 (15.4%)	427 (33.1%)	180 (14.0%)
Atrial fibrillation	N/A	25 (1.9%)	N/A	83 (6.4%)
Coronary artery disease	N/A	36 (2.8%)	N/A	138 (10.7%)
Myocardial infarction	0 (0%)	13 (1.0%)	4 (0.3%)	89 (6.9%)
Angina pectoris	2 (0.2%)	N/A	7 (0.5%)	N/A
Stroke	1 (0.1%)	28 (2.2%)	1 (0.1%)	64 (5.0%)
Diabetes	4 (0.3%)	61 (4.7%)	3 (0.2%)	142 (11.0%)
Antihypertensive medication	13 (1.0%)	390 (30.05)	21 (1.6%)	509 (39.5%)
Hypertension	143 (11.0%)	741 (56.9%)	393 (30.5%)	832 (64.5%)
Heart failure	N/A	10 (0.8%)	N/A	25 (1.9%)
LAV_{max} (ml)	N/A	46.2 ± 12.8	N/A	57.9 ± 17.7
$LAVi_{max}$ (ml/m^2)	N/A	25.4 ± 6.5	N/A	27.7 ± 8.0
LAV_{min} (ml)	N/A	25.1 ± 8.9	N/A	32.4 ± 14.2
$LAVi_{min}$ (ml/m^2)	N/A	13.8 ± 4.6	N/A	15.4 ± 6.4
LAEF (%)	N/A	45.9 ± 9.0	N/A	45.0 ± 10.1

Values are mean ± SD for continuous data and n (%) for categorical data. BSA, body surface area; BMI, body mass index; Coronary artery disease was defined as myocardial infarction, coronary artery by-pass graft surgery, and/or percutaneous coronary intervention; Hypertension was defined as antihypertensive medication use, systolic blood pressure above 140 mm Hg, and/or diastolic blood pressure above 90 mm Hg; LAV_{max}, left atrial (LA) end-systolic volume; $LAVi_{max}$, LAV_{max} indexed to body surface area; LAV_{min}, LA end-diastolic volume; $LAVi_{min}$, LAV_{min} indexed to body surface area; LAEF, LA emptying fraction; N/A, not available as this variable was not assessed in the current health examination

Table S5. Association between systolic blood pressure at age 40-43 and left atrial volumes at age 62-65, stratified by sex

	Model 1		Model 2	
Dependent variable at age 62-65	β (95% CI) systolic blood pressure at age 40-43	p-value	β (95% CI) systolic blood pressure at age 40-43	p-value
Female				
LAV_{max} (ml)	0.06 (0.01, 0.12)	0.027	0.06 (0.01, 0.12)	0.034
LAV_{min} (ml)	0.02 (-0.02, 0.06)	0.228	0.03 (-0.01, 0.07)	0.106
LAEF (%)	0.03 (-0.01, 0.07)	0.154	0.01 (-0.03, 0.05)	0.632
Male				
LAV_{max} (ml)	0.14 (0.06, 0.21)	0.001	0.11 (0.03, 0.19)	0.006
LAV_{min} (ml)	0.09 (0.02, 0.15)	0.007	0.06 (-0.00, 0.12)	0.064
LAEF (%)	0.01 (-0.04, 0.05)	0.778	0.02 (-0.03, 0.07)	0.387

Model 1: Unadjusted. Model 2: Adjusted for body mass index, smoking, heart rate and antihypertensive treatment, all assessed at age 40-43. *β (95% CI):* regression coefficient per 1 mm Hg systolic blood pressure at age 40-43 with 95% confidence interval, *LAVimax:* body surface area indexed left atrial end-systolic volume, *LAVimin:* body surface area indexed left atrial end-diastolic volume, *LAEF:* left atrial emptying fraction

Table S6. Sensitivity analyses of the association between systolic blood pressure at age 40-43 and left atrial volumes and emptying fraction at age 62-65.

	Model 1		Model 2	
Dependent variable at age 62-65	β (95% CI) systolic blood pressure at age 40-43	p-value	β (95% CI) systolic blood pressure at age 40-43	p-value
Excluding individuals using antihypertensive medication at age 62-65, n=1692				
LAV_{max} (ml)	0.23 (0.18, 0.29)	<0.001	0.07 (0.01, 0.14)	0.019
LAV_{min} (ml)	0.10 (0.06, 0.14)	<0.001	0.01 (-0.03, 0.06)	0.605
LAEF (%)	0.06 (0.02, 0.09)	0.002	0.06 (0.02, 0.10)	0.007
Excluding individuals with atrial fibrillation and heart failure diagnosis at age 62-65, n=2457				
LAV_{max} (ml)	0.20 (0.15, 0.24)	<0.001	0.07 (0.03, 0.12)	0.002
LAV_{min} (ml)	0.09 (0.06, 0.12)	<0.001	0.03 (-0.01, 0.06)	0.124
LAEF (%)	0.03 (0.01, 0.06)	0.018	0.03 (0.00, 0.06)	0.043

Model 1: Unadjusted. Model 2: Adjusted for sex, body mass index, smoking, heart rate and antihypertensive treatment, all assessed at age 40-43. *β (95% CI):* regression coefficient per 1 mm Hg systolic blood pressure at age 40-43 with 95% confidence interval, *LAVmax:* left atrial end-systolic volume, *LAVmin:* left atrial end-diastolic volume, *LAEF:* left atrial emptying fraction

Table S7. Association between systolic blood pressure at age 40-43 and body surface area indexed left atrial volumes at age 62-65

	Model 1		Model 2	
Dependent variable at age 62-65	β (95% CI) systolic blood pressure at age 40-43	p-value	β (95% CI) systolic blood pressure at age 40-43	p-value
$LAVi_{max}$ (ml/m^2)	0.05 (0.03, 0.07)	<0.001	0.05 (0.02, 0.07)	<0.001
$LAVi_{min}$ (ml/m^2)	0.03 (0.02, 0.05)	<0.001	0.03 (0.01, 0.04)	0.007

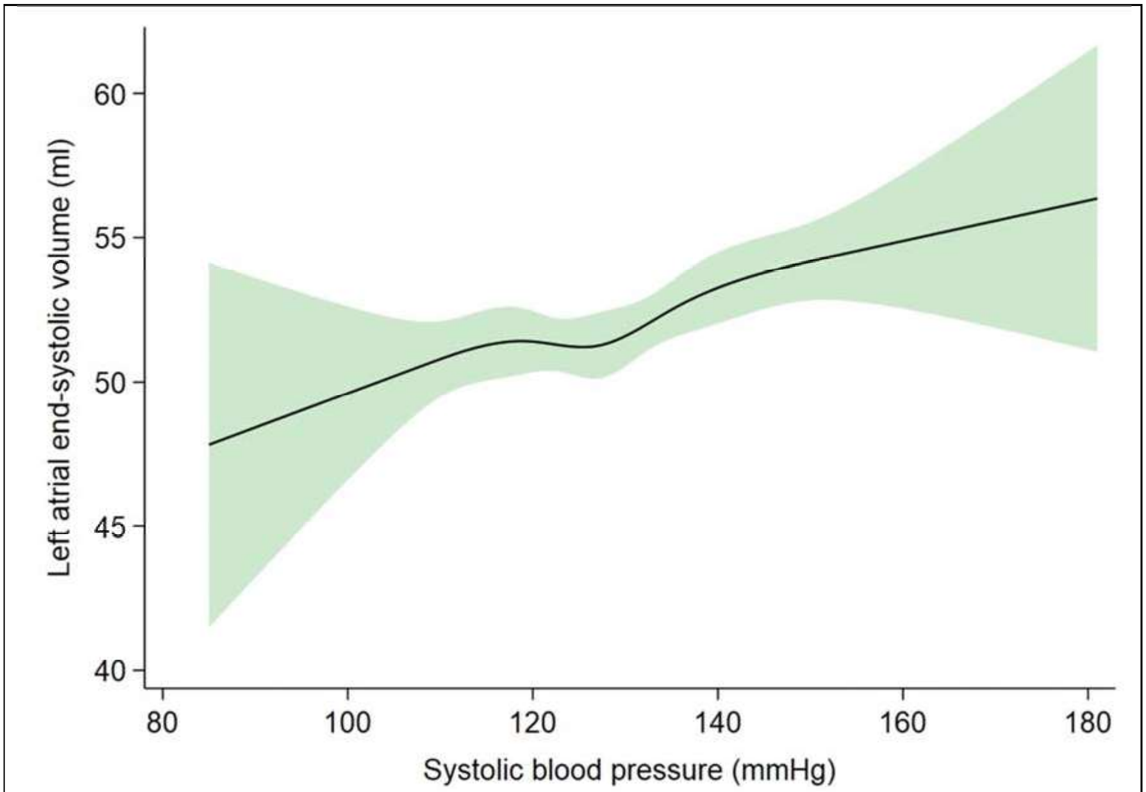
Model 1: Unadjusted. Model 2: Adjusted for sex, body mass index, smoking, heart rate and antihypertensive treatment, all assessed at age 40-43. *β (95% CI):* regression coefficient per 1 mm Hg systolic blood pressure at age 40-43 with 95% confidence interval, *LAVimax:* body surface area indexed left atrial end-systolic volume, *LAVimin:* body surface area indexed left atrial end-diastolic volume

Table S8. Association between systolic blood pressure at age 40-43 and echocardiographic variables at age 62-65

	Model 1		Model 2	
Dependent variable at age 62-65	β (95% CI) systolic blood pressure at age 40-43	p-value	β (95% CI) systolic blood pressure at age 40-43	p-value
TRVmax	0.002 (0.001, 0.002)	<0.001	0.002 (0.001, 0.003)	0.001
E/A	-0.002 (-0.003, -0.001)	<0.001	-0.001 (-0.002, 0.000)	0.079
e’	0.000 (0.000, 0.000)	<0.001	-0.000 (0.000, 0.000)	0.012
E/e’	0.023 (0.016, 0.031)	<0.001	0.034 (0.025, 0.042)	<0.001
Left ventricular mass	0.879 (0.759, 0.998)	<0.001	0.222 (0.103, 0.341)	<0.001
Left ventricular relative wall thickness	0.000 (0.000, 0.000)	0.483	0.000 (0.000, 0.000)	0.961
Global longitudinal strain	0.020 (0.012, 0.029)	<0.001	-0.005 (-0.015, 0.005)	0.323
Right atrial end-systolic area	0.040 (0.028, 0.051)	<0.001	-0.007 (-0.019, 0.006)	0.297
Right ventricular end-diastolic area	0.076 (0.061, 0.091)	<0.001	-0.010 (-0.025, 0.005)	0.205

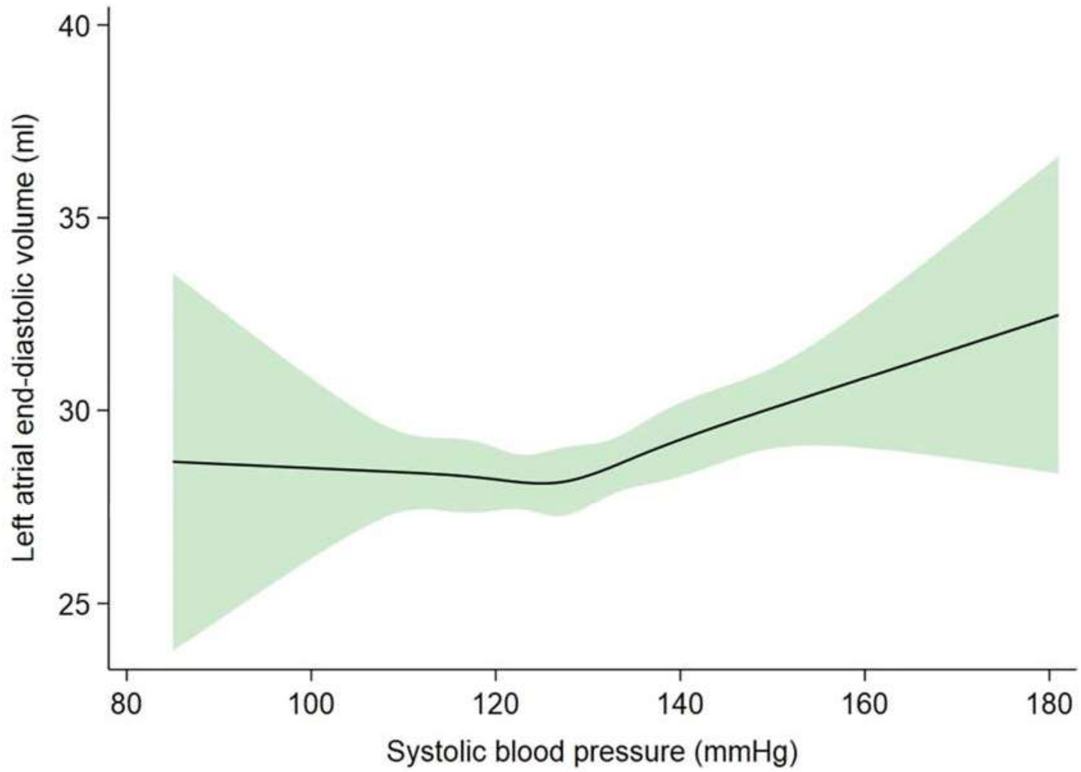
Model 1: Unadjusted. Model 2: Adjusted for sex, body mass index, smoking, heart rate and antihypertensive treatment, all assessed at age 40-43. *β (95% CI):* regression coefficient per 1 mm Hg systolic blood pressure at age 40-43 with 95% confidence interval, *TRVmax:* maximal tricuspid regurgitation velocity, *E/A:* ratio of peak velocity early and late mitral flow, *e’:* early peak velocity of the mitral annulus, *E/e’:* ratio of peak velocity early mitral flow and early peak velocity of the mitral annulus

Figure S1



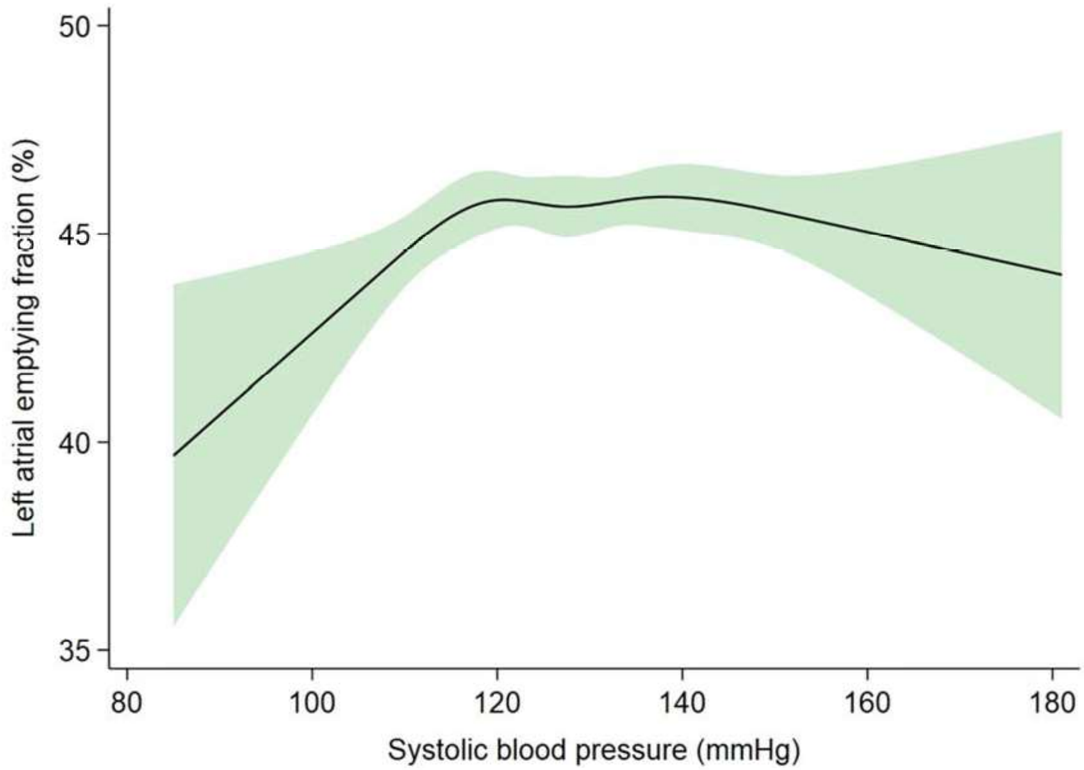
Association between systolic blood pressure at age 40-43 and left atrial end-systolic volume at age 62-65. Assessed by restricted cubic splines with knots placed at the 5th, 27.5th, 50th, 72.5th, and 95th sample percentiles. Green area represents 95% confidence interval. Adjusted for sex, body mass index, smoking, heart rate, and antihypertensive treatment assessed at age 40-43.

Figure S2



Association between systolic blood pressure at age 40-43 and left atrial end-diastolic volume at age 62-65. Assessed by restricted cubic splines with knots placed at the 5th, 27.5th, 50th, 72.5th, and 95th sample percentiles. Green area represents 95% confidence interval. Adjusted for sex, body mass index, smoking, heart rate, and antihypertensive treatment assessed at age 40-43.

Figure S3



Association between systolic blood pressure at age 40-43 and left atrial emptying fraction at age 63-65. Assessed by restricted cubic splines with knots placed at the 5th, 27.5th, 50th, 72.5th, and 95th sample percentiles. Green area represents 95% confidence interval. Adjusted for sex, body mass index, smoking, heart rate, and antihypertensive treatment assessed at age 40-43.