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CLINICAL RESEARCH

Determinants of left atrioventricular coupling index: The Multi-Ethnic Study of Atherosclerosis (MESA)☆

Déterminants de l'indice de couplage auriculo-ventriculaire gauche : l'étude multiethnique de l'athérosclérose (MESA)

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KEYWORDS
Cardiac magnetic resonance;
Left atrium;

Summary
Background. — Recent studies have described a novel left atrioventricular coupling index (LACI), which had a better prognostic value in predicting cardiovascular events than individual left atrial (LA) or left ventricular (LV) variables.

Abbreviations: BMI, body mass index; CMR, cardiac magnetic resonance; CVD, cardiovascular disease; ECV, extracellular volume; LA, left atrium/atrial; LACI, left atrioventricular coupling index; ΔLACI, annualized change in LACI over 10 years; LV, left ventricle/ventricular; MESA, Multi-Ethnic Study of Atherosclerosis; MVR, mass-to-volume ratio; NT-proBNP, N-terminal prohormone of B-type natriuretic peptide.

☆ Tweet: First paper to investigate the determinants of left atrioventricular coupling using a new index, the LACI defined by cardiac MRI! Study from MESA by @PezelT and @HopkinsMedicine.

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Left ventricle;
Coupling;
Multi-Ethnic Study of Atherosclerosis (MESA)

Aims. — To identify determinants of LACI and its 10-year annual change (ΔLACI), measured by cardiac magnetic resonance (CMR), and to better understand the variables governing this left atrioventricular coupling.
Methods. — In the Multi-Ethnic Study of Atherosclerosis, 2112 study participants, free from cardiovascular disease at baseline, had LACI assessed by CMR imaging at baseline ($LACI_{Baseline}$; 2000—2002) and 10 years later (2010—2012). The LACI was defined as the ratio of LA to LV end-diastolic volumes. Linear regression analyses were performed to identify independent determinants of $LACI_{Baseline}$ and ΔLACI.
Results. — In the 2112 participants (mean age 58.8 ± 9.1 years; 46.6% male), after adjustment for all covariates, age was independently associated with $LACI_{Baseline}$ (R^2 = 0.10, slope = 0.16) and ΔLACI (R^2 = 0.15, slope = 0.008; both P < 0.001). African Americans had the highest $LACI_{Baseline}$ value (18.0 ± 7.7%). Although there was no difference in $LACI_{Baseline}$ between women and men (P = 0.19), ΔLACI was higher in women (1.0 ± 1.1 vs 0.8 ± 1.1%/year; P < 0.001). Diabetes and higher body mass index (BMI) were independently associated with $LACI_{Baseline}$ (both P < 0.001). $LACI_{Baseline}$ was independently associated with LV myocardial fibrosis markers (native T1: R^2 = 0.11, slope = 0.09 [P = 0.038]; extracellular volume: R^2 = 0.08, slope = 0.28 [P = 0.035]) and N-terminal prohormone of B-type natriuretic peptide (NT-proBNP) concentration (R^2 = 0.10, slope = —1.11; P < 0.001), but was not associated with interleukin 6 or high-sensitivity C-reactive protein.
Conclusions. — Age, sex, ethnicity, diabetes and BMI were independent determinants of LACI. LACI was independently associated with myocardial fibrosis markers and NT-proBNP concentration.

MOTS CLÉS
Imagerie par résonance magnétique cardiaque ;
Oreillette gauche ;
Ventricule gauche ;
Couplage ;
Étude Multi-Ethnique de l'Athérosclérose (MESA)

Résumé
Contexte. — Des études récentes ont décrit un nouvel indice de couplage auriculo-ventriculaire gauche (LACI), qui avait une meilleure valeur pronostique que la mesure individuelle de tous les paramètres structurels ou de fonction de l'oreillette gauche (OG) ou du ventricule gauche (VG) pour prédire la survenue d'événements cardiovasculaires.
Objectifs. — Identifier les déterminants de ce nouvel indice, le LACI, et de sa variation annuelle sur 10 ans (ΔLACI), mesurés par imagerie par résonance magnétique (IRM) cardiovasculaire, et mieux comprendre les paramètres régissant ce couplage auriculo-ventriculaire gauche.
Méthodes. — Dans le cadre de l'étude MESA (Multi-Ethnic Study of Atherosclerosis), 2112 participants à l'étude, sans maladie cardiovasculaire au recrutement, ont eu une mesure de leur LACI évalué par IRM cardiaque au départ (2000—2002) et 10 ans plus tard (2010—2012). Le LACI a été défini comme le rapport entre le volume télé-diastolique de l'OG et le volume télé-diastolique du VG. Des analyses de régression linéaire ont été effectuées pour identifier les déterminants indépendants du LACI mesuré au début de l'étude ou du ΔLACI.
Résultats. — Chez les 2112 participants (58,8 ± 9,1 ans; 46,6 % d'hommes), après ajustement pour toutes les covariables, l'âge était indépendamment associé à la fois au LACI mesuré au début de l'étude (R^2 = 0,10) et au ΔLACI (R^2 = 0,15; tous deux p < 0,001). Les Afro-Américains avaient la valeur de LACI mesurée au début de l'étude la plus élevée (18,0 ± 7,7 %). Bien qu'il n'y ait pas de différence de la valeur du LACI mesuré au début de l'étude entre les femmes et les hommes (p = 0,19), le ΔLACI était plus élevé chez les femmes que chez les hommes (1,0 ± 1,1 contre 0,8 ± 1,0 %/an; P < 0,001). Le diabète et un IMC plus élevé étaient indépendamment associés à la valeur du LACI mesurée au début de l'étude (p < 0,001 dans les deux cas). Le LACI mesuré au début de l'étude était indépendamment associé aux marqueurs de fibrose du myocarde VG (T1 natif: R^2 = 0,11 [p = 0,038]; et volume extracellulaire: R^2 = 0,08 [P = 0,035]) et de la valeur du NT-proBNP (R^2 = 0,10; p < 0,001), mais n'était pas associé aux marqueurs de l'inflammation.
Conclusions. — L'âge, le sexe, l'origine ethnique, le diabète et l'IMC étaient des déterminants indépendants de la valeur du LACI mesuré au début de l'étude. Le LACI était indépendamment associée aux marqueurs de fibrose myocardique du VG et de la valeur du NT-proBNP.

Background

Given the important medicoeconomic burden associated with cardiovascular disease (CVD) [1], it is crucial to develop simple and powerful variables in clinical routines for stratifying the CVD risk of individuals in primary prevention. Using cardiovascular imaging, several left ventricular (LV) structural and functional variables have shown prognostic value in predicting the occurrence of cardiovascular events [2,3]. Some left atrial (LA) structural and functional variables have also consistently exhibited prognostic value in predicting cardiovascular events [4,5]. The left atrium (LA) and left ventricle (LV) interact throughout the cardiac cycle. Knowing this close physiological relationship between the LA and LV [6,7], our working group has recently developed, from the Multi-Ethnic Atherosclerosis Study (MESA) cohort, a novel left atrioventricular coupling index (LACI), defined as the ratio between the LA end-diastolic volume and the LV end-diastolic volume using cardiac magnetic resonance (CMR) [8]. We demonstrated the incremental prognostic value of LACI for predicting incident heart failure, incident atrial fibrillation, hard CVD and cardiovascular death, along with traditional risk factors. More recently, using a longitudinal analysis, our team has shown the incremental prognostic value of annualized change in LACI over 10 years (ΔLACI), along with traditional risk factors, which had a better prognostic value than individual changes in LA or LV variables measured separately to predict incident heart failure [9] and incident atrial fibrillation [10]. All of these findings support the physiological concept of left atrioventricular coupling by this LA/LV coupling index, which has a better prognostic value than individual LA or LV variables measured separately.

Beyond the prognostic value of this index, it is important to identify the determinants of LACI, to better understand the factors involved in the physiology of this LA/LV coupling. However, to our knowledge, because of a lack of tools to measure LA/LV coupling, no research has explored the potential determinants of this coupling. Therefore, the aim of this study was to identify the determinants of LACI as a left atrioventricular coupling marker, and its 10-year annual change (ΔLACI), using the MESA, to better understand the variables governing this left atrioventricular coupling.

Methods

Study population

The MESA is a prospective population-based multi-ethnic (African American, White, Chinese and Hispanic) cohort study of subclinical CVD. The details of the study design have been described previously [11]. In summary, between 2000 and 2002 (Exam 1), 6814 men and women aged 45—84 years who were free of clinical CVD at enrolment were recruited from six field centres in the USA (Baltimore, MD; Chicago, IL; Forsyth County, NC; Los Angeles County, CA; Northern Manhattan, NY; and St. Paul, MN). Exam 1 was followed by Exam 2 (2002—2004), Exam 3 (2004—2005), Exam 4 (2005—2007) and Exam 5 (2010—2012). Participants with significant valvular disease at baseline or between the two CMR examinations were excluded. The methodology for collection of baseline characteristics is detailed in Appendix A. All participants provided written informed consent. All study protocols were approved by the institutional review boards of each participating field centre.

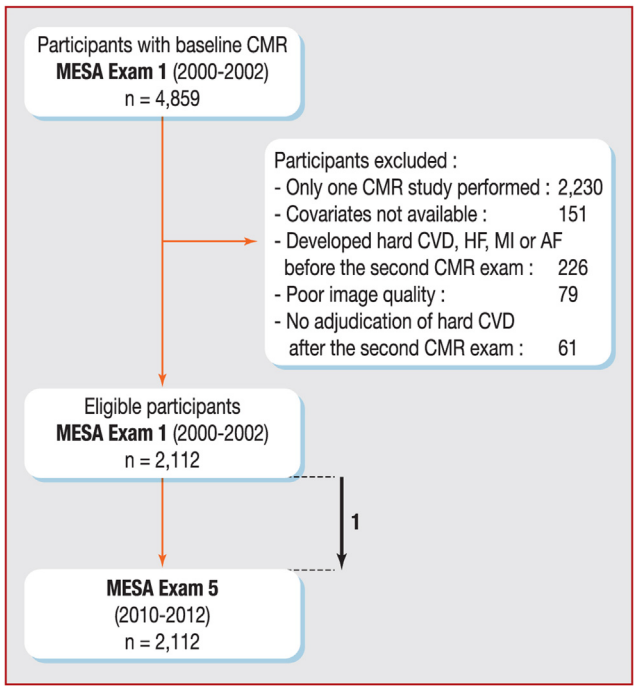

Figure 1. Flowchart of the study. 1 = mean time between the baseline and second cardiac magnetic resonance (CMR) examinations: 9.5 ± 0.6 years. AF: atrial fibrillation; CVD: cardiovascular disease; HF: heart failure; MESA: Multi-Ethnic Study of Atherosclerosis; MI: myocardial infarction.

A flowchart of the MESA population investigated in the current study is shown in Fig. 1. Participants were excluded: (1) if they did not have the second CMR examination; (2) if their images were of insufficient quality to allow the measurement of volumes; or (3) if they developed any cardiovascular events between Exams 1 and 5. The collection of outcomes is described in Appendix B. Of the 4859 participants with baseline CMR that included LA volume assessment (Exam 1), 2112 participants underwent a second CMR examination at Exam 5 after a mean time of 9.5 ± 0.6 years, and were included in the study.

CMR protocol and image analysis

The CMR protocol has been described previously [12]. Briefly, CMR was performed using 1.5-Tesla scanners (Appendix C). Long-axis cine images were obtained from two-chamber and four-chamber views using fast gradient-echo pulse sequences. A stack of short-axis cine images was acquired, and LV end-diastolic volume was measured using cardiac image modelling software (CIM version 6.0, University of Auckland, New Zealand). The complete CMR protocol, as well as details of the image analysis and data quality control have been published previously [12]. Multimodality tissue tracking (MTT) software, version 6.0 (Toshiba Medical Systems, Tokyo, Japan) was used to quantify LA volume and strain from two- and four-chamber cine CMR images (Appendix D). This method has been validated previously, with good-to-excellent intra- and inter-reader

reproducibility [13—15]. Using the marked points, the software creates endocardial borders, and then tracks LA tissue in subsequent frames. The endocardial and epicardial contours generated by the software are then followed by the operator during the cardiac cycle.

LACI

As recently described by our working group [8], LACI was calculated using the following formula: ''LA end-diastolic volume/LV end-diastolic volume'', assessed by CMR. The LA and LV volumes were measured with a match in the same end-diastolic phase, defined by mitral valve closure. Of note, LA end-diastolic and end-systolic volumes correspond respectively to the minimum left atrial volume index ($LAVI_{min}$) and the maximum left atrial volume index ($LAVI_{max}$) (Central Illustration). The intra- and inter-reader reproducibility of the LACI were assessed using a random sample size of 100 participants following a method published previously [8]. The LACI value is expressed as a percentage, and a higher LACI value indicates greater disproportionality between the LA and LV volumes at ventricular end-diastole, reflecting greater impairment of left atrioventricular coupling. Moreover, the ΔLACI is defined by the annual difference in the LACI value measured at baseline at Exam 1 ($LACI_{Baseline}$) and the LACI value measured after 10 years at Exam 5, and the ΔLACI value is expressed as a percentage per year.

Statistical analyses

The participants' characteristics at baseline and after 10 years are presented as means ± standard deviations for continuous variables, and as counts and percentages for categorical variables (Table 1). Using boxplots to assess the relationship between the categorical variables LACI and ΔLACI, comparison tests were based on the Cochran-Armitage test for trends. We used multivariable linear regression to identify demographic data, traditional cardiovascular risk factors, inflammation biomarkers (interleukin 6, high sensitivity C-reactive protein), myocardial fibrosis variables (native T1 mapping, extracellular volume [ECV]) and cardiovascular biomarkers (high-sensitivity cardiac troponin T, N-terminal prohormone of B-type natriuretic peptide [NT-proBNP]) at baseline that were independently associated with $LACI_{Baseline}$ and ΔLACI. In a series of three models, we introduced interaction terms between sociodemographic variables, significant cardiovascular risk factors and the LV mass-to-volume ratio (MVR) as a measure of LV remodelling and diastolic dysfunction, as follows: Model 1 (demographic): adjusted for age, sex, ethnicity, level of education and body mass index (BMI); Model 2 (demographic + cardiovascular risk factors): adjusted for the variables in Model 1 in addition to systolic blood pressure, diabetes mellitus, smoking status, low-density lipoprotein and high-density lipoprotein; Model 3 (demographic + cardiovascular risk factors + LV structure): adjusted for the variables in Model 2 in addition to the LV MVR assessed by CMR.

Multivariable regression coefficients (B) were reported for each analysis and R^2 coefficients for each variable. The correlation between $LACI_{Baseline}$ or ΔLACI and the other variables was assessed using Pearson's correlation test for variables with a normal distribution, or Spearman's correlation test for variables with a non-normal distribution. For the linear regression, the variables with a non-normal distribution underwent a logarithmic transformation. A two-tailed P-value < 0.05 was considered statistically significant. All data were analysed using R software, version 3.6.1 (R Project for Statistical Computing, Vienna, Austria).

Results

Study population

Among the 4859 MESA participants with baseline CMR studies including LA volume assessment, 2112 (43.5%) had at least two CMR examinations (baseline and after 10-year follow-up) with LA and LV data available (mean age 58.8 ± 9.1 years; 46.6% men). Among these, 42.8% were White, 24.6% were African American, 20.6% were Hispanic and 12.0% were Chinese. Among the 2112 participants, 36.0% had hypertension, with 29.5% on antihypertensive therapy, 11.4% were current smokers, 9.4% had diabetes mellitus and the mean BMI was 27.8 ± 5.0 kg/m^2. The characteristics of the study population at Exam 1 and Exam 5 (after a mean time of 9.5 ± 0.6 years) are presented in Table 1. The population characteristics of all eligible MESA participants at baseline are described in Table A.1. Of note, the eligible participants at baseline (n = 6814) were older and had a higher rate of hypertension, diabetes mellitus and current smoking than the participants in this current analysis (n = 2112).

LACI and annualized change in LACI

For the entire study population, the mean $LACI_{Baseline}$ value was 16.4 ± 7.5%, and at follow-up the mean LACI value measured after 10 years at Exam 5 was 25.9 ± 11.0%, with a mean ΔLACI of 1.1 ± 1.0%/year (Fig. A.1). Changes in LACI (ΔLACI) and individual LA and LV variables over 9.5 ± 0.6 years are shown in Table A.2. Regarding the evolution of LACI over 10 years, as stratified by the $LACI_{Baseline}$ value, a lower value of $LACI_{Baseline}$ was associated with a higher ΔLACI over 10 years (Fig. A.2). The intra- and inter-reader reproducibilities of the LACI were good, with intraclass correlation coefficients of 0.93 (95% confidence interval 0.90 to 0.96) and 0.81 (95% confidence interval 0.71 to 0.88), respectively [8].

Determinants of LACI and ΔLACI

Using multivariable linear regression analysis, the variables independently associated with LACI were age, African American ethnicity, BMI, diabetes mellitus and LV MVR. Similarly, the independent determinants of ΔLACI were age, male sex, high level of education versus other and LV MVR (Table 2).

Age in relation to LACI and ΔLACI

Association between age and LACI or ΔLACI is depicted in Fig. 2. Using four age categories, there was a positive association between age at baseline and the $LACI_{Baseline}$ value, with 14.9%, 16.3%, 18.0% and 19.8% for participants aged 45—54 years, 55—64 years, 65—74 years and 75—84

Table 1 Characteristics of participants at Exam 1 and Exam 5.

Variables	Exam 1 (baseline)	Exam 5, 9.5 ± 0.6 years after baseline
	(*n* = 2112)	(*n* = 2112)
Age (years)	58.8 ± 9.1	68.3 ± 9.0
Male sex	985 (46.6)	985 (46.6)
Ethnicity		
White	43	43
Chinese American	12	12
African American	25	25
Hispanic	21	21
Education		
< High school	443 (21.0)	443 (21.0)
High school, technical school or associate degree	1062 (50.3)	1062 (50.3)
College, graduate or professional school	607 (28.7)	607 (28.7)
Hypertension	761 (36.0)	1166 (55.2)
Systolic blood pressure (mmHg)	123 ± 20	122 ± 20
Diastolic blood pressure (mmHg)	72 ± 10	69 ± 10
Hypertension medication	624 (29.5)	1064 (50.4)
BMI (kg/m^2)	27.8 ± 5.0	28.1 ± 5.1
Glycaemic status		
Normal	1684 (79.7)	1325 (62.7)
Impaired fasting glucose	229 (10.8)	433 (20.5)
Diabetes mellitus	199 (9.4)	354 (16.8)
Smoking status		
Never	1108 (52.5)	980 (46.4)
Former	764 (36.2)	972 (46.0)
Current	240 (11.4)	160 (7.6)
Total cholesterol (mg/dL)	195 ± 34	185 ± 36.2
HDL cholesterol (mg/dL)	52 ± 15	56 ± 16
Lipid-lowering medication	296 (14.0)	756 (35.8)
Glomerular filtration rate[a] (mL/min)	80 ± 15	81 ± 17
NT-proBNP (pg/mL)	69 ± 101	–
hs-cTnT (pg/mL)	6.8 ± 8.3	–
IL-6 (pg/mL)	1.7 ± 1.4	–
hsCRP (mg/L)	4.3 ± 6.2	–
Heart rate (beats/min)	62 ± 9	64 ± 10
LA variables		
$LAVI_{min}$ (mL/m^2)	11.6 ± 5.7	15.9 ± 7.2
$LAVI_{max}$ (mL/m^2)	29.5 ± 9.0	34.9 ± 10.7
$LAVI_{preA}$ (mL/m^2)	21.8 ± 7.3	26.7 ± 9.0
Peak LA strain (%)	37.3 ± 11.0	32.0 ± 13.5
LV variables		
LV EDVi (mL/m^2)	70.1 ± 11.8	64.2 ± 13.3
LVEF (%)	62.6 ± 5.6	62.1 ± 7.0
LV mass index (g/m^2)	64.9 ± 11.6	65.9 ± 13.7
LV MVR (g/mL)	0.93 ± 0.17	1.04 ± 0.22
Native T1 mapping (ms)	978 ± 43	–
ECV (%)	27.0 ± 3.0	–
LACI (%)	16.4 ± 7.5	25.9 ± 11.0

Data are expressed as mean ± standard deviation, number (%) or %. BMI: body mass index; ECV: extracellular volume; EDVi: end-diastolic volume index; HDL: high-density lipoprotein; hsCRP: high-sensitivity C-reactive protein; hs-cTnT: high-sensitivity cardiac troponin T; IL-6: interleukin-6; LA: left atrial; LACI: left atrioventricular coupling index; $LAVI_{max}$: maximum left atrial volume index; $LAVI_{min}$: minimum left atrial volume index; $LAVI_{preA}$: left atrial volume index before atrial contraction; LV: left ventricular; LVEF: left ventricular ejection fraction; MVR: mass-to-volume ratio; NT-proBNP: N-terminal prohormone of B-type natriuretic peptide.

[a] Calculated by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) method.

Table 2 Multivariable regression models for association of clinical, biological and cardiac magnetic resonance variables with left atrioventricular coupling index or annualized change in left atrioventricular coupling index over 10 years (regression coefficients B and *P* value).

Variables measured at baseline	$LACI_{Baseline}$[a]		ΔLACI[b]	
	Coefficient B (95% CI)	*P*	Coefficient B (95% CI)	*P*
Age, per 5 years	1.47 (1.09 to 1.85)	<0.001	0.3 (0.2 to 0.4)	<0.001
Male sex	0.50 (—0.22 to 1.22)	0.17	—0.1 (—0.3 to—0.2)	0.015
Ethnicity (African American versus other)	1.48 (0.72 to 2.24)	<0.001	0.0 (—0.1 to 0.1)	0.94
BMI, per kg/m^2	0.24 (0.17 to 0.31)	<0.001	0.2 (—0.1 to 0.4)	0.09
High level of education versus other	0.22 (—0.79 to 1.23)	0.67	—0.2 (—0.3 to—0.1)	0.013
Systolic blood pressure, per mmHg	—0.10 (—0.21 to 0.10)	0.60	0.0 (—0.1 to 0.1)	0.56
Diabetes mellitus	1.75 (0.65 to 2.86)	<0.001	0.1 (—0.1 to 0.3)	0.11
Current smoker versus non-smoker	—0.82 (—1.81 to 0.18)	0.11	0.1 (—0.1 to 0.4)	0.06
LDL cholesterol, per mg/dL	—0.10 (—0.12 to 0.10)	0.77	—0.0 (—0.1 to 0.1)	0.60
HDL cholesterol, per mg/dL	—0.22 (—0.10 to 0.40)	0.17	0.0 (—0.1 to 0.1)	0.08
LV MVR, per unit	4.15 (2.05 to 6.26)	<0.001	0.4 (0.1 to 0.7)	0.005

BMI: body mass index; CI: confidence interval; HDL: high-density lipoprotein; LACI: left atrioventricular coupling index; ΔLACI: annualized change in left atrioventricular coupling index over 10 years; LDL, low-density lipoprotein; LV: left ventricular; MVR: mass-to-volume ratio.

[a] Model 3 (demographic + cardiovascular risk factors + LV remodelling) adjusted for: age, sex, ethnicity, high level of education (≥ college, graduate or professional school), BMI, systolic blood pressure, diabetes mellitus, smoking status, LDL, HDL and LV MVR assessed by cardiac magnetic resonance.

[b] Model adjusted for: the variables in Model 3 in addition to $LACI_{Baseline}$.

Table 3 Regression models for association of left atrioventricular coupling index or annualized change in left atrioventricular coupling index over 10 years with age, according to sex (regression coefficients B and *P* value).

		Model 1[a]		Model 2[b]		Model 3[c]	
		Coefficient B (95% CI)	*P*	Coefficient B (95% CI)	*P*	Coefficient B (95% CI)	*P*
Association of $LACI_{Baseline}$ with age (% per 5 years of age)	Women	1.65 (1.20 to 2.25)	< 0.001	1.43 (1.12 to 1.89)	<0.001	1.22 (1.08 to 1.77)	0.001
	Men	1.60 (1.11 to 2.23)	<0.001	1.37 (1.07 to 1.67)	0.002	1.18 (1.04 to 1.60)	0.008
Association of ΔLACI with age (%/year per 5 years of age)	Women	0.25 (0.19 to 0.42)	<0.001	0.23 (0.16 to 0.39)	<0.001	0.17 (0.11 to 0.25)	0.001
	Men	0.22 (0.16 to 0.41)	<0.001	0.21 (0.14 to 0.38)	<0.001	0.14 (0.08 to 0.23)	0.001

CI: confidence interval; $LACI_{Baseline}$: left atrioventricular coupling index at baseline; ΔLACI: annualized change in left atrioventricular coupling index over 10 years.

[a] Model 1 (demographic) adjusted for: age, sex, ethnicity, level of education and body mass index.

[b] Model 2 (demographic + cardiovascular risk factors) adjusted for: the variables in Model 1 in addition to systolic blood pressure, diabetes mellitus, smoking status, low-density lipoprotein and high-density lipoprotein.

[c] Model 3 (demographic + cardiovascular risk factors + left ventricular remodelling) adjusted for: the variables in Model 2 in addition to left ventricular mass-to-volume ratio assessed by cardiac magnetic resonance.

years, respectively (*P* trend < 0.001; Table A.3). Consistent with this, the ΔLACI over 10 years increased significantly with the age categories at baseline (*P* trend < 0.001, Table A.3). In the multivariable analysis, after adjustments for all covariates in Model 3, there was a linear relationship between age at baseline and the $LACI_{Baseline}$ value (adjusted R^2 = 0.10, slope = 0.16; *P* < 0.001) and ΔLACI (adjusted R^2 = 0.15, slope = 0.008; *P* < 0.001). Both associations were constant, regardless of the sex of participants (Fig. A.3). For the relationship of age with $LACI_{Baseline}$ and ΔLACI, Table 3 shows the regression coefficients (B) derived from the multivariable linear regression analyses.

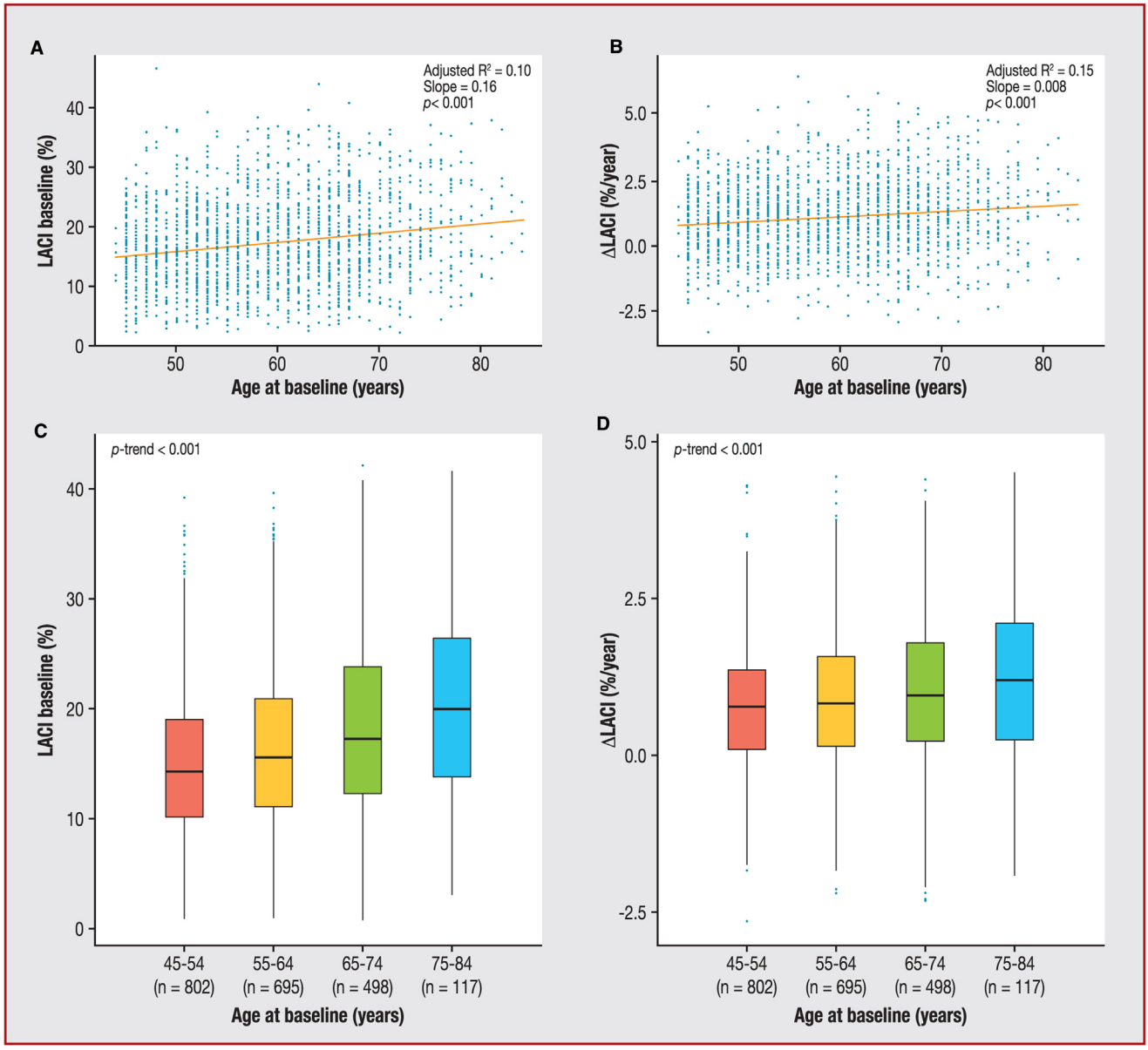

Figure 2. Association between age and left atrioventricular coupling index (LACI) or annualized change in LACI over 10 years (ΔLACI). A—B. Regression plot between age and the baseline LACI value ($LACI_{Baseline}$) (A) and ΔLACI (B) in all cohorts after adjustments for all covariates in Model 3. C—D. Mean $LACI_{Baseline}$ value (C) and ΔLACI (D) in each age category; the bottom and top of each box are the first and third quartiles, and the band inside each box is the median.

$LACI_{Baseline}$ and ΔLACI were positively associated with age in all adjusted models, regardless of sex.

Sex in relation to LACI and ΔLACI

Although there was no significant difference in the $LACI_{Baseline}$ value between women and men (16.2 ± 7.6 vs 16.6 ± 7.4%, respectively; $P = 0.19$), ΔLACI was higher in women than in men (1.0 ± 1.1 vs 0.8 ± 1.1%/year; $P < 0.001$) (Table A.3). In addition, women had a higher ΔLACI than men in all age categories (Fig. 3). In the multivariable linear regression analysis, there was no relationship between sex and the $LACI_{Baseline}$ value ($P = 0.17$), but male sex was inversely related to ΔLACI (multivariable regression coefficient B: −0.10 per year; $P = 0.015$) (Table 2).

Ethnicity in relation to LACI and ΔLACI

$LACI_{Baseline}$ and ΔLACI values differed by race/ethnicity ($P < 0.001$) (Table A.3). African Americans had the highest $LACI_{Baseline}$ value (18.0 ± 7.7%), whereas Chinese participants had the lowest $LACI_{Baseline}$ (13.8 ± 6.4%; $P < 0.001$) (Fig. A.4).

Although there was no significant difference in the ΔLACI value between African Americans and non-African Americans (0.9 ± 1.1 vs. 0.9 ± 1.1%/year; $P = 0.95$), the $LACI_{Baseline}$ was higher in African Americans than in non-African Americans (18.0 ± 7.7 vs. 15.8 ± 7.4%; $P < 0.001$) (Table A.3). Assessing the age interaction, African Americans aged

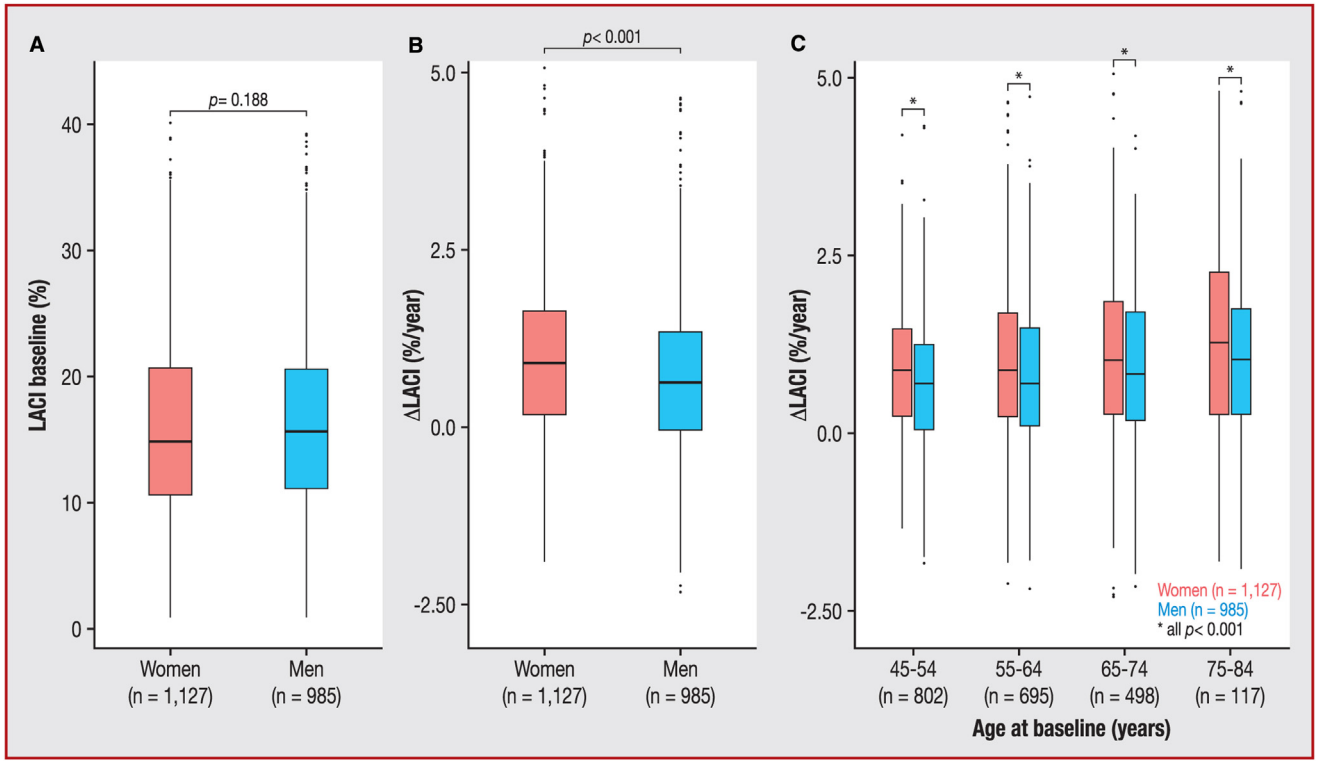

Figure 3. Association between sex and left atrioventricular coupling index (LACI) or annualized change in LACI over 10 years (ΔLACI). A—B. Boxplot distribution of the baseline LACI value ($LACI_{Baseline}$) (A) and ΔLACI (B) stratified by sex. C. The mean ΔLACI value in each age category at baseline is stratified according to sex. The bottom and top of each box are the first and third quartiles, and the band inside each box is the median.

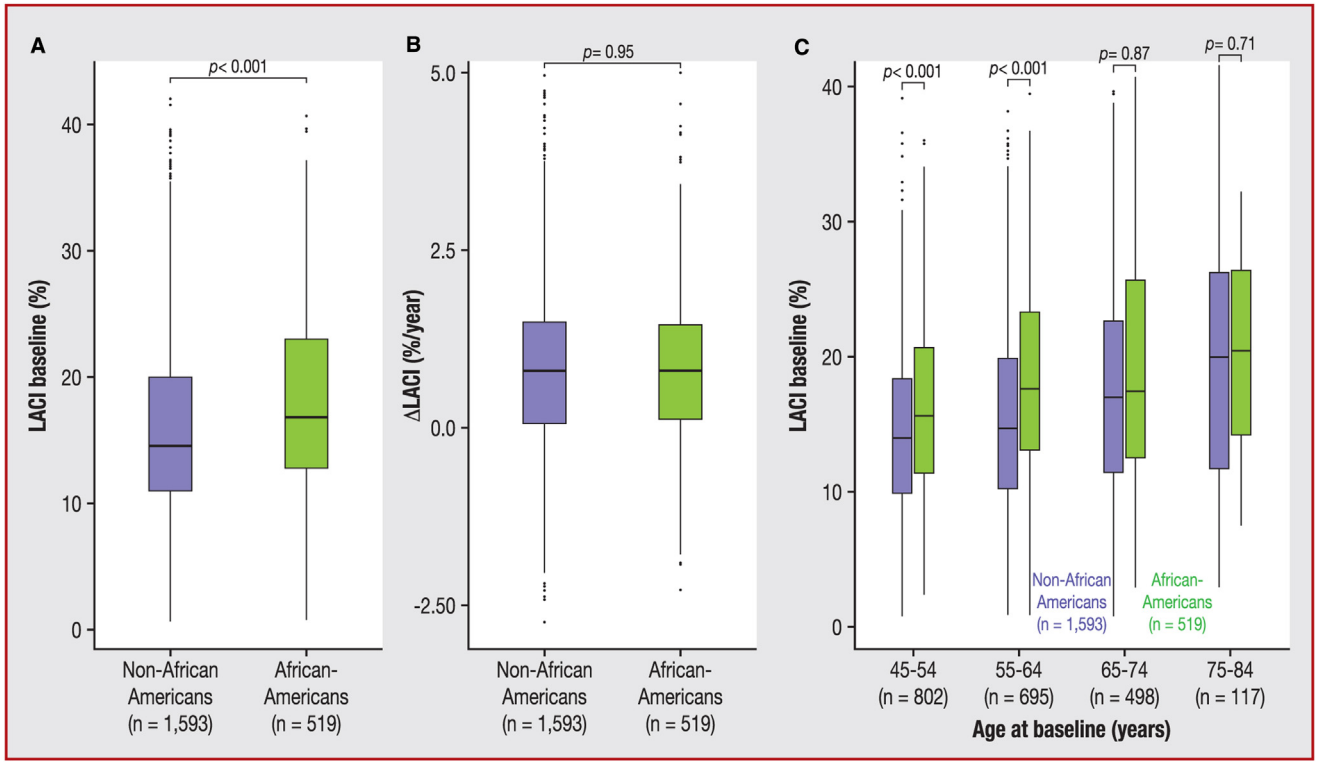

Figure 4. Association between ethnicity and left atrioventricular coupling index (LACI) or annualized change in LACI over 10 years (ΔLACI) A—B. Boxplot distribution of the baseline LACI value ($LACI_{Baseline}$) (A) and ΔLACI (B) stratified by ethnicity (African American versus non-African American). C. The mean $LACI_{Baseline}$ value in each age category at baseline is stratified according to ethnicity. The bottom and top of each box are the first and third quartiles, and the band inside each box is the second quartile (the median).

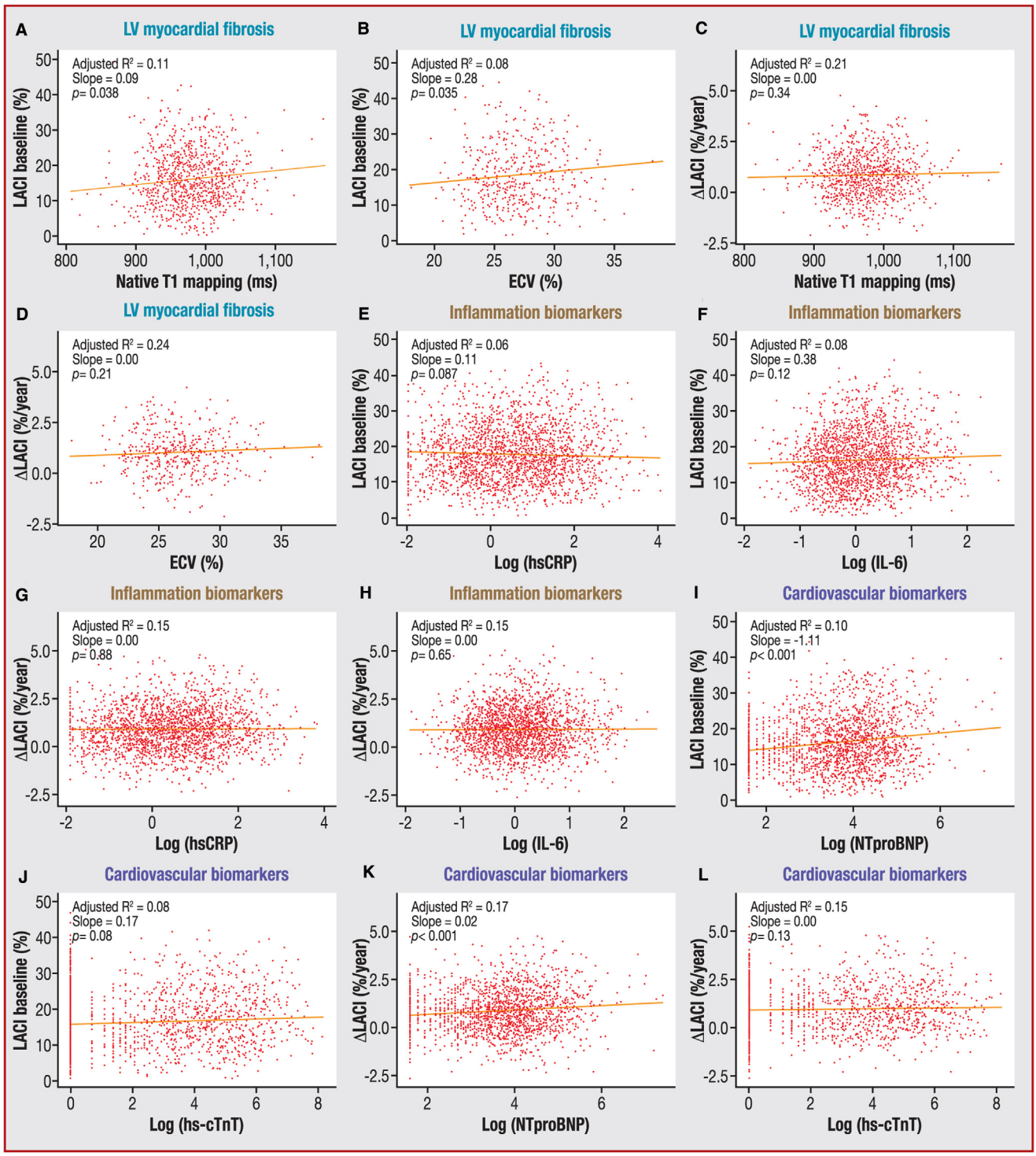

Figure 5. Association between left atrioventricular coupling index (LACI) or annualized change in LACI over 10 years (ΔLACI) and left ventricular (LV) myocardial fibrosis, inflammation and cardiovascular biomarkers at baseline. A–L. After adjustments for all covariates in Model 3, a regression plot between LACI at baseline ($LACI_{Baseline}$) and LV myocardial fibrosis markers (native T1 mapping, A; extracellular volume [ECV], B), inflammation biomarkers (high-sensitivity C-reactive protein [hsCRP], E; interleukin-6 [IL-6], F) and cardiovascular biomarkers (N-terminal prohormone of B-type natriuretic peptide [NT-proBNP], I; high-sensitivity cardiac troponin T [hs-cTnT], J); after adjustments for all covariates in Model 3, a regression plot between ΔLACI and LV myocardial fibrosis markers (native T1 mapping, C; ECV, D), inflammation biomarkers (hsCRP, 6; IL-6, H) and cardiovascular biomarkers (NT-proBNP, K; hs-cTnT, L).

45–64 years had a higher $LACI_{Baseline}$ value than non-African Americans (17.8 ± 7.8% vs. 15.2 ± 7.9%; $P < 0.001$), whereas after age ≥ 65 years, there was no difference between African Americans and non-African Americans (18.6 ± 8.2% vs. 18.4 ± 8.1%; $P = 0.72$) (Fig. 4). In the multivariable linear regression analysis, there was an independent relationship

between African American ethnicity and the $LACI_{Baseline}$ value (multivariable regression coefficient B: 1.48; $P < 0.001$), but there was no relationship between ethnicity and ΔLACI ($P = 0.94$) (Table 2).

Cardiovascular risk factors at baseline in relation to LACI and ΔLACI

In the multivariable linear regression analysis, there was a relationship between diabetes mellitus and $LACI_{Baseline}$ (coefficient B: 1.75%; $P < 0.001$) and BMI and $LACI_{Baseline}$ (coefficient B: 0.24% per increment of BMI; $P < 0.001$), which was not the case for ΔLACI ($P = 0.09$) (Table 2). In addition, there was no relationship between hypertension, smoking status, low-density lipoprotein cholesterol or high-density lipoprotein cholesterol and $LACI_{Baseline}$ or ΔLACI.

Myocardial fibrosis, inflammation and cardiovascular biomarkers at baseline in relation to LACI and ΔLACI

In the multivariable analysis, after adjustments for all covariates in Model 3, both native T1 value and ECV as LV myocardial fibrosis markers at baseline were independently associated with the $LACI_{Baseline}$ value [adjusted $R^2 = 0.11$, slope = 0.09 ($P = 0.038$) and adjusted $R^2 = 0.08$, slope = 0.28 ($P = 0.035$), respectively], but not with ΔLACI. In addition, NT-proBNP concentrations were also independently associated with both $LACI_{Baseline}$ and ΔLACI [adjusted $R^2 = 0.10$, slope = −1.11 ($P < 0.001$) and adjusted $R^2 = 0.17$, slope = 0.02 ($P < 0.001$), respectively]. There was no association between baseline high-sensitivity C-reactive protein or interleukin 6 (as inflammation biomarkers) or baseline high-sensitivity cardiac troponin T and $LACI_{Baseline}$ or ΔLACI (Fig. 5).

Relationship of baseline LA or LV variables with LACI and ΔLACI

In the multivariable analysis, after adjustments for all covariates in Model 3, $LAVI_{min}$, $LAVI_{max}$, LV mass and LV MVR were positively associated with the $LACI_{Baseline}$ value, but peak LA strain was inversely related to the $LACI_{Baseline}$ value (all $P < 0.001$) (Fig. A.5).

Discussion

In a population of participants free of clinical CVD, this study has emphasized important findings regarding the determinants of the LACI at baseline and its 10-year annual change (ΔLACI) as markers of LA/LV coupling: (1) an increase in age was independently associated with an increase in both $LACI_{Baseline}$ and ΔLACI after adjustment for all covariates; (2) although there was no difference in $LACI_{Baseline}$ between women and men, ΔLACI was higher in women than in men; (3) regarding the ethnicity of participants, African Americans had the highest $LACI_{Baseline}$ value, whereas Chinese participants had the lowest; (4) diabetes mellitus and higher BMI were independently associated with $LACI_{Baseline}$; (5) $LACI_{Baseline}$ was independently associated with LV myocardial fibrosis markers and NT-proBNP concentration, but there was no association between $LACI_{Baseline}$ and inflammation biomarkers or high-sensitivity cardiac troponin T.

The LACI identifies an earlier stage of LA remodelling associated with impaired LV compliance when compared with individual LA variables, and has a higher prognostic value for predicting cardiovascular events after adjustment for traditional risk factors [8—10]. With increased age, there are changes in LA volume or function and LV filling [16]. However, the data are insufficient for us to understand whether these age-dependent changes in LA volume and function result from isolated LA physiological alterations or from impaired LA/LV coupling. In the current study, aging was one of the most important determinants of LACI and its evolution. Indeed, age was strongly associated with both $LACI_{Baseline}$ and ΔLACI, regardless of the sex of participants. Moreover, this age-related degradation of LA/LV coupling over 10 years (ΔLACI) was more accelerated for older participants. The hypothesis of the impact of aging on LA/LV coupling has already been raised by a CMR study performed in 40 healthy individuals to investigate the effects of aging on LA/LV coupling and LV filling [17]. The oldest individuals had larger LA and smaller LV volumes, with larger LA/LV end-diastolic volume ratios.

Although there was no difference between women and men for the LACI value at baseline, the degradation of the LA/LV coupling over 10 years, assessed by ΔLACI, was more accelerated for women than men, regardless of age. To explain these findings, we can hypothesize that menopausal status and sex hormone concentrations could play a role in LA/LV coupling and modulation of the LACI value in women [18]. A recent study assessing 14,550 postmenopausal women from the UK Biobank indicated that menopause was independently associated with a lower LV end-diastolic volume [19]. Another recent study emphasized the significant relationship between sex hormone concentrations and changes in LV structure [20]. Beyond these consequences for LV remodelling, some studies have also suggested an effect of menopause on LA remodelling [21].

This study suggests that the LACI value was different depending on the ethnicity of the participants. By stratifying the population as White, African American, Hispanic and Chinese, African Americans had the highest $LACI_{Baseline}$ values. This higher LACI value among African Americans led us to conduct a second analysis comparing African Americans and non-African Americans. Although there was no significant difference in ΔLACI between African Americans and non-African Americans, $LACI_{Baseline}$ was higher in African Americans than in non-African Americans. In the subgroup analysis investigating the age interaction, African Americans aged 45—64 years had a higher $LACI_{Baseline}$ value than non-African Americans, whereas in participants aged ≥ 65 years, there was no difference between African Americans and non-Africans. All these results suggest that there was worse LA/LV coupling (higher LACI value) in young African Americans than in non-African Americans, but after the age of 65 years, the age-related degradation of the LA/LV coupling was similar in both populations. These findings are in line with studies reporting that African American participants present a higher risk of CVD (hazard ratio of 3 for cardiovascular death).

Regarding cardiovascular risk factors, only diabetes and higher BMI were associated with the LACI value at baseline.

These findings are consistent with studies reporting that LV end-diastolic volume decreased and LA volumes increased in patients with diabetes [22]. Therefore, recent reports suggest that LA/LV coupling is an important predictor of CVD in patients with diabetes [23]. Consistent with this, a recent study has shown a mechanical impact of diabetes on this coupling through a decrease in global atrioventricular strain using echocardiography [24].

Our study also describes the independent association between native T1 and ECV values as markers of LV myocardial fibrosis and the LACI value at baseline. These findings reinforce the hypothesis of a mechanical phenomenon involving LA/LV coupling and myocardial fibrosis. In line with reports indicating that ECV and native T1 values are correlated with NT-proBNP concentrations [25], this study showed a significant correlation between LACI and NT-proBNP concentrations. Whereas chronic inflammation and its biomarkers (high-sensitivity C-reactive protein and interleukin 6) may have roles in the genesis and prediction of CVD [26], there was no association between inflammation biomarkers and LACI values in this study. Although this study provides several hypotheses about the determinants of LACI, its 10-year annual change and factors involved in LA/LV coupling, future studies should be conducted to confirm these results.

Beyond the determinants of LACI explored in this study, several studies performed by our working group have shown the incremental prognostic value of LACI beyond any separately assessed LA or LV variable in predicting the risk of incident heart failure or atrial fibrillation [8—10]. All these results suggest a potential role for LACI as a screening tool to improve our management of patients in primary prevention.

Study limitations

First, ΔLACI was averaged across 10 years, thus assuming linearity over time. This method may not have fully captured the variation in year-to-year measurements, which provides additional precedence for further investigation. Second, the exclusion of patients who presented a cardiovascular event between the two CMR examinations limits the assessment of the clinical value of LACI in daily practice. However, the exclusion of these patients avoided potential confounding factors in the mechanistic description of left atrioventricular coupling in patients without CVD. Therefore, the results of this study cannot be applied to patients with severe LA or LV enlargement. In addition, there was a significant selection bias related to the exclusion of a high proportion of patients with only one CMR examination. Third, the current study identified the determinants of reduced LACI rather than LACI itself. Thus, further physiology studies are needed to investigate the determinants of left atrioventricular coupling more thoroughly itself. Fourth, we used two-dimensional instead of three-dimensional methods to measure LA volumes, which may have underestimated the true volumes by 11.5—20% [27]. However, this method has been widely used and validated in clinical studies [13,16]. Fifth, one limitation of the native T1 and ECV CMR methods is that these indices may vary depending on the magnetic resonance imaging technique, field strength, gadolinium contrast agent and dosage used for the T1 measurement [2]. Sixth, the study population was at very low risk of cardiovascular events, with an event rate of only 4.6% after 10 years of follow-up. Finally, the effects of age on the cardiovascular system are probably inseparable from multifactorial events accumulated over a lifetime, including both known and unknown factors that affect the myocardium.

Conclusions

In a large multi-ethnic population free of clinical CVD, we identified some independent determinants of a LACI and its 10-year annual change (ΔLACI), namely age, sex, ethnicity, diabetes and a higher BMI. In addition, LACI was independently associated with LV myocardial fibrosis markers and NT-proBNP concentrations, but was not associated with inflammation biomarkers.

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Disclosure of interest

The authors declare that they have no competing interest.

Online Supplement. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.acvd.2022.04.011.

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