Blood pressure trajectories in early adulthood and myocardial structure and function in later life

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Abstract

**Aims** This study sought to investigate the association between blood pressure (BP) trajectories from early to middle adulthood and echocardiographic indices of structure and function in middle age.

**Methods and results** This prospective cohort study included 4717 black and white adults aged 18–30 years at baseline (1985–86) who were followed over 30 years in the Coronary Artery Risk Development in Young Adults (CARDIA) study. Trajectories of systolic BP (SBP), diastolic BP (DBP), and pulse pressure (PP) from the Year 0 examination to Year 30 examination were identified using latent mixture modelling. Echocardiographic indices of myocardial structure, systolic function, and diastolic function were assessed at the Year 30 examination. Five distinct SBP trajectory groups were identified: low-stable [1110 participants (23.5%)], moderate-stable [2188 (46.4%)], high-stable [850 (18.0%)], moderate-increasing [416 (8.8%)], and high-increasing [153 (3.2%)]. After adjustment for clinical variables, a significant decreasing trend was observed from the high-increasing and moderate-increasing groups through to the low-stable group for left ventricular (LV) mass index \( \text{mean (SE)}: \text{high-increasing, 112.3 (3.4); moderate-increasing, 99.3 (2.6); high-stable, 88.9 (2.5); moderate-stable, 86.1 (2.3); low-stable, 82.1 (2.4), P trend < 0.01, as well as LV end-diastolic dimension, left atrial volume index, and E/e}', while an increasing trend was apparent for LV longitudinal strain, E/A ratio, and average e' velocities. Results were generally consistent for trajectories of DBP and PP.

**Conclusions** Higher BP trajectories from early to middle adulthood were associated with worse indices of myocardial modelling and LV systolic and diastolic function at middle age.

**Keywords** Blood pressure; Trajectories; Echocardiography; Myocardial structure and function

Background

Heart failure (HF) is a major cause of morbidity and mortality and has deleterious impacts on economic burden worldwide.1–3 Hypertension is a well-established risk factor for the development of HF.4,5 Most longstanding hypertension ultimately leads to HF.5 According to the model proposed by Vasan and Levy, the time course of progression from hypertension to HF may take several decades.6 Therefore, prevention of hypertension early in life may substantially prolong HF-free survival. Epidemiological studies have shown that elevated blood pressure (BP) is associated with adverse alterations in myocardial structure and function.7,8 However, most studies were conducted in middle aged or older adults and mainly included myocardial structure as the outcome of interest.

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Importantly, previous investigations primarily focused on assessing the relationship between cumulative and average BP levels, and subsequent echocardiographic outcomes. In actuality, individual patterns of BP changes throughout the life course are often highly variable among individuals. These prior studies ignored the dynamic changes in BP over time and the potential diversity in BP developmental patterns.

Recent evidence suggests heterogeneous BP trajectories exist and are associated with an increased risk for cardiovascular disease (CVD). The association of the longitudinal trajectories of BP from early adulthood onwards with myocardial structure and left ventricular (LV) systolic and diastolic function in middle age remains unknown. Assessing trajectories of BP over time might better characterize the association between BP and echocardiography outcomes.

**Aims**

Using data from the Coronary Artery Risk Development in Young Adults (CARDIA) study, we sought to evaluate the association of trajectory of BP from early adulthood (ages 18–30 years) to middle age (ages 48–60 years) with echocardiographic indices of cardiac structure and function in middle age.

**Methods**

**Data availability**

Anonymized data were obtained from the CARDIA Coordinating Center (cardia.dopm.uab.edu/contact-cardia). The National Heart, Lung, and Blood Institute policies governing the data and describing its access are described online (https://www.cardia.dopm.uab.edu/study-information/nhbi-data-repository-data). This article has been reviewed by CARDIA for scientific content.

**Study population**

The CARDIA is a prospective multicentre population-based longitudinal cohort study designed to investigate the development of cardiovascular risk and disease. A total of 5115 black and white men and women aged 18 to 30 years between 1985 and 1986 (Year 0) were recruited from 4 US cities (Birmingham, Alabama; Chicago, Illinois; Minneapolis, Minnesota; and Oakland, California). Study recruitment was approximately balanced on age, sex, race, and education. Serial follow-up examinations were conducted at Years 2, 5, 7, 10, 15, 20, 25, and 30 after baseline (Year 0), and retention rates across examinations were 91%, 86%, 81%, 79%, 74%, 72%, 72%, and 71%, respectively. All participants provided written informed consent at each examination, and institutional review boards from each field centre approved the study protocols. For the current analysis, participants with BP measures at 3 or more examinations during the 30 years of follow-up (Year 0 to Year 30) and echocardiography available at Year 30 were included in the analysis. Of the 5115 participants, 4717 with 3 or more BP measurements during follow-up were included in BP trajectory modelling. Of these, 3174 participants with Year 30 echocardiography data were included in investigating the association between BP trajectories and echocardiographic outcomes.

**Blood pressure measurements**

Blood pressure was measured on the right arm with a Hawksley random zero sphygmomanometer (WA Baum Company, Copague, NY) by trained research staff using standardized methods after the participant had rested for 5 min at Years 0, 2, 5, 7, 10, and 15. From Year 20 onwards, a digital BP monitor (Omron HEM-907XL; Online Fitness, Santa Monica, CA) was used. Three measurements were obtained at 1 min intervals. The average of the second and third measurements was used for the analysis. These BP measurements were calibrated and standardized to the sphygmomanometer measures, so that no machine bias remained.

We evaluated trajectories in systolic BP (SBP), diastolic BP (DBP), and pulse pressure (PP).

**Echocardiography**

Comprehensive two-dimensional, M-mode, and Doppler echocardiography was performed using standard equipment (Apilo Artida scanner; Toshiba Medical Systems) by trained sonographers across all field centres at the Year 30 examination. Quality control procedures assessed intrasonographer and intersonographer reliability throughout the Year 30 examination. Sonographers made measurements from digitized images using a standard off-line image analysis system (Digisonics, Houston, Texas). Studies were sent electronically to the echocardiography core reading centre (Johns Hopkins University, Baltimore, Maryland). Left atrial (LA) volume and LV ejection fraction were measured using the apical two-chamber and four-chamber views based on the American Society of Echocardiography guidelines. LV mass was calculated using the Devereux formula. LV end-diastolic dimension was measured from the parasternal long-axis view. LV mass, LA volume, and LV diastolic dimension were indexed to body surface area. Peak velocities of the early phase (E) and late phase (A) of the mitral inflow, and their ratio (E/A ratio) were measured from pulse-wave Doppler echocardiography.
raphy recordings of mitral flow. Early peak diastolic mitral annular velocities (e') were measured using tissue Doppler at the lateral and septal mitral annulus. E/e' was defined as the E wave divided by the average of the septal and lateral e’ velocities and was used as an index of LV filling pressures. Speckle-tracking echocardiography was performed using dedicated semiautomated software (Toshiba Medical Systems). LV strain curves were generated using three cardiac cycles. LV longitudinal strain curves were assessed from the apical four-chamber view. LV circumferential strain was assessed from the mid-LV cavity short-axis view. Peak systolic strain was obtained from six segments of the LV in either the apical or short-axis views. LV longitudinal strain and LV circumferential strain were subsequently calculated by averaging the peak systolic strain of the six segments from the apical four-chamber and short-axis views.

Covariates

Demographics, years of education, smoking status, history of alcohol use, and antihypertensive medication use were obtained by self-administered and interviewer-administered questionnaires. The Physical Activity History questionnaire was used to query the amount of time per week spent in 13 categories of leisure, occupational, and household physical activities during the previous 12 months. The details are described in the Methods in the Supporting Information. Body mass index (BMI) was calculated as weight in kilograms divided by height in metres squared. Glucose was measured using hexokinase coupled to glucose-6-phosphate dehydrogenase by Linco Research (St. Louis, MO). Total cholesterol was assayed enzymatically.

Statistical analysis

Trajectories of SBP, DBP, and PP were modelled among 4717 CARDIA participants with BP measured during at least three or more examinations from Year 0 to Year 30. BP data for Year 0 and Year 30 were available for all participants. Models were fit using PROC TRAJ in SAS Version 9.4 statistical software (SAS Institute, Inc).17 The Traj procedure is a semiparametric, group-based modelling strategy that uses a discrete mixture model to identify subgroups of CARDIA participants who shared similar underlying BP trajectories. Models were tested with different numbers of trajectory groups (ranging from 2 to 5) and with different orders of polynomials (linear, quadratic, or cubic). Model fit was assessed using the Bayesian information criterion (Supporting Information, Table S2). The posterior probability of group membership, that is, the probability of an individual belonging to each of the trajectory groups, was calculated for each individual to assess model’s discrimination power. Ideally, average posterior probability equals 1, with values closer to 1 indicating greater precision. An average posterior probability > 0.7 was considered satisfactory.10,17,18 The supplement includes additional details on the trajectory modeling process.

Differences between groups were tested by the χ² test for categorical data, and one-way ANOVA or Kruskal–Wallis for continuous data. Multivariable linear models were used to assess the association of trajectory group with echocardiographic outcomes: myocardial structure (LV mass index, LV diastolic dimension, and LA volume index), LV systolic function (LV ejection fraction, LV longitudinal strain, and LV circumferential strain), and LV diastolic function (E/A ratio, average e’ velocity, and average E/e’ ratio). Models were adjusted for the Year 30 covariates: age, sex, race, education, smoking, alcohol consumption, BMI, physical activity, antihypertensive medication use (Year 0 to Year 30), baseline SBP and DBP, diabetes mellitus, hyperlipidaemia, atrial fibrillation, and myocardial infarction. P trend for linear associations across the trajectory groups were calculated.

To test the robustness of our findings, we performed the following three sensitivity analyses: (i) We evaluated trajectories in mean arterial pressure (MAP, calculated as 1/3 SBP + 2/3 DBP); (ii) to assess whether antihypertensive medication use could change BP trajectory patterns, participants taking antihypertensive medications during follow-up were excluded; and (iii) the main analysis was repeated applying inverse probability of censoring weights (IPCW) to account for biases introduced by participants who did not attend the Year 30 examination. IPCW is a statistical method that corrects for bias resulting from the exclusion of study participants that are systematically different from those included.19 Using this method, observations are weighted by the inverse of the probability of the observation being included in the study.

A P value < 0.05 was considered statistically significant. All tests were two-sided. All analyses were performed using SAS, Version 9.4 (SAS Institute).

Results

Population characteristics

The 4717 participants who had at least 3 measures of BP over the 30 year follow-up period from early adulthood to middle age were included in trajectory analyses. Of these, 3174 participants with Year 30 echocardiography data were included in the final analytic cohort. Compared with the final analytic cohort, those who were excluded were slightly younger (25.0 years vs. 24.4 years), more likely to be black, male, current smokers, and to have a higher SBP level and fasting glucose at baseline. There was no significant difference in BMI levels, alcohol consumption, physical activity, total
cholesterol, and DBP level (Supporting Information, Table S2). Participant characteristics at the Year 0 and Year 30 examinations are shown in Supporting Information, Table S3.

Characteristics of BP trajectory groups

Trajectories were modelled separately for three BP indices, namely, SBP, DBP, and PP. Five distinct trajectories were identified for SBP and DBP (Figure 1), namely, low-stable, moderate-stable, high-stable, moderate-increasing, and high-increasing trajectories [distribution of participants among the aforementioned trajectories: SBP: 1110 (23.5%), 2188 (46.4%), 850 (18.0%), 416 (8.8%), 153 (3.2%); DBP: 905 (19.2%), 2118 (44.9%), 954 (20.2%), 526 (11.2%), 214 (4.5%)]. The mean posterior probability for all trajectories was high indicating good discrimination of trajectory assignment (mean posterior probability for each trajectory was SBP: 0.90, 0.86, 0.86, 0.94; DBP: 0.86, 0.82, 0.81, 0.79, 0.91). Trajectories in SBP and DBP shared several common characteristics. For SBP and DBP trajectories, the low-stable, moderate-stable, and high-stable trajectories maintained consistently low, moderate, and high BP levels, respectively, throughout follow-up. The moderate-increasing and high-increasing groups started with moderate and high BP levels, respectively. For SBP trajectories, BP values in the moderate-increasing groups rose at a rapid rate from the

Figure 1. Trajectories of (A) systolic blood pressure and (B) diastolic blood pressure over 30 years. Dashed lines indicate 95% confidence intervals.
Year 10 examination, while a more constant increase was apparent for DBP. The high-increasing groups maintained relatively elevated BP levels throughout follow-up.

In addition, five distinct trajectories were identified for PP (Figure 2A), namely, low-stable, moderate-stable, high-stable, low-increasing, and moderate-increasing trajectories [distribution of participants among PP trajectories: 2222 (47.1%), 434 (9.2%), 130 (2.8%), 1638 (34.7%), 293 (6.2%)]. The mean posterior probability for each trajectory follows: 0.86, 0.76, 0.87, 0.79, 0.87. The low-stable, moderate-stable, and high-stable trajectories maintained consistently low, moderate, and high BP levels, respectively, throughout follow-up. The low-increasing group started with low BP levels and experienced a rapid increase from the Year 10 examination. The moderate-increasing group started with moderate BP levels and experienced a rapid increase from the Year 10 examination.

Of the 3174 participants, 36 participants had a history of HF, and 3 of them had new onset HF. Characteristics of the participants at the Year 30 examination in each SBP group are presented in Table 1. Compared with participants in the low-stable group, those in the moderate-increasing and high-increasing groups were more likely to be black, less highly educated, and to have more pronounced CVD risk factors (Table 2). Group characteristics for DBP and PP trajectories had similar Year 30 characteristics to corresponding SBP trajectory groups (Supporting Information, Tables S4 and S5).

Figure 2. Trajectories of (A) pulse pressure and (B) mean arterial pressure over 30 years. Dashed lines indicate 95% confidence intervals.
Blood pressure trajectories and myocardial structure and function

Values of myocardial structural and functional indices across trajectories for SBP, DBP, and PP, after multivariable adjustment, are shown in Tables 2–4.

For SBP trajectories (Table 2), a significant decreasing trend was observed from the high-increasing and moderate-increasing groups through to the low-stable group for LV mass index, LV end-diastolic dimension, LA volume index, and E/e’ ratio, while an increasing trend was apparent for LV longitudinal strain, E/A ratio, and age-e’ velocities. There were no significant trends in LV ejection fraction.

For DBP trajectories (Table 1), a significant decreasing trend was observed from the high-increasing and moderate-increasing groups through to the low-stable group for LV mass index and higher E/e’ ratio, while an increasing...
A significant decreasing trend was apparent for LV ejection fraction, LV longitudinal strain, LV circumferential strain, E/A ratio, and average e' velocities. There were no significant trends in LV end-diastolic dimension or LA volume index.

For PP trajectories (Table 4), a significant decreasing trend was observed from the moderate-increasing and low-increasing groups through to the low-stable group for LV mass index, LV end-diastolic dimension, LA volume index, and E/e', while an increasing trend was apparent for average e' velocities. There were no significant trends in LV ejection fraction, LV longitudinal strain, LV circumferential strain, or E/A ratio.

### Sensitivity analyses

In sensitivity analyses, (i) trajectory patterns in MAP were similar to those in SBP and DBP (Figure 2B). The association between MAP trajectory groups and echocardiographic outcomes was generally consistent with SBP and DBP trajectory groups (Supporting Information, Table S6). (ii) Excluding participants taking antihypertensive medications during follow-up produced generally similar trajectory patterns (Supporting Information, Figure S2) and did not substantially alter the significant association of BP trajectory groups with echocardiographic outcomes (Supporting Information, Figure S3).
Table S7). (iii) Additionally, on accounting for selective attrition using IPCW, results were similar to the main analysis (Supporting Information, Table S8).

Discussion

In this community-based cohort of young adults followed up over 30 years, we identified five distinct trajectories in SBP, DBP, and PP that were significantly associated with adverse alterations in myocardial structure, and systolic and diastolic LV function in middle age independent of baseline BP levels. In particular, groups with sustained high BP levels across early to middle adulthood (high-increasing group) and those with a rapid increase in BP levels (moderate-increasing group) had the highest degree of adverse myocardial structural and functional changes in middle age.

Prior studies have revealed associations between elevated BP and adverse myocardial structural and functional changes. The Framingham Heart Study demonstrated that 30 year average SBP is a better predictor of LV mass and wall thickness compared with current BP. The British Birth Cohort study investigated the relationship of changes in SBP between two time points over different periods of adulthood (36–43, 43–53, 53–60/64 years) with myocardial remodelling and identified 43–53 years as a potential sensitive period when rise in SBP is associated with higher LV mass index. However, these prior studies did not describe the specific patterns of BP development and thus fail to quantify the population impact of different BP trajectories over time on later-life echocardiographic outcomes.

Through the utilization of a group-based modelling approach, the developmental course of BP may be mapped, and individuals can be categorized into exclusive groups across their lifespan. This helps to conceptualize the pathways of progression of BP levels and their impact on cardiovascular events. A number of studies have prospectively explored BP trajectories at different periods of life and consistently found higher BP trajectories to be associated with subsequently increased risk of adverse health outcomes including coronary artery calcification, impaired renal function, incident atrial fibrillation, and stroke.

The Georgia Stress and Heart (GSH) study, to our knowledge, is the only study to have used group-based modelling to investigate BP trajectory in relation to myocardial structure. Three trajectory groups in BP over 23 years from childhood to young adulthood were identified in 683 participants. A faster rate of increase in BP was significantly associated with LV mass index levels in young adulthood. However, this study was limited as the sample was small and relatively young. Additionally, only one echocardiographic parameter (i.e. LV mass index) was analysed as an outcome of interest. The present study addresses these deficiencies by following a sizeable sample, representing an older age group (early to middle adulthood), and including comprehensive echocardiographic outcomes (myocardial structure and function) in the analysis.

This study comprehensively assesses the association of BP trajectories from early adulthood throughout middle age with myocardial structure and systolic and diastolic LV function in middle age. The results extend existing knowledge by demonstrating that individuals with sustained high BP levels and with a rapid increase in BP levels across early to middle adulthood had the highest degree of myocardial remodelling and dysfunction in midlife, and this association was also present among those not taking antihypertensive medication.

Elevated BP induces an increase in LV afterload and arterial stiffness, which leads to myocyte hypertrophy and interstitial fibrosis, and results in alterations of LV contractility and relaxation. Herein, we found participants in the moderate-increasing group and in the high-increasing group had the highest degree of adverse myocardial structural and functional attributes, despite participants in the moderate-increasing group being in the range of normotensive BP or prehypertension most of the time. This suggests a role of BP trajectory, rather than elevated BP alone, in the development and progression of CVD.

Current evidence suggests that normalization of BP with antihypertensive medication does not completely mitigate the lifetime cardiovascular burden associated with elevated BP. However, it remains to be seen whether interventions at an earlier phase, targeted towards modifying BP trajectories, may reduce myocardial remodelling and dysfunction and subsequently slow the progression to clinical HF. This approach may be particularly important for those who initially exhibit normal BP levels but subsequently experience a rapid increase in BP (i.e. moderate-increasing group in our study). Speculatively, intervening early in this trajectory may reduce associated late-life CVD risk.

Different trajectory profiles across the life course may reflect aetiological heterogeneity, differences in prevention measures, and treatment. Further studies examining the determinants of increases in BP levels might facilitate effective prevention of hypertension and maintenance of optimal BP levels throughout a lifetime. Genome-wide association studies have identified genetic variants related with BP and hypertension. Identifying the contributions of genetics and individual health practices to these specific BP trajectories would provide critical insights into personalized clinical treatment approaches and prevention strategies.

By evaluating BP from a life-course perspective, we assessed the impact of long-term BP trajectory patterns on later-life myocardial remodelling and dysfunction. Thereby, we were able to identify two high-risk trajectories. These findings have important clinical implications. Given the widespread adoption of electronic medical records, it is clinically...
feasible for physicians to map BP trajectories across multiple time points and identify individuals in high-risk trajectories. Further work is required to determine the optimal type (lifestyle or pharmacological) and timing of interventions that may alter the future risk of myocardial remodelling and dysfunction in these high-risk individuals. Our results are notable because myocardial remodelling and subclinical LV systolic and diastolic dysfunction are important precursors of incident HF and are associated with increased risk of adverse cardiovascular outcomes and mortality.30–33

Strengths of this study include a large, community-based biracial cohort; long duration of follow-up (30 years of BP measurement) with nine examinations enabling assessment of long-term patterns of BP from early to middle adulthood; and a comprehensive echocardiographic assessment allowing assessment of myocardial structure, and systolic and diastolic LV function. This study has several limitations. First, not all participants had BP measurements available at all visits. However, of those who were included in the trajectory model analysis, the median and interquartile range of BP measurement was 8 (6 to 9), with 95.3% of participants completing at least 6 measurements. Therefore, the bias introduced due to missing BP measurements may be quite limited. Second, 24 h ambulatory BP monitoring was not available in our study; masked or white-coat hypertension may have been missed. Third, potential bias related to selective attrition is a concern. Participants who were lost to follow-up, attended fewer than three BP assessments, or had missing Year 30 echocardiographic data were excluded. However, when accounting for attrition using IPCW, the associations remained similar. In addition, those who were excluded had a higher comorbidity burden; exclusion of these generally higher-risk participants would tend to bias our results to the null. Therefore, the true associations between BP trajectories and myocardial structure and function may have been underestimated. Furthermore, even though we adjusted our analyses for major confounders, residual confounding cannot be excluded. Finally, our cohort consisted of a biracial black and white population and these results may not be generalizable to other racial and ethnic groups.

Conclusions

BP trajectories from early to middle adulthood are independently associated with myocardial remodelling and LV systolic and diastolic dysfunction in middle age. Trajectories associated with the highest risk of adverse myocardial structural and functional changes include patients with sustained high or rapidly increasing BP levels. Public health efforts should focus on mapping BP trajectories across the life course, which may allow the identification of high-risk trajectories and facilitate tailored treatment approaches and prevention strategies.

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Conflict of interest

None declared.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Estimation of trajectory groups for SBP, DBP, PP and MAP.
Table S2. Comparison of baseline characteristics of participants who were included and excluded from the current study.
Table S3. Participant characteristics at the CARDIA Year-0 and Year-30 examinations.
Table S4. Participants characteristics at Year-30 examination by DBP trajectory group.
Table S5. Participants characteristics at Year-30 examination by PP trajectory group.
Table S6. Association of MAP Trajectory Groups with Indices of Myocardial Structure and Function at Year-30 examination.
Table S7. Association of BP trajectory groups with indices of myocardial structure and function among participants who never used antihypertensive medication.
Table S8. Sensitivity analyses accounting for participants with missing Year-30 data: association of BP trajectory groups with indices of myocardial structure and function.
Figure S1. Trajectories in (A) SBP (B) DBP (C) PP in the CARDIA Cohort (sensitivity analysis).
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