

BMJ Open Association of early adult modifiable cardiovascular risk factors with left atrial size over a 20-year follow-up period: the CARDIA study

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ABSTRACT

Objectives: We investigate how early adult and 20-year changes in modifiable cardiovascular risk factors (MRF) predict left atrial dimension (LAD) at age 43–55 years.

Methods: The Coronary Artery Risk Development in Young Adults (CARDIA) study enrolled black and white adults (1985–1986). We included 2903 participants with echocardiography and MRF assessment in follow-up years 5 and 25. At years 5 and 25, LAD was assessed by M-mode echocardiography, then indexed to body surface area (BSA) or height. Blood pressure (BP), body mass index (BMI), heart rate (HR), smoking, alcohol use, diabetes and physical activity were defined as MRF. Associations of MRF with LAD were assessed using multivariable regression adjusted for age, ethnicity, gender and year-5 left atrial (LA) size.

Results: The participants were 30±4 years; 55% white; 44% men. LAD and LAD/height were modest but significantly higher over the follow-up period, but LAD/BSA decreased slightly. Increased baseline and 20-year changes in BP were related to enlargement of LAD and indices. Higher baseline and changes in BMI were also related to higher LAD and LAD/height, but the opposite direction was found for LAD/BSA. Increase in baseline HR was related to lower LAD but not LAD indices, when only baseline covariates were included in the model. However, baseline and 20-year changes in HR were significantly associated to LA size.

Conclusions: In a biracial cohort of young adults, the most robust predictors for LA enlargement over a 20-year follow-up period were higher BP and BMI. However, an inverse direction was found for the relationship between BMI and LAD/BSA. HR showed an inverse relation to LA size.

INTRODUCTION

Left atrial (LA) remodelling is an important independent predictor of cardiovascular (CV) events in diverse populations. LA is structurally and functionally linked to the left ventricle, functioning as a reservoir during

Strengths and limitations of this study

- We show the long-term effect of modifiable cardiovascular risk factors on left atrial size, over a 20-year follow-up period.
- This large cohort study helps understanding the role of risk factors on the left ventricular filling pressures over young adulthood.
- We used the left atrial diameter assessment by M-mode echocardiography, a practical, low cost and validated method. However, it may lack accuracy as it is based on the linear measurement of the anteroposterior diameter and may not account for the left atrial eccentric remodelling.

ventricular systole, a conduit during early diastole and contracting during late diastole to aid ventricular filling. Echocardiography is validated for the assessment of LA structure. M-mode echocardiography technique may evaluate the LA size by assessing the anteroposterior linear LA diameter (LAD), a widely used method in clinical practice and research.^{1 2}

Similarly to other cardiac structures, LA scales with body size.^{1 3} Several indexing methods have been proposed to adjust LA size for anthropometrics, but indexing by body surface area (BSA) is the most common and recommended.¹ Analyses of indexing left ventricular structure for body size indicate that BSA may over adjust for obesity-related increases in the left ventricular mass.⁴ However, indexing cardiac structures to height theoretically reduces confounding effects and improves clinical management when compared with BSA.⁵

The National Heart, Lung and Blood Institute's Coronary Artery Risk Development in Young Adults (CARDIA) study investigates prospectively CV disease risk factors and

subclinical disease in a young population. In the CARDIA study, LAD has an association with subclinical atherosclerosis independent of other coronary artery disease risk factors.⁶ There is no information on longitudinal determinants of LAD during the transition from young adulthood to middle age.

This study assesses how modifiable risk factors in young adulthood associate with LA size over a 20-year period. We investigate how early adult and 20-year changes in modifiable CV factors predict LAD at age 43–55 years. In addition, we explore how this prediction is affected by indexing LAD by BSA or height.

METHODS

Study design and sample

The CARDIA study is a prospective observational investigation that has completed 25 years of follow-up.⁷ Between 1985 and 1986, 5115 African-American and white participants (aged 18–30 years) were enrolled in four field centres (Birmingham, Alabama; Oakland, California; Chicago, Illinois; and Minneapolis, Minnesota, USA). Then, the participants underwent follow-up examination in years 0, 2, 5, 7, 10, 15, 20 and 25, with echocardiograms performed in the entire cohort at years 5 and 25. We included participants who underwent echocardiography assessment and had data on LAD and modifiable CV risk factors at CARDIA examination years 5 and 25. From the 3240 participants who attended CARDIA examination year 5 (baseline in this study) and examination year-25, 24 participants did not have echocardiography performed at year 25 and 313 had incomplete data on covariates at CARDIA examination year 5 or 25. The final analytic cohort for this study included 2903 participants. All participants gave written informed consent.

Echocardiography

The CARDIA year 5 echocardiography standard protocol has been described.⁸ Briefly, echocardiograms were performed in each field centre using an Acuson cardiac ultrasound machine (Siemens Healthcare; Erlangen, Germany), recorded in super-VHS tapes, and then interpreted following the American Society of Echocardiography (ASE) recommendations⁹ at a single reading centre (University of California, Irvine, USA). In the field centres, parasternal long-axis two-dimensional views were used to guide the assessment of M-mode anteroposterior images from the aortic root and the left atrium. During the echocardiography interpretation, the LA linear dimension was measured from the leading edge of the posterior aortic wall to the leading edge of the posterior LA wall. CARDIA examination year 25 echocardiography used Artida cardiac ultrasound machines (Toshiba Medical Systems, Otawara, Japan), following acquisition and interpretation protocols similar to examination year 5. LADs from examination years 5 and 25 were indexed to BSA and height (in meters) from the corresponding examination year.

Risk factors assessment

We explored biological and lifestyle risk factors by assessing the association between modifiable risk factors and LA size. Although other factors may be related to LA size, modifiable risk factors were chosen among major CV risk factors known to be associated to LAD and that could be favourably modified by a healthy lifestyle, such as blood pressure (BP), use of medication for hypertension, body mass index (BMI), heart rate (HR), smoking status, alcohol use, physical activity score and diabetes status.

Assessment methods for risk factor variables have been described for the CARDIA study.¹⁰ Briefly, use of medication, alcohol consumption (in milliliter of ethanol consumed per day) and smoking status (not smoking or current smoker) were assessed using questionnaires. After 5 min rest, the last two of a total of three measurements of BP were averaged for computing systolic (SBP) and diastolic BP (DBP) values; and HR was assessed in 30 s. A physical activity score was obtained from the CARDIA Physical Activity History, as previously described.⁵ In the CARDIA study, the presence of diabetes was assessed at each examination based on a combination of history of medication use (every visit), fasting glucose ≥ 126 mg/dL (years 0, 7, 10, 15, 20 and 25), glucose tolerance test (years 10, 20 and 25; glucose ≥ 200 mg/dL) or glycated haemoglobin $\geq 6.5\%$ (years 20 and 25). We defined presence of diabetes at baseline if any of these criteria was present at examination year 5. New cases of diabetes at examination year 25 were computed if the criteria for diabetes were established over the period between examination year 5 and the end of follow-up at examination year 25.

Data analysis

Continuous variables were described as mean \pm SD and categorical variables in per cents. For each participant, we compared all parameters assessed at CARDIA examination years 5 and 25. The differences between mean values were tested by paired t test and between proportions by McNemar's.

Cross-sectional relations between risk factors and LA size (both at year 5) were assessed by multivariate linear regression. The longitudinal relation between LA size at years 5 and 25 was also assessed. Multivariable regression models assessed the influence of examination year 5 modifiable risk factors on examination year 25 LAD, LAD/BSA and LAD/height. In sequence, multivariable regression models assessed the influence of modifiable risk factors at examination year 5 and their 20-year change on examination year 25 LAD, LAD/BSA and LAD/height. Ethnic-specific analysis for LAD/height was also performed for the fully adjusted model to explore ethnic particularities (for results see online supplementary material).

The association between LAD and BP was explored by including antihypertensive medication use with SBP or DBP as covariates in the regression models. The relation between diabetes and LAD was assessed using presence of diabetes at baseline and new cases of diabetes at

examination year 25. All multivariable regression models were adjusted for other known CV risk factors, here defined as non-modifiable by a healthy lifestyle: age, ethnicity, gender and examination year 5 LA size. Maximum education attained was tested, but did not show an association with LAD, and, therefore, was not included in the regression models (data not shown).

RESULTS

The participant characteristics at CARDIA examination years 5 and 25 are shown in table 1. Over 20 years (CARDIA examination 5–25), alcohol consumption, BMI and SBP increased significantly in the study cohort, while HR, tobacco use and the physical activity score decreased significantly. Although statistically significant, changes in mean alcohol consumption, heart rate and cigarette use over 20 years were not substantial. In the same period, the proportion of participants with hypertension and diabetes increased. LAD and LAD/height were modestly higher over the follow-up period, but LAD/BSA had a slight decrease.

In a cross sectional analysis at CARDIA examination year-5, BMI was directly related to LAD and LAD/height and an inverse relation was found for LAD/BSA. Being a current smoker and having higher resting HR were consistently related to higher LAD, LAD/BSA and LAD/height. Antihypertensive medication use, SBP and physical activity had significant direct relations to LAD, but no association was found after indexing LAD by height or BSA. Neither alcohol use nor presence of diabetes had cross-sectional association with LA size (table 2).

Table 3 shows the multivariable linear regression models for the influence of examination year 5

modifiable CV risk factors on LAD and its indices over a 20-year follow-up period, adjusted for age, race, gender and baseline LA size. Higher values of baseline SBP were significantly related to higher LAD and LAD/BSA over 20 years, with marginal significance for LAD/height. No significant relationship between LA size and DBP was found, when DBP was tested replacing SBP in the model. Higher BMI was related to higher CARDIA examination year 25 LAD and LAD/height. However, the opposite direction was found for baseline BMI in the regression model for LAD/BSA. Increase in baseline HR was related to lower values of LAD and LAD indices. Neither baseline smoking status, alcohol consumption nor physical activity score had significant prediction ability for LAD or LAD indices. The presence of diabetes at baseline was associated with enlarged LA size after a 20-year follow-up period.

In table 4, we show the results for multivariable regression models assessing simultaneously baseline (CARDIA examination year 5) and 20-year change covariates for the endpoints (measured at CARDIA examination year 25) of LAD, LAD/BSA and LAD/height. Lower baseline HR and HR 20-year changes showed a significant relationship to higher LAD and LAD indices at CARDIA examination year 25. Higher values of baseline SBP and SBP 20-year changes also related directly to LAD and LAD indices at year 25. Compared with SBP, DBP had a weaker relation to LA size when tested in the same models (see online supplementary table S1). Higher BMI and BMI changes were related to enlargement in LAD and LAD/height. However, again an inverse correlation was found for baseline BMI and changes when LAD/BSA was used as the endpoint. Neither smoking status, alcohol consumption nor physical activity score at baseline or over 20-year changes had significant

Table 1 Participant characteristics at examination year 5 and after a 20-year follow-up period (n=2903)

Variables	Examination year 5 Mean (SD)	Examination year 25 Mean (SD)	p Value
Age (years)	30 (4)	50 (4)	NA
BMI (kg/m ²)	26 (6)	30 (7)	<0.0001
SBP (mm Hg)	107 (11)	119 (16)	<0.0001
HR (bpm)	68 (10)	66 (10)	<0.0001
Alcohol use (mL/day)	11 (22)	12 (23)	0.006
Physical activity score (units)	378 (289)	339 (272)	<0.0001
Cigarettes (number/day)	3 (7)	2 (5)	<0.0001
LAD (cm)	35 (5)	37 (5)	<0.0001
LAD/BSA(cm/m ²)	1.9 (0.2)	1.8 (0.2)	<0.0001
LAD/height(cm/m)	2.1 (0.3)	2.2 (0.3)	<0.0001
	Proportion	Proportion	
White ethnicity	56%	NA	NA
Male gender	44%	NA	NA
Current smoker	26%	16%	<0.0001
Hypertension	4%	34%	<0.0001
Diabetes	1%	14%	0.0001

p Values for differences between mean values were tested by paired t test and between proportions by McNemar's test.

BMI, body mass index; BSA, body surface area; HR, heart rate; LAD, left atrial diameter assessed by M-mode echocardiography; NA, not applicable; SBP, systolic blood pressure.

Table 2 Multivariable linear regression for cross-sectional association of modifiable risk factors with left atrial size, both measured at examination year 5 (n=2903)

Variable	Unindexed LAD (cm) (R ² =0.29)		LAD/BSA (cm/m ²) (R ² =0.08)		LAD/height (cm/m) (R ² =0.25)	
	Coefficient	p Value	Coefficient	p Value	Coefficient	p Value
Presence of diabetes	-0.065	0.507	-0.028	0.626	-0.034	0.561
BMI (5 kg/m ²)	0.183	<0.0001	-0.025	<.0001	0.113	<0.0001
SBP (10 mm Hg)	0.021	0.005	0.004	0.374	0.007	0.125
HR (10 bpm)	-0.066	<0.0001	-0.033	<.0001	-0.037	<0.0001
Current smoker	0.070	<0.0001	0.041	<.0001	0.043	<0.0001
Using medication for HTN	0.174	0.005	0.062	0.0848	0.097	0.009
Alcohol consumption (20 mL/day)	0.010	0.159	0.007	0.0714	0.008	0.058
Physical activity score (300 u)	0.026	0.001	0.006	0.2091	0.009	0.049

Cross-sectional regression models adjusted for age, ethnicity and gender.

BMI, body mass index; BSA, body surface area; HR, heart rate; HTN, hypertension; LAD, left atrial dimension; SBP, systolic blood pressure.

prediction ability for LAD or LAD indices. Higher LAD was associated with baseline diabetes, but no statistical significance was found for the presence of diabetes at examination year 25. Caucasian and African-American participants showed similar results for the influence of risk factors on LA size (see online supplementary table S2).

DISCUSSION

In this study, we show how modifiable CV risk factors in a large cohort of young adults are associated with LAD over a 20-year period. During early adulthood, the most robust predictors for LA enlargement over a 20-year follow-up period were higher SBP, lower heart rate and higher BMI. In addition, the presence of diabetes at baseline showed a significant relation to high LA size at examination year 25. However, alcohol use, physical activity and smoking status did not show significant longitudinal influence.

Cardiac remodelling plays a central role in CV disease and may be characterised by heart chamber enlargement and dysfunction. The LA remodelling process

strongly relates to increase in left ventricular filling pressures. Furthermore, LA structure and function show important associations to CV risk burden and clinical events prediction.^{2 4 11} In a longitudinal assessment over 10 years in the CARDIA cohort, LAD assessed on 2724 participants at examination year 5 was associated with the presence of coronary calcium at CARDIA examination year 15 (2000–2001), independent of other risk factors such as age, sex, race, BMI, SBP, smoking and lipids.⁶ The intensity of exposure to CV risk factors in youth correlates to early coronary disease.¹² However, there are limited data regarding how long-term risk factor exposure influences LA size.

LAD assessment by M-mode echocardiography is a practical, low cost and validated method.^{9 13 14} It has high consistency, but may lack accuracy as it is based on the relationship between anteroposterior LAD and other spatial dimensions in the LA remodelling process.¹ Despite this intrinsic limitation, previous studies have shown the association between increased LAD by M-mode echocardiography and incident CV outcomes, particularly atrial fibrillation and cerebrovascular events.^{15 16} Moreover, the LIFE Study followed with

Table 3 Multivariable linear regression for association of examination year 5 (baseline) modifiable risk factors with left atrial size over a 20-year follow-up period (n=2903)

Variable	Unindexed LAD (cm) (R ² =0.29)		LAD/BSA (cm/m ²) (R ² =0.22)		LAD/height (cm/m) (R ² =0.26)	
	Coefficient	p Value	Coefficient	p Value	Coefficient	p Value
Diabetes at baseline	0.231	0.029	0.119	0.030	0.142	0.024
BMI (5 kg/m ²)	0.108	<0.0001	-0.037	<0.0001	0.065	<0.0001
SBP (10 mm Hg)	0.020	0.011	0.010	0.016	0.009	0.061
HR (10 bpm)	-0.019	0.029	-0.005	0.257	-0.010	0.042
Current smoker	0.018	0.350	0.005	0.583	0.015	0.181
Using medication for HTN	-0.041	0.539	0.011	0.741	-0.024	0.549
Alcohol consumption (20 mL/day)	-0.010	0.188	0.004	0.319	-0.004	0.370
Physical activity score (300 u)	0.005	0.564	0.004	0.356	-0.001	0.846

Models adjusted for age at baseline, ethnicity, gender and left atrial size at baseline. Left atrial size at baseline refers to unindexed LAD, LAD/BSA or LAD/height, according to the endpoint in the regression model.

BMI, body-mass index; BSA, body surface area; HR, heart rate; HTN, hypertension; LAD, left atrial dimension; SBP, systolic blood pressure.

Table 4 Multivariable linear regression for influence of CARDIA examination year 5 (baseline) and 20-year change modifiable risk factors on left atrial size at CARDIA examination year 25 (n=2903)

Variable	Unindexed LAD (cm) (R ² =0.35)		LAD/BSA (cm/m ²) (R ² =0.31)		LAD/height (cm/m) (R ² =0.33)	
	Coefficient	p Value	Coefficient	p Value	Coefficient	p Value
Diabetes at baseline (year 5)	0.254	0.013	0.122	0.019	0.154	0.011
Diabetes at follow-up, but not baseline	0.017	0.480	-0.001	0.963	0.006	0.677
BMI at baseline (5 kg/m ²)	0.108	<0.0001	-0.040	<0.0001	0.065	<0.0001
BMI changes (5 kg/m ²)	0.126	<0.0001	-0.076	<0.0001	0.075	<0.0001
SBP at baseline (10 mm Hg)	0.034	<0.0001	0.014	0.002	0.018	<0.001
SBP changes (10 mm Hg)	0.025	<0.0001	0.012	<0.0001	0.017	<0.0001
HR at baseline (5 beats/30 s)	-0.048	<0.0001	-0.021	<0.0001	-0.028	<0.0001
HR changes (5 beats/30 s)	-0.049	<0.0001	-0.025	<0.0001	-0.030	<0.0001
Smoking status (vs never smoked)						
Not baseline, yes Y25	-0.057	0.295	-0.037	0.185	-0.036	0.264
Yes baseline, no Y25	0.007	0.771	-0.003	0.815	0.004	0.796
Yes baseline, yes Y25	0.010	0.680	0.010	0.381	0.013	0.325
Medication for HTN (vs never used)						
Not baseline, yes Y25	0.031	0.118	0.020	0.044	0.025	0.035
Yes baseline, no Y25	0.055	0.685	0.008	0.904	0.024	0.769
Yes baseline, yes Y25	-0.012	0.865	0.018	0.633	0.002	0.970
Alcohol consumption at baseline (20 mL/day)	-0.002	0.850	0.005	0.301	0.001	0.799
Alcohol consumption changes (20 mL/day)	0.006	0.423	0.006	0.128	0.004	0.322
Physical activity score at baseline (300 u)	0.013	0.217	0.003	0.574	0.004	0.541
Physical activity score changes (300 u)	0.008	0.402	0.004	0.383	0.005	0.399

Models adjusted for age at baseline, ethnicity, gender and left atrial size at baseline. Left atrial size at baseline refers to unindexed LAD, LAD/BSA or LAD/height, according to the endpoint in the regression model. BMI, body mass index; BSA, body surface area; HR, heart rate; HTN, hypertension; LAD, left atrial dimension; SBP, systolic blood pressure; Y25, CARDIA study examination year 25.

echocardiograms 939 hypertensive patients for 4.8 years and found that enlarged baseline LAD increased risk for atrial fibrillation whereas reduction of LAD reduced the risk in models adjusted for age, LV mass, SBP and Framingham risk score.¹⁷

Similar to our study, cross-sectional relations between CV risk factors and LAD have been reported in the literature. Cuspidi *et al*¹⁸ found significantly higher BMI and SBP with enlarged LAD in a population of 2500 uncomplicated patients with hypertension. Tsang *et al*¹⁵ investigated 423 patients and also found cross-sectional relations of LAD with BMI and SBP. In a cross-sectional assessment of 4059 CARDIA participants at examination year 5, a low CV risk burden was associated with more favourable values for LA size. In this study, Gidding *et al*¹⁹ showed that higher BMI, higher SBP, lower heart rate, tobacco use, higher serum glucose and higher self-reported physical activity were independently associated with enlarged LAD/height.

There are limited data on the longitudinal determinants of LA size. In this study, we assessed a generally healthy cohort examined at ages 23–35 and 43–55 years. BP, particularly SBP and BMI emerged as very robust risk factors associated with LAD and LAD change over 20 years. McManus *et al*²⁰ reported similar findings following an older population of 4403 Framingham Study participants over a 16-year follow-up period. BP and BMI were the major factors related to LAD enlargement. BP and obesity are known determinants of LV diastolic

dysfunction and cardiac remodelling,^{21 22} strongly associated with elevated filling pressures and LA enlargement. In fact, higher BP was a consistent determinant of LAD enlargement in our study. In our cohort of young participants, the association between BP and LA size was weaker in cross-sectional as compared with longitudinal regression models. This emphasises the importance of chronic exposure to high BP and subclinical cardiac endpoints, including LA size.

Obesity, as assessed by BMI, strongly relates to CV risk.²³ BMI was also consistently related to LA size in our study, but the relationship varied depending on the method used to index LAD. In this regard, indexing LAD by BSA may overadjust for deleterious effects of excess adiposity-producing values that underestimate risk in obese participants.^{24 25} This is suggested by our results where the relationship between change in BMI and LAD/BSA was inverse despite the knowledge that BMI is strongly related to LAD in cross-sectional analyses, and BMI and LAD contribute to CVD risk. A cross-sectional study of 244 children found an independent association of LAD with body fat mass, body fat as a percentage of body mass, abdominal fat mass and body fat distribution.²⁶ Adjusting CV parameters for height alone appear to provide more stable longitudinal assessment.³

In our study, resting HR was associated to LAD and LAD/height but not to LAD/BSA at CARDIA examination year 25, when only year 5 variables were included in the regression models (table 2). Furthermore, lower



HR at baseline and its 20-year decrease emerged as significant determinants of LAD enlargement over the 20-year follow-up period (table 3). HR is inversely related to stroke volume at rest and a higher resting HR has shown an association with adverse events.^{27–29} However, there may be a threshold effect for the adverse association of elevated HR. Values above 80 bpm may have a stronger association to CV risk in older populations, possibly related to the association of a higher oxygen consumption with higher prevalence of existing coronary disease and adverse cardiac function in this population.³⁰ These data suggest that some changes in LA size may be adaptive as opposed to adverse and are consistent with the cross-sectional inverse relationship between HR and LAD reported in the literature.^{15 18 19}

Diabetes is a known risk factor for CV disease including heart failure. However, LA size had no cross-sectional association with diabetes in our study. Moreover, LA enlargement was related to baseline diabetes, but not its new development after 20 years. These findings suggest that the period of exposure to diabetes may play an important role in atrial remodelling.

LAD enlargement may be related to an adaptation process in exercise conditioning. Evidence of the association between physical activity and LAD have been reported in high-performance athletes,^{31 32} and also in a cross-sectional analysis of CARDIA participants.¹⁹ However, our study did not find a significant relationship between LAD and physical activity at baseline or with its 20-year changes. This is likely secondary to the small number of elite athletes in the cohort. Smoking is a major CV risk factor and is related to left ventricular fibrosis, mass and diastolic function. In fact, being a smoker had a cross-sectional relation with the higher LA size in our study. However, smoking status was not a significant longitudinal determinant of LA size in young adults over a 20-year follow-up period. Previous cross-sectional studies also failed to find significant relations regarding tobacco use and LA size.^{15 18} Alcohol use also had no significant relation to LAD. Alcohol consumption has a controversial association to CV risk, probably influenced by the amount and type of the agent used.³³ In this regard, our study is limited by not accounting for the type of beverage used by the participants.

In a large biracial cohort of young adults, BP and BMI played a major role in LA enlargement over a 20-year period; resting HR and its 20-year changes were inversely related to LAD. In addition, diabetes at age 23–35 years, but not incident, was significantly related to a higher LAD size. Particularly interesting results were found regarding the LAD indexing process, with negative correlations between change in BMI and LAD/BSA values. Therefore, LAD indexed to BSA may not be the best indexing method for longitudinal assessment of LA size. Future studies directly comparing indexing methods in clinical event prediction are needed to establish the best method for indexing LA size.

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Data sharing statement The CARDIA study has provided the National Heart, Lung, and Blood Institute data repository datasets. Additional information can be found on the CARDIA Study website <http://www.cardia.dopm.uab.edu/>

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