






# Age-related longitudinal change in cardiac structure and function in adults at increased cardiovascular risk

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## Abstract

**Aim** Heart failure (HF) incidence increases markedly with age. We examined age-associated longitudinal change in cardiac structure and function, and their prediction by age and cardiovascular disease (CVD) risk factors, in a community-based cohort aged  $\geq 60$  years at increased CVD risk but without HF.

**Methods and results** CVD risk factors were recorded in 3065 participants who underwent a baseline echocardiographic examination, of whom 2358 attended a follow-up examination 3.8 [median, inter-quartile range (IQR) 3.5, 4.2] years later. Median age was 71 (IQR 67, 76) years and 55% of participants were male. Age was associated with longitudinal increase in left ventricular (LV) mass index (LVMI); decrease in LV volumes; increase in LV ejection fraction; decrease in mitral annular systolic velocity; decrease in diastolic function (decreased mitral early diastolic annular velocity ( $e'$ ); and increase in left atrial volume index, mitral peak early diastolic flow velocity (E)/ $e'$  ratio, and tricuspid regurgitant velocity ( $TR_{Vmax}$ ) in men and women, except for  $TR_{Vmax}$  in men). In multivariable analysis, longitudinal increase in LVMI was explained by CVD risk factors alone, whereas age, together with CVD risk factors, independently predicted longitudinal change in all other echocardiographic parameters. CVD risk factors were differentially associated with longitudinal change in different echocardiographic parameters.

**Conclusions** Whereas the increase in LVMI with age was explained by CVD risk factors alone, age, together with risk factors, independently predicted longitudinal change in all other echocardiographic parameters, providing evidence for age-specific mechanisms of change in cardiac structure and function as people age. Age-associated change in LVMI, LV volumes, and diastolic function resembled what might be expected for the evolution of HF with preserved ejection fraction. Given the differential association of different CVD risk factors with longitudinal change in different echocardiographic parameters, therapies aimed at attenuation of age-associated change in cardiac structure and function, and HF evolution, will likely need to address multiple CVD risk factors.

**Keywords** Heart failure; Aging; Risk factors; Echocardiography

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## Introduction

Heart failure (HF) incidence and prevalence increase strikingly with age, with a lifetime risk of 20–46%,<sup>1</sup> making it the

quintessential cardiovascular syndrome of aging that results from age-associated changes in cardiovascular structure and function and cardiovascular disease (CVD) risk factors.<sup>2</sup> Key to the prevention of age-associated changes in cardiac

structure and function that lead to HF is an understanding of the relative contribution of age and CVD risk factors to these changes.

Most information about the association of age with cardiac structure and function comes from cross-sectional studies,<sup>3–15</sup> and fewer studies examined longitudinal change in cardiac structure and function.<sup>16–21</sup> Both cross-sectional and longitudinal studies report decrease in left ventricular (LV) end-diastolic volume index (LVEDVI), left ventricular end-systolic volume index (LVESVI), and left ventricular stroke volume index (LVSVI)<sup>5,6,9–11,20</sup> and increase in LV mass (LVM)/end-diastolic volume (EDV) ratio with age.<sup>6,15,20</sup> Additionally, cross-sectional studies report decrease in mitral annular systolic velocity (*S'*) and mitral early diastolic annular velocity (*e'*) and increase in mitral peak early diastolic flow velocity (*E*)/*e'* ratio and pulmonary artery systolic pressures [derived from tricuspid regurgitant velocity ( $TR_{Vmax}$ )] with age.<sup>5,7,12,14,15</sup> There are, however, discrepancies between reports of age-associated change in cardiac structure and function. LVM or LVM index (LVMI) is reported to increase with age in some studies,<sup>5,9,10,15,16,18</sup> but not in others,<sup>3,4,6</sup> or to increase in men and decrease in women.<sup>20</sup> LV ejection fraction (LVEF) is reported to increase,<sup>6,9,10,17</sup> to not change,<sup>15</sup> or to decrease with age.<sup>21</sup> Left atrial volume (LAV) and LAV index (LAVI) are reported either to not change<sup>5,10</sup> or to increase with age.<sup>8,13</sup>

In addition to uncertainty about age-associated change in cardiac structure and function, there is limited information about the contribution of age and CVD risk factors to these changes.<sup>15,16,18–20,22</sup> To define the effect of age on cardiac structure and function, and the relationship of CVD risk factors with age-associated change in cardiac structure and function, we performed serial echocardiographic examinations in the participants of the SCReening Evaluation of the Evolution of New HF (SCREEN-HF) study,<sup>23–26</sup> a prospective community-based cohort study of men and women  $\geq 60$  years of age without HF but with risk factors for HF.

## Methods

### Study population

The SCREEN-HF study is a community-based evaluation of the use of plasma amino-terminal-pro-B-type natriuretic peptide (NT-proBNP) to identify individuals with cardiac dysfunction (as assessed by echocardiography) and increased risk of HF and other cardiovascular events.<sup>23–26</sup> A flow chart for participant recruitment and follow-up is shown in *Figure S1*. In summary, 44 000 members of private health fund Bupa and residents of Melbourne or Shepparton, Victoria, Australia, were invited to participate. Inclusion criteria were age  $\geq 60$  years with one or more of self-reported treatment

for hypertension or diabetes for  $\geq 2$  years, myocardial infarction (MI), or other ischaemic heart disease (IHD) or valvular heart disease, irregular or rapid heart rhythm, cerebrovascular disease, or renal impairment. We excluded individuals with previously diagnosed HF and those with well-recognized HF risk such as previous valve surgery or documented valve abnormality graded  $>$  mild, LVEF  $<$  50%, or other known cardiac abnormality on previous echocardiography or other cardiac imaging. We did not exclude individuals with previously reported diastolic dysfunction because it was infrequently reported on, and because of the lack of consensus regarding classification of diastolic dysfunction in the years before recruitment, which commenced in May 2007 and was completed in January 2010. Documentation of previous cardiac imaging was requested from hospitals and from the participant's primary care provider, physician, and cardiologist. However, for this community-based cohort, most participants had not had cardiac imaging before enrolment.

Of the 4054 individuals enrolled at the baseline visit (Visit 1), 3847 met the inclusion and exclusion criteria and were invited to attend for echocardiographic examination (Visit 2). Excluding participants who developed HF before Visit 2, echocardiography was performed in 3190 participants at a median of 1.3 [inter-quartile range (IQR) 0.5, 1.9] years after enrolment. We previously reported comparison of participants who came for the baseline echocardiographic examination and those who did not.<sup>25</sup> Participants were invited to return for a second echocardiographic examination (Visit 3) at a median of 3.8 (IQR 3.5, 4.2) years after the baseline echocardiographic examination.<sup>25</sup> Participants who were diagnosed with HF and/or MI between Visit 2 and Visit 3 ( $n = 125$ ) were excluded, and the number of participants with baseline echocardiography for this study was 3065, of which 2358 returned for a second echocardiographic examination. The SCREEN-HF study was approved by the Alfred Human Research Ethics Committee and conformed to the ethical standards of the Declaration of Helsinki, and written informed consent was obtained from all participants. The study was registered at ClinicalTrials.gov NCT00400257, NCT00604006, and NCT01581827.

### Clinical assessment

The baseline visit was conducted by a study research nurse who consented, interviewed, and examined the participant. Height, weight, waist circumference, and blood pressure (BP) were measured at interview, and age, sex, and past medical history were recorded. Self-reported details of lifestyle factors included exercise, smoking history, and alcohol intake. Physical activity was assessed using the New York Heart Association questionnaire,<sup>27</sup> and physical inactivity refers to participants who did not walk for, on average,  $\geq 30$  min/day and/or participate in, on average,  $\geq 10$  min/day of more

vigorous exercise, including housework. Alcohol > 2 drinks/day refers to consumption of more than two standard drinks on any day.<sup>28</sup>

Participants brought details of their medications to the baseline study visit, which were recorded. A non-fasting blood sample was taken for measurement of electrolytes, creatinine, urea, glucose, and NT-proBNP and for full blood examination. Details of clinical history and medication were updated; measurement of height, weight, waist circumference, and BP was repeated at Visit 2; and a non-fasting blood sample was taken for measurement of HbA1c, serum lipids, and NT-proBNP.

BP was measured with an automatic BP monitor (A&D Medical, Kensington, Victoria), as previously described.<sup>23</sup> Body mass index (BMI) was calculated as the ratio of weight to height squared ( $\text{kg}/\text{m}^2$ ). Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.<sup>29</sup> Serum NT-proBNP was measured by electrochemiluminescence immunoassay using an Elecsys instrument (Roche Diagnostics, Basel, Switzerland) with a lower limit of detection of 0.6 pmol/L (to convert pmol/L to pg/mL, multiply by 8.457). HbA1c was measured by high-performance liquid chromatography using an Akray Adams HA-8160 HbA1c analyser. Whereas data for eGFR, haemoglobin, white cell and platelet count were from Visit 1, NT-proBNP, HbA1c, and lipid measurements were from Visit 2. The haemoglobin, white cell, and platelet count cut points were the lower (for haemoglobin and platelet count) and upper (for white cell count) limits of the normal range for the laboratory (Table 1).

## Echocardiography

Cardiac structure and function were assessed using transthoracic echocardiography with either a Vivid 7 ( $n = 2834$ ) or Vivid i ( $n = 231$ ) instrument (GE Healthcare, Chicago, Illinois, USA).<sup>25</sup> Echocardiography was performed according to American Society of Echocardiography and European Association of Cardiovascular Imaging guidelines.<sup>11,30–32</sup> Data were stored in raw data format and analysed offline by two experienced cardiologists. Inter-observer intraclass correlation coefficients (ICCs) for M-mode measurements were >0.78 for wall thickness, >0.88 for LA diameter and >0.9 for other M-mode measurements,  $\geq 0.87$  for two-dimensional (2D) measurements, >0.85 for standard Doppler measurements except pulmonary vein (PV) A wave velocity, and >0.92 for tissue Doppler measurements. Intra-observer ICCs were generally higher than for inter-observer ICCs.

LV dimensions were estimated using the 2D-guided M-mode approach.<sup>11</sup> LVM was calculated using the linear method<sup>11</sup> and indexed to body surface area. LVEF was calculated using the modified Simpson's biplane method. Where endocardial definition was poor in both four-chamber and

two-chamber views, the LVEF was visually estimated and LV volumes were not calculated.

LAV was calculated using the biplane method of disks from LA areas measured in the apical four-chamber and two-chamber views in the frame prior to mitral valve opening.<sup>11</sup> LV inflow was obtained using pulsed wave Doppler in the apical four-chamber view and E velocity measured; medial and lateral mitral S' and e' velocities were measured from pulsed tissue Doppler imaging, and the ratio of E velocity to the average of medial and lateral e' (E/e' ratio) was obtained. Peak  $\text{TR}_{\text{Vmax}}$  was measured by continuous-wave Doppler.<sup>32</sup>

## Statistical analysis

Data are reported as median (IQR) or numbers (percent) unless otherwise specified. Baseline values for each echocardiographic parameter were adjusted for regression to the mean, separately for men and women, as described by James.<sup>33</sup>

Data were analysed using linear regression when the baseline echocardiographic parameter was the outcome variable and using mixed-effects models when the outcome was the covariate effect on the longitudinal change (gradient) in the outcome variable. All linear regression models included age and gender as covariates. Mixed-effects model analysis of longitudinal change in echocardiographic parameters was performed as described by Eng *et al.*<sup>20</sup> The time covariate was equal to 0 for the baseline echocardiographic parameters; for the follow-up parameters, the time variable was equal to the elapsed time between baseline and follow-up examinations. Time was treated as a random effect, with uncorrelated random intercept and slope by subject in the mixed-effects model; risk factors were considered fixed effects that were constant between baseline and follow-up time points.<sup>34</sup> Data were analysed with two multivariable mixed-effects regression models. For Model 1, age at baseline, follow-up time, and gender were covariates, with interaction terms between gender and the other two covariates, and the interaction term between all three covariates represented how longitudinal change varied with age. For Model 2, multivariable models for longitudinal change included age at baseline, gender, and the respective baseline echocardiographic parameter value, with interaction terms between each covariate and follow-up time that represented the covariate effect on the longitudinal change of the outcome variable (gradient in echocardiographic parameter value).<sup>20</sup> Model fit to the data were assessed by inspecting plots of residuals against predicted values to look for non-random patterns that may indicate non-linearity or heteroscedasticity.

Multivariable models of CVD risk factors were constructed using stepwise forward selection. Excluded variables were reassessed for entry into the model when a new variable was retained by the model, and competing models were compared using Akaike's information criteria.

**Table 1** Characteristics of SCREEN-HF participants at baseline echocardiographic study

Characteristic	<i>n</i> = 3065
Age (years)	71 (67, 76)
Male (%)	1673 (55%)
Systolic blood pressure (mmHg)	139 (128, 150)
Diastolic blood pressure (mmHg)	76 (69, 83)
Pulse pressure (mmHg)	62 (54, 72)
Body mass index (kg/m <sup>2</sup> )	28 (26, 31)
Body surface area (m <sup>2</sup> )	1.9 (1.8, 2.1)
Waist circumference (cm)	98 (90, 106)
Cardiovascular disease risk factors	
Hypertension	2792 (91%)
Diabetes	529 (17%)
Obesity	1066 (35%)
Previous myocardial infarction	312 (10%)
Total ischaemic heart disease	694 (23%)
Previous stroke or transient ischaemic attack	347 (11%)
Peripheral vascular disease	110 (3.6%)
Cardiovascular disease	987 (32%)
Atrial fibrillation	359 (12%)
Pacemaker	69 (2.3%)
Obstructive sleep apnoea	217 (7.1%)
Current or former smoker	1487 (49%)
Current smoker	93 (3.0%)
Alcohol >2 drinks/day	614 (20%)
Physical inactivity	2011 (66%)
Medication use	
Beta-blocker	702 (23%)
ACE inhibitor	948 (31%)
ARB	1507 (49%)
ACE inhibitor and/or ARB	2359 (77%)
Calcium channel blocker	930 (30%)
Statin therapy	1687 (55%)
Thiazide diuretic	1003 (33%)
Loop diuretic	108 (3.5%)
Mineralocorticoid antagonist	23 (0.8%)
Digoxin therapy	84 (2.7%)
Aspirin therapy	1360 (44%)
Clopidogrel therapy	207 (6.8%)
Warfarin therapy	180 (5.9%)
NSAID therapy	318 (10.4%)
Insulin therapy	91 (3.0%)
Oral anti-diabetic medication	372 (12%)
Nitrate therapy	148 (4.8%)
Biochemistry and haematology	
NT-proBNP (pmol/L), <i>n</i> = 2941	12 (6, 25)
Total cholesterol (mmol/L), <i>n</i> = 2939	4.8 (4.1, 5.5)
Triglycerides (mmol/L), <i>n</i> = 2939	1.5 (1.1, 2.1)
High-density lipoprotein cholesterol, <i>n</i> = 2939	1.2 (1.0, 1.5)
eGFR (mL/min/1.73 m <sup>2</sup> ), <i>n</i> = 3065	76 (64, 86)
eGFR <60 mL/min/1.73 m <sup>2</sup>	613 (20%)
HbA1c (%), <i>n</i> = 2797	5.6 (5.4, 5.9)
Haemoglobin (g/dL), <i>n</i> = 3064	14.0 (13.2, 14.9)
Low haemoglobin (<13 g/L, male; <12 g/L, female)	291 (9.5%)
White cell count (×10 <sup>9</sup> /L), <i>n</i> = 3064	7.0 (6.0, 8.2)
High white cell count (>11 × 10 <sup>9</sup> /L)	70 (2.3%)
Platelets (×10 <sup>9</sup> /L), 3058	228 (194, 266)
Low platelet count (<150 × 10 <sup>9</sup> /L)	123 (4.0%)

Data shown as median (inter-quartile range) or *n* (%). Alcohol >2 drinks/day refers to consumption of more than two standard drinks on any day. Total ischaemic heart disease refers to myocardial infarction, coronary revascularization, coronary artery disease detected on coronary angiography, and angina. Cardiovascular disease refers to total ischaemic heart, cerebrovascular, and peripheral vascular disease. Data for cardiovascular disease, diabetes, obstructive sleep apnoea, smoking, alcohol intake, drug therapy, and physical activity were from self-report. Physical inactivity refers to failure to walk ≥ 30 min/day and/or participate in, on average, ≥10 min/day of more vigorous exercise, including housework.

ACE, angiotensin-converting enzyme; ARB, angiotensin II type 1 receptor blocker; eGFR, estimated glomerular filtration rate calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation<sup>29</sup>; NT-proBNP, amino-terminal pro-B-type natriuretic peptide; NSAID, non-steroidal anti-inflammatory drug.

The choice of risk factors, including haemoglobin level, white cell, and platelet count, was based in part on predictors of HF previously identified in the SCREEN-HF cohort.<sup>24</sup> Although frequently a statistically significant predictor of the outcome variable in univariate analysis, NT-proBNP was not included in multivariable models because it was considered to be primarily a response to change in cardiac structure and function, rather than a potential cause. Data were analysed using Statview version 5.0.1 (SAS Institute, Cary, NC, USA) and R version 3.6.0.

## Results

### Subject characteristics

Baseline characteristics (Table 1) corresponded to the inclusion and exclusion criteria. Median age of the 3065 participants was 71 (IQR 67, 76) years, 55% were male, and 91% were Bupa members.

### Age-associated change in cardiac structure and function

Because this was a community-based study, varying image quality did not allow measurement of all echocardiographic parameters in all participants, with TR<sub>Vmax</sub> measured in 45% of participants at the baseline examination and 61% of participants at the follow-up examination (Table 2).

Age was associated with longitudinal increase in LVMI, LVM/EDV ratio, and relative wall thickness (RWT), decrease in LV chamber volumes (LVEDVI, LVESVI, and LVSVI), increase in LVEF, decrease in mitral S', and decrease in diastolic function (decrease in mitral e' and increase in LAVI, mitral E/e' ratio, and TR<sub>Vmax</sub>) in men and women, except for TR<sub>Vmax</sub> in men (Table 3, Figures 1 and 2). Cross-sectional changes in LVMI, LVM/EDV ratio, RWT, LVEDVI, and LVSVI were in the same direction, but of lesser magnitude than longitudinal changes in these parameters (Table 3). There was no cross-sectional change in LVESVI and a cross-sectional decrease in LVEF, in contrast to longitudinal increase in LVEF. Cross-sectional changes in mitral S', LAVI, mitral e', and E/e' ratio were in the same direction, but of lesser magnitude than longitudinal change in these parameters, whereas a cross-sectional change in TR<sub>Vmax</sub> was in the same direction and of similar magnitude to its longitudinal change.

The interaction between longitudinal and cross-sectional changes allowed estimation of how longitudinal change varied with age (Table 3). Longitudinal increase in LVMI and RWT increased with age in women, and longitudinal increase in LVM/EDV ratio increased with age in both men and women. Longitudinal decreases in LVEDVI and LVSVI did not

change with age. However, longitudinal decrease in LVESVI and increase in LVEF were of greater magnitude in older women, whereas longitudinal decrease in S' was of greater magnitude in older men. The longitudinal decrease in e' and longitudinal increases in LAVI, E/e' ratio, and TR<sub>Vmax</sub> were all of greater magnitude as age increased in both men and women.

### Multivariable predictors of baseline echocardiographic parameters

Univariate predictors of baseline echocardiographic parameters are shown in Tables S1–S12; multivariable predictors are shown in Tables S13–S24 and summarized in Table S25. Abridged data are presented in Table 4 for multivariable predictors of baseline LVMI, LVEDVI, S', e', and E/e' ratio. Given that the predominant cross-sectional and longitudinal changes in these five parameters were increase in LVMI; decrease in LVEDVI, S', and e'; and increase in E/e' ratio, Figure 3 summarizes multivariable predictors of higher baseline LVMI; lower baseline LVEDVI, S', and e'; and higher baseline E/e' ratio.

Prediction of baseline echocardiographic parameters by age in multivariable analysis with CVD risk factors (Tables 4, S13–S24) was in agreement with the cross-sectional change per decade of baseline age for men and women, separately, without adjustment for CVD risk factors (Table 3). Age was a predictor of all baseline echocardiographic parameters except for LVESVI, predicting higher LVMI, LVM/EDV ratio, and RWT; lower LVEDVI, LVSVI, LVEF, and S'; and impaired diastolic function (lower e' and higher LAVI, E/e' ratio, and TR<sub>Vmax</sub>) in multivariable analysis (Tables 4, S13–S25). Similarly, prediction of baseline echocardiographic parameters by male gender in multivariable analysis with CVD risk factors (Tables 4, S13–S24) was in agreement with the effect of gender without adjustment for CVD risk factors (Table 3). Male gender predicted higher baseline LVMI and LAVI, whereas female gender predicted higher LVM/EDV ratio, LVEF, and E/e' ratio and lower LV volumes, S', and e' (Tables 4, S13–S25).

CVD risk factors were differentially associated with baseline echocardiographic parameters in multivariable analysis (Tables 4, S13–S25). A history of hypertension, but not systolic BP (SBP) measured at the baseline echocardiographic visit, predicted higher LVMI and LVM/EDV ratio and lower e', whereas SBP predicted higher LVEF, LAVI, and TR<sub>Vmax</sub> and lower S'. Diastolic BP (DBP) predicted higher RWT and E/e' ratio and lower LVSVI, LVEF, S', and e'. Pulse pressure (PP) predicted higher LVMI, LVEDVI, LVSVI, e', E/e' ratio, and TR<sub>Vmax</sub>. Antihypertensive therapies differed in their prediction of baseline echocardiographic parameters. Both calcium channel blocker (CCB) and angiotensin-converting enzyme inhibitor (ACEI) therapies predicted higher LAVI. CCB therapy, but not ACEI and/or ARB therapies, predicted higher LVMI,

**Table 2** Echocardiographic parameters at baseline and follow-up echocardiographic studies

Parameter	Baseline echocardiographic examination (n = 3065)		Follow-up echocardiographic examination (n = 2358)	
	n	Median (inter-quartile range)	n	Median (inter-quartile range)
LVMI (g/m <sup>2</sup> )	2553	90 (82, 99)	1852	94 (82, 110)
LVM/EDV ratio (g/mL)	1983	2.00 (1.85, 2.18)	1340	2.24 (1.93, 2.61)
RWT	2561	0.36 (0.34, 0.39)	1849	0.43 (0.39, 0.48)
LVEDVI (mL/m <sup>2</sup> )	2280	45 (41, 51)	1567	42 (37, 48)
LVESVI (mL/m <sup>2</sup> )	2280	18 (16, 21)	1567	16 (14, 19)
LVSVI (mL/m <sup>2</sup> )	2280	27 (25, 30)	1567	25 (22, 29)
LVEF (%)	3062	60 (58, 61)	2356	60 (58, 63)
S' (cm/s)	2801	7.50 (7.02, 8.03)	2286	7.18 (6.31, 8.18)
LAVI (mL/m <sup>2</sup> )	2925	33 (29, 38)	2349	37 (31, 43)
e' (cm/s)	2842	7.41 (6.77, 8.04)	2324	6.57 (5.53, 7.64)
E/e' ratio	2753	9.22 (8.20, 10.49)	2322	10.64 (8.67, 12.97)
TR <sub>Vmax</sub> (m/s)	1390	2.42 (2.34, 2.51)	1445	2.44 (2.27, 2.61)

Data shown as median (inter-quartile range).

BSA, body surface area; e', average early diastolic mitral annular tissue Doppler velocity; E/e' ratio, peak early diastolic mitral flow velocity/e' ratio; LAVI, left atrial volume indexed to BSA; LVEDVI, left ventricular end-diastolic volume indexed to BSA; LVEF, left ventricular ejection fraction; LVESVI, left ventricular end-systolic volume indexed to BSA; LVM/EDV ratio, left ventricular mass/end-diastolic volume ratio; LVMI, left ventricular mass (linear method) indexed to BSA; LVSVI, left ventricular stroke volume indexed to BSA; RWT, relative wall thickness; S', average systolic mitral annular tissue Doppler velocity; TR<sub>Vmax</sub>, peak tricuspid regurgitant flow velocity.

LVEDVI, LVSVI, E/e' ratio, and TR<sub>Vmax</sub>, whereas ACEI and/or ARB therapy predicted higher LVEF.

MI and/or IHD did not predict baseline LVM, although MI predicted lower RWT and LVEF and higher LVEDVI, LVESVI and LAVI, and IHD predicted lower S' in multivariable analysis. Atrial fibrillation (AF) (or warfarin or digoxin therapy) predicted higher LVMI, LVM/EDV ratio, RWT, LAVI, e', and TR<sub>Vmax</sub> and lower LVEF and S'.

Diabetes (or HbA1c) and/or anti-diabetic therapy did not predict baseline LVMI, LVEF, S', or TR<sub>Vmax</sub> but predicted higher LVM/EDV ratio, RWT, and E/e' ratio and lower LV volumes, LAVI, and e' in multivariable analysis. Neither BMI nor waist circumference predicted baseline LVMI, and they predicted opposite changes in LVM/EDV ratio; BMI predicted higher LVM/EDV ratio, consistent with its prediction of lower LVEDVI, whereas waist circumference predicted lower LVM/EDV ratio. BMI also predicted higher E/e' ratio, whereas waist circumference predicted higher RWT, S', and TR<sub>Vmax</sub> and lower LVEF. Consistent with the effects of diabetes (or HbA1c), serum triglyceride level predicted higher LVM/EDV ratio and lower LV volumes, LAVI, and e'. Triglyceride level also predicted higher S'.

Physical inactivity was associated with amplification of age-associated changes in baseline echocardiographic parameters, predicting higher LVM/EDV ratio and E/e' ratio and lower LVEDVI, LVSVI, LVEF, and S' in multivariable analysis.

### Multivariable predictors of longitudinal change (gradient) in echocardiographic parameters

Longitudinal change in echocardiographic parameters represented the rate of change over time (per decade). Thus, predictors of longitudinal change within a multivariable model

may predict a positive change in gradient (more rapid increase or less rapid decrease in longitudinal change) or negative change in gradient (more rapid decrease or less rapid increase). Univariate predictors of longitudinal change in echocardiographic parameters are shown in *Tables S1–S12*; multivariable predictors are shown in *Tables S13–S24* and summarized in *Table S26*. Abridged data for multivariable predictors of longitudinal change in LVMI, LVEDVI, S', e', and E/e' ratio are presented in *Table 5*. Multivariable predictors of the predominant longitudinal change in these five parameters—more rapid increase in LVMI; more rapid decrease in LVEDVI, S', and e'; and more rapid increase in E/e' ratio—are summarized in *Figure 4*.

The complexity of interaction of CVD risk factors with longitudinal change in echocardiographic parameters was illustrated by the variable effects of gender in multivariable analysis. LVMI, LVM/EDV ratio, LVEF, E/e' ratio, and TR<sub>Vmax</sub> gradients were positive for both men and women, and women had a more rapid increase than men (*Tables 5, S13–S24, S26, Figures 1, 2, and 4*). By contrast, S' gradient was negative for men and women, and men had a more rapid decrease than women (*Figures 2 and 4*). LVEDVI and e' gradients were also negative for men and women, and women had a more rapid decrease than men (*Figures 1, 2, and 4*).

In contrast to the varying interaction between longitudinal and cross-sectional changes per decade when analysed without CVD risk factors (*Table 3*), age was a predictor of longitudinal change in all echocardiographic parameters except for LVMI in multivariable analysis with CVD risk factors (*Tables S13–S24, S26, Figure 4*). Age predicted more rapid increase in LVM/EDV ratio, RWT, LVEF, LAVI, E/e' ratio, and TR<sub>Vmax</sub> and more rapid decrease in LVEDVI, LVESVI, LVSVI, S', and e'.

SBP, together with PP, at the time of the baseline echocardiographic examination predicted more rapid increase in

**Table 3** Sex-specific cross-sectional and longitudinal differences in echocardiographic parameters in participants who underwent both baseline and follow-up echocardiographic examinations

Parameter	Sex		Cross-sectional change per decade of baseline age		Longitudinal change per decade of follow-up		Interaction between longitudinal and cross-sectional changes, per decade squared	
	Male-female difference	Sex	Male	Female	Male	Female	Male	Female
LVMl (g/m <sup>2</sup> )	11 (10–12)*		2.7 (1.6, 3.7)*	2.7 (1.8, 3.7)*	16 (12, 19)*	17 (14, 20)*	3.8 (–2.0, 9.5)	5.5 (0.4, 10.7)§
LVM/EDV ratio (g/mL)	–0.09 (–0.07, –0.11)*		0.06 (0.04, 0.09)*	0.08 (0.06, 0.11)*	0.71 (0.62, 0.80)*	0.84 (0.72, 0.95)*	0.20 (0.03, 0.36)§	0.46 (0.26, 0.65)§
RWT (×100)	0.03 (–0.01, 0.04)		0.5 (0.3, 0.8)*	0.7 (0.4, 1.0)*	19 (18, 20)*	19 (18, 21)*	1.6 (–0.3, 3.5)	4.0 (2.0, 6.0)*
LVEDVI (mL/m <sup>2</sup> )	7.7 (7.2, 8.3)*		–0.7 (–0.1, –1.4)§	–0.8 (–0.4, –1.3)†	–10 (–9, –11)*	–8 (–7, –9)*	–0.9 (–3.1, 1.3)	–0.9 (–3.0, 1.1)
LVEDVI (mL/m <sup>2</sup> )	4.1 (3.8, 4.4)*		0.11 (–0.29, 0.51)	–0.19 (–0.43, 0.05)	–4.5 (–3.8, –5.3)*	–4.1 (–3.4, –4.8)*	–0.3 (–1.6, 1.1)	–1.2 (–0.1, –2.4)§
LVSVI (mL/m <sup>2</sup> )	3.7 (3.4, 3.9)*		–0.7 (–0.4, –1.0)*	–0.5 (–0.3, –0.8)*	–5.5 (–4.7, –6.3)*	–3.9 (–3.1, –4.6)*	–0.9 (–2.4, 0.5)	0.0 (–1.3, 1.3)
LVEF (%)	–1.8 (–1.6, –2.0)*		–0.6 (–0.3, –0.8)*	–0.2 (–0.0, –0.3)§	1.7 (1.0, 2.3)*	2.8 (2.1, 3.5)*	–0.8 (–1.9, 0.3)	1.7 (0.6, 2.8)‡
S' (cm/s)	0.8 (0.7, 0.8)*		–0.3 (–0.2, –0.3)*	–0.2 (–0.1, –0.2)*	–1.1 (–0.9, –1.3)*	–0.5 (–0.3, –0.7)*	–0.6 (–0.2, –0.9)‡	–0.3 (–0.6, 0.1)
LAVI (mL/m <sup>2</sup> )	2.2 (1.6, 2.7)*		2.0 (1.4, 2.6)*	2.3 (1.8, 2.8)*	12 (11, 14)*	12 (10, 13)*	2.9 (0.6, 5.1)§	6.7 (4.4, 9.0)*
e' (cm/s)	0.5 (0.4, 0.6)*		–0.5 (–0.4, –0.5)*	–0.5 (–0.4, –0.6)*	–2.1 (–1.9, –2.3)*	–2.5 (–2.3, –2.7)*	–0.8 (–0.4, –1.1)*	–0.7 (–0.4, –1.0)*
E/e' ratio	–1.3 (–1.0, –1.6)*		0.7 (0.5, 0.9)*	0.9 (0.7, 1.1)*	4.3 (3.3, 5.3)*	5.7 (4.4, 7.0)*	1.4 (0.7, 2.1)†	2.2 (1.4, 3.0)*
TR <sub>Vmax</sub> (m/s, ×10)	0.2 (0.0, 0.3)§		0.5 (0.3, 0.7)*	0.5 (0.4, 0.6)*	0.5 (–0.0, 1.0)	0.8 (0.3, 1.3)‡	1.3 (0.5, 2.1)‡	1.8 (0.9, 2.6)*

Data from mixed model analysis (Model 1) as described by Eng et al.,<sup>20</sup> shown as mean (95% confidence interval); numbers shown in Table 2. Abbreviations shown in legend to Table 2.

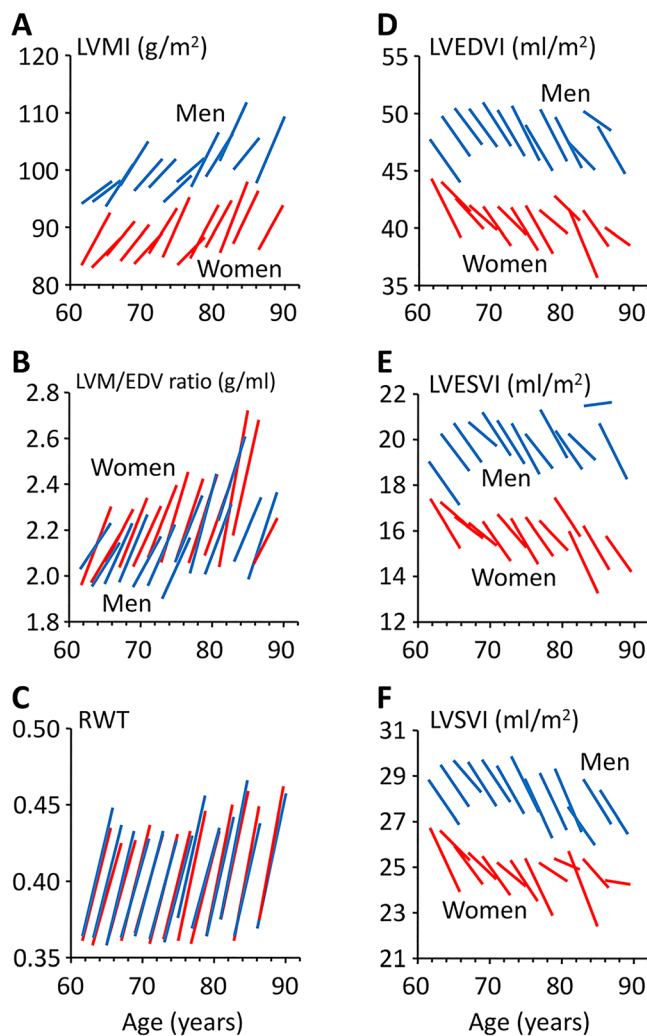
\**P* < 0.0001.

§*P* < 0.05.

†*P* < 0.001.

‡*P* < 0.01.

**Figure 1** Age-related longitudinal and cross-sectional changes in (A) left ventricular mass index (LVMI), (B) left ventricular mass/end-diastolic volume (LVM/EDV) ratio, (C) relative wall thickness (RWT), (D) left ventricular end-diastolic volume index (LVEDVI), (E) left ventricular end-systolic volume index (LVESVI), and (F) left ventricular stroke volume index (LVSVI) for men (blue) and women (red). Individual line segments represent observed longitudinal changes for each age group (in 2 year intervals from age 60–61 to  $\geq 84$  years), and the trends between successive line segments represent cross-sectional patterns among the age groups. Numbers per line: LVMI, 15–132 (men) and 15–125 (women); LVM/EDV ratio, 9–90 (men) and 5–86 (women); RWT, 15–131 (men) and 15–125 (women); LVEDVI, 13–113 (men) and 10–96 (women); LVESVI, 13–113 (men) and 10–96 (women); LVSVI, 13–113 (men) and 10–96 (women).



LVMI; SBP also predicted less rapid decrease in LVEDVI and LVESVI and more rapid increase in LVEF and LAVI in multivariable analysis. Hypertension predicted more rapid increase in LVM/EDV ratio, RWT, and LAVI. DBP predicted more rapid decrease in LVSVI, less rapid increase in LVEF, less rapid decrease in  $S'$ , and less rapid increase in  $E/e'$  ratio. PP predicted less rapid decrease in LVSVI, less rapid increase in LVEF, less rapid decrease in  $e'$ , and more rapid increase in  $E/e'$  ratio and  $TR_{V_{max}}$ . Both CCB and ACEI and/or ARB therapies predicted less rapid decrease in LVEDVI and more rapid longitudinal increase in  $E/e'$  ratio. CCB, but not ACEI and/or ARB therapies, predicted more rapid increase in LVMI, LAVI, and  $TR_{V_{max}}$  and less rapid decrease in  $S'$ . Whereas ACEI

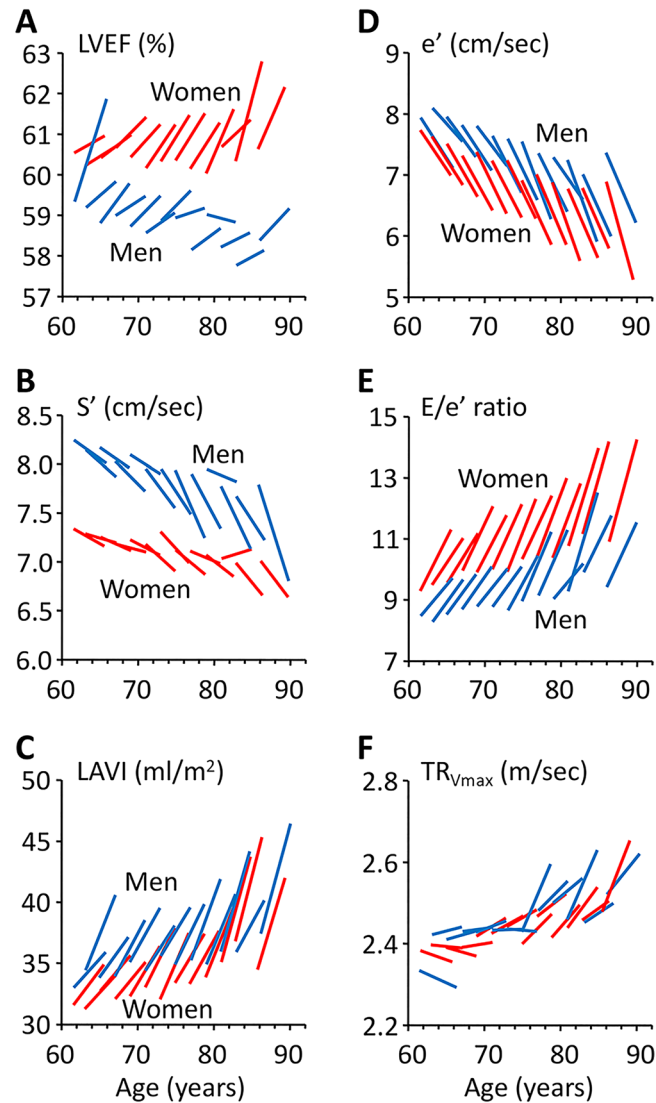
therapy predicted more rapid decrease in LVSVI, CCB therapy predicted a less rapid decrease.

A history of MI before the baseline echocardiographic examination predicted more rapid increase in LVMI, LVM/EDV ratio, and LAVI; less rapid decrease in LVEDVI and LVESVI; and less rapid increase in LVEF in multivariable analysis. A history of AF (or warfarin or digoxin therapy) before the baseline echocardiographic examination predicted more rapid increase in LVMI, LVM/EDV ratio, LAVI, and  $TR_{V_{max}}$ ; more rapid decrease in LVEDVI, LVSVI, and  $S'$ ; less rapid decrease in LVESVI and  $e'$ ; and less rapid increase in LVEF.

Although HbA1c predicted more rapid longitudinal increase in LVMI in univariate analysis (Table S1), neither



**Figure 2** Age-related longitudinal and cross-sectional changes, and multivariable predictors of longitudinal change in (A) left ventricular ejection fraction (LVEF), (B) average systolic mitral annular tissue Doppler velocity ( $S'$ ), (C) left atrial volume index (LAVI), (D) average early diastolic mitral annular tissue Doppler velocity ( $e'$ ), (E) peak early diastolic mitral flow velocity/ $e'$  ( $E/e'$ ) ratio, and (F) peak tricuspid regurgitant flow velocity ( $TR_{Vmax}$ ) for men (blue) and women (red). Individual line segments represent observed longitudinal changes for each age group (in 2 year intervals from age 60–61 to  $\geq 84$  years), and the trends between successive line segments represent cross-sectional patterns among the age groups. Numbers per line: LVEF, 24–182 (men) and 26–150 (women);  $S'$ , 20–165 (men) and 23–138 (women); LAVI, 22–180 (men) and 24–149 (women);  $e'$ , 23–173 (men) and 25–139 (women);  $E/e'$  ratio, 22–166 (men) and 24–135 (women);  $TR_{Vmax}$ , 6–54 (men) and 12–69 (women).



diabetes, HbA1c, nor anti-diabetic therapy predicted longitudinal change in LVMI or LVM/EDV ratio in multivariable analysis (Tables 5, S13, S14, S26, Figure 4). Both HbA1c and anti-diabetic therapy predicted more rapid increase in  $E/e'$  ratio (Figure 4). Whereas diabetes predicted less rapid increase in RWT, anti-diabetic therapy predicted more rapid increase in RWT. HbA1c predicted more rapid decrease in LVSVI, whereas anti-diabetic therapy predicted more rapid increase in LVEF and less rapid increase in LAVI. Whereas waist circumference predicted more rapid increase in LVMI, BMI predicted more rapid increase in LVM/EDV ratio and RWT, and neither

BMI nor waist circumference predicted a change in LV volumes. BMI also predicted less rapid increase in LVEF, more rapid increase in LAVI and  $E/e'$  ratio, and less rapid increase in  $TR_{Vmax}$ , whereas waist circumference predicted less rapid decrease in  $S'$  and more rapid increase in  $TR_{Vmax}$ . Triglyceride level predicted more rapid increase in LVM/EDV ratio, more rapid decrease in LVSVI, and less rapid decrease in  $e'$ , whereas high-density lipoprotein cholesterol predicted less rapid increase in LVMI and LVM/EDV ratio.

Physical inactivity predicted less rapid decrease in LVEDVI. Obstructive sleep apnoea predicted more rapid increase in

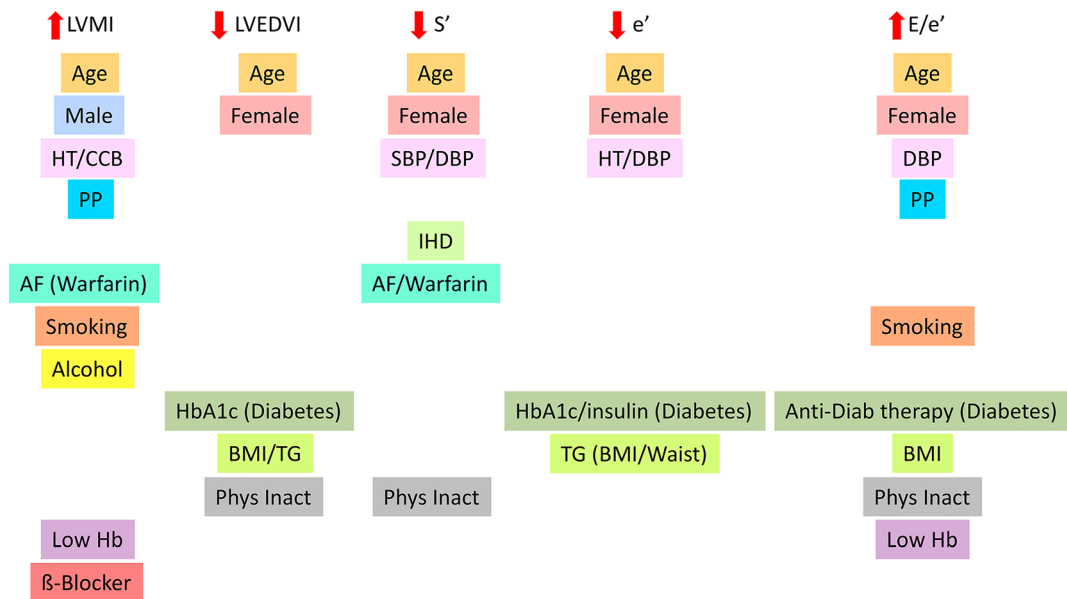
**Table 4** Multivariable predictors of baseline left ventricular mass indexed to body surface area (LVMI), left ventricular end-diastolic volume indexed to body surface area (LVEDVI), peak systolic mitral annular velocity (S'), average peak early diastolic mitral annular velocity (e'), and peak early diastolic mitral velocity to average peak early diastolic mitral annular velocity ratio (E/e' ratio)

	Change in baseline LVMI (g/m <sup>2</sup> ), mean (95% CI)	Change in baseline LVEDVI (mL/m <sup>2</sup> ), mean (95% CI)	Change in baseline S' (cm/s), mean (95% CI)	Change in baseline e' (cm/s), mean (95% CI)	Change in baseline E/e' ratio, mean (95% CI)
Age (per decade)	1.76 (0.98, 2.55)	-1.44 (-0.97, -1.90)	-0.15 (-0.11, -0.19)	-0.54 (-0.48, -0.59)	0.69 (0.58, 0.80)
Male gender	10.66 (9.68, 11.64)	7.72 (7.17, 8.28)	0.81 (0.76, 0.86)	0.48 (0.41, 0.54)	-1.33 (-1.20, -1.46)
Hypertension	2.34 (0.64, 4.04)			-0.21 (-0.09, -0.33)	
SBP quintile					
DBP quintile					
Pulse pressure quintile	0.72 (0.36, 1.07)	0.52 (0.32, 0.73)	-0.02 (-0.00, -0.04)	-0.12 (-0.09, -0.14)	0.07 (0.02, 0.12)
Diabetes			-0.03 (-0.01, -0.05)	0.05 (0.03, 0.08)	0.18 (0.13, 0.22)
HbA1c quintile				-0.04 (-0.02, -0.07)	0.11 (0.06, 0.15)
BMI quintile		-0.49 (-0.30, -0.69)			
Waist circumference quintile		-0.23 (-0.02, -0.44)	0.03 (0.01, 0.05)		
Triglyceride quintile		-0.47 (-0.28, -0.67)	0.02 (0.00, 0.04)	-0.06 (-0.03, -0.08)	
Myocardial infarction		1.76 (0.84, 2.67)			
Ischaemic heart disease			-0.18 (-0.11, -0.24)		
Atrial fibrillation	2.54 (1.02, 4.05)		-0.15 (-0.05, -0.24)		0.14 (0.00, 0.27)
Physical inactivity		-0.79 (-0.22, -1.36)	-0.07 (-0.02, -0.12)		0.17 (0.04, 0.30)
Obstructive sleep apnoea			0.09 (0.03, 0.16)		0.46 (0.25, 0.68)
Current or former smoker	1.21 (0.25, 2.17)				0.39 (0.19, 0.59)
Alcohol > 2 glasses/day	1.31 (0.09, 2.54)				0.72 (0.33, 1.11)
Low haemoglobin	1.98 (0.37, 3.58)				
Low platelet count					
Oral hypoglycaemic therapy		1.61 (0.66, 2.56)			
Insulin therapy	2.10 (1.07, 3.13)	1.91 (0.53, 3.28)		-0.26 (-0.06, -0.46)	
CCB therapy	1.95 (0.84, 3.07)				
Beta-blocker therapy					
Warfarin therapy			-0.19 (-0.04, -0.34)	0.42 (0.24, 0.61)	

Data shown as mean [95% confidence interval (CI)]. Predictors of baseline variables from linear regression analysis, adjusted for age and gender. These data are from Tables S13, S16, S20, S22, and S23.

BMI, body mass index; CCB, calcium channel blocker; DBP, diastolic blood pressure; SBP, systolic blood pressure.

**Figure 3** Diagrammatic summary of multivariable predictors of increase in baseline ventricular mass indexed to body surface area (LVMI), decrease in baseline left ventricular end-diastolic volume indexed to body surface area (LVEDVI), decrease in baseline peak systolic mitral annular velocity ( $S'$ ), decrease in baseline average peak early diastolic mitral annular velocity ( $e'$ ), and increase in baseline peak early diastolic mitral velocity to average peak early diastolic mitral annular velocity ratio ( $E/e'$  ratio). AF, atrial fibrillation; BMI, body mass index; CCB, calcium channel blocker; DBP, diastolic blood pressure; Hb, haemoglobin; HT, hypertension; IHD, ischaemic heart disease; PP, pulse pressure; SBP, systolic blood pressure; TG, triglyceride. Data from Table 4. Shown in parentheses are univariate predictors associated with the multivariable predictors (from Tables S1, S4, S8, S10, and S11).



LVM/EDV ratio and more rapid decrease in LVEDVI and LVESVI. Renal dysfunction ( $eGFR < 60 \text{ mL}/1.73 \text{ m}^2$ ) was associated with amplification of age-associated longitudinal change in echocardiographic parameters, predicting more rapid increase in LVM/EDV ratio and RWT and more rapid decrease in LVEDVI, LVESVI, and  $S'$ .

### Differential prediction of baseline echocardiographic parameters and longitudinal change by cardiovascular disease risk factors in multivariable analysis

CVD risk factor prediction of a baseline echocardiographic parameter was often discordant with their prediction of longitudinal change in that parameter in multivariable analysis (Tables 4, 5, S13–S26, Figures 3 and 4). Male gender predicted higher baseline LVMI, whereas female gender predicted more rapid increase in LVMI (Figures 3 and 4). Moreover, female gender predicted lower baseline  $S'$ , whereas male gender predicted more rapid decrease in  $S'$ . Hypertension predicted higher baseline LVMI, whereas SBP and PP predicted more rapid increase in LVMI. AF predicted higher baseline LVMI, whereas warfarin therapy (but not AF in either univariate or multivariable analysis) predicted more rapid increase in LVMI. However, AF predicted both higher baseline LVM/EDV ratio and more rapid increase in

LVM/EDV ratio. AF (or warfarin or digoxin therapy) did not predict baseline LV volumes, although it predicted a more rapid decrease in LVEDVI and LVESVI. Neither MI nor IHD predicted baseline LVMI, but a history of MI before the baseline echocardiographic examination predicted more rapid increase in LVMI and LVM/EDV ratio. BMI predicted lower baseline LVEDVI but did not predict longitudinal change in LVEDVI. Neither reduced eGFR nor obstructive sleep apnoea predicted baseline LV volumes, but both predicted more rapid decrease in LVEDVI and LVESVI. In contrast to its prediction of lower baseline LVEDVI, physical inactivity predicted less rapid decrease in LVEDVI in both univariate and multivariable analyses (Tables S4, S16).

## Discussion

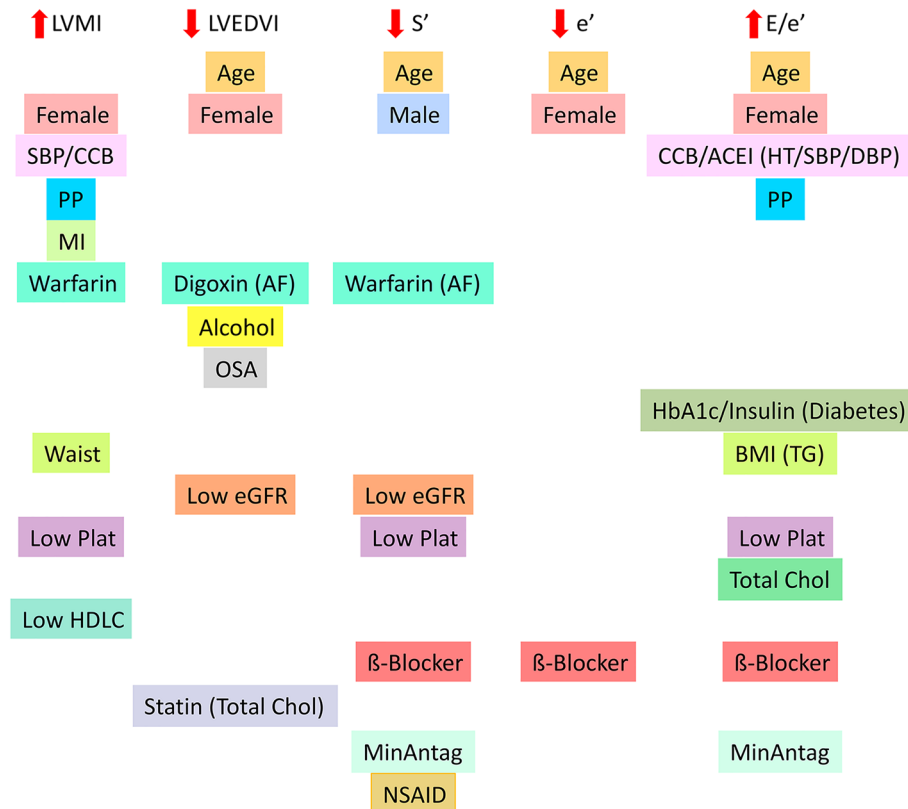
Age-associated longitudinal change in cardiac structure and function included increase in LVMI, decrease in LV volumes, increase in LVEF, decrease in  $S'$ , and deterioration in diastolic function. Whereas CVD risk factors alone explained the increase in LVMI, age, together with risk factors, independently predicted longitudinal change in all other echocardiographic parameters, providing evidence for age-specific mechanisms of change in cardiac structure and function as people age. CVD risk factors were differentially associated with longitudinal change in different echocardiographic parameters.

**Table 5** Multivariable predictors of longitudinal change (gradient) in left ventricular mass indexed to body surface area (LVMI), left ventricular end-diastolic volume indexed to body surface area (LVEDVI), peak systolic mitral annular velocity (S'), average peak early diastolic mitral annular velocity (e'), and peak early diastolic mitral velocity to average peak early diastolic mitral annular velocity ratio (E/e' ratio)

	Change in LVMI gradient (g/m <sup>2</sup> per decade), mean (95% CI)	Change in LVEDVI gradient (mL/m <sup>2</sup> per decade), mean (95% CI)	Change in S' gradient (cm/s per decade), mean (95% CI)	Change in e' gradient (cm/s per decade), mean (95% CI)	Change in E/e' ratio gradient (per decade), mean (95% CI)
Age (per decade)	-6.23 (-2.60, -9.86)	-1.39 (-0.53, 2.25)	-0.23 (-0.06, -0.40)	-0.53 (-0.36, -0.69)	0.62 (0.02, 1.23)
Male gender		3.26 (1.88, 4.65)	-0.73 (-0.50, -0.97)	0.24 (0.04, 0.44)	-1.95 (-1.46, -2.44)
Hypertension					
SBP quintile	1.66 (0.15, 3.17)	0.83 (0.42, 1.25)	0.09 (0.02, 0.16)	0.13 (0.05, 0.20)	-0.54 (-0.37, -0.71)
DBP quintile	1.61 (0.06, 3.17)				0.59 (0.42, 0.76)
Pulse pressure quintile					0.24 (0.08, 0.41)
HbA1c quintile					0.43 (0.26, 0.60)
BMI quintile	2.79 (1.60, 3.99)		0.23 (0.16, 0.31)		0.47 (0.31, 0.64)
Waist circumference quintile					
Total cholesterol quintile	-1.50 (-0.34, -2.65)			0.14 (0.08, 0.21)	
HDL cholesterol quintile	16.28 (11.08, 21.48)	5.32 (3.25, 7.39)		0.64 (0.24, 1.03)	
Triglyceride quintile					
Myocardial infarction					
Atrial fibrillation					
Physical inactivity		1.69 (0.52, 2.86)			
Obstructive sleep apnoea		-2.06 (-0.55, -3.56)			
Alcohol >2 glasses/day		-1.62 (-0.13, -3.11)	0.28 (0.03, 0.53)		
Low haemoglobin		5.59 (3.43, 7.75)			
Low platelet count					
eGFR <60 mL/min/1.73 m <sup>2</sup>	12.99 (5.37, 20.61)	-3.08 (-1.38, -4.77)	-0.89 (-0.39, -1.39)		1.82 (0.68, 2.96)
Insulin therapy			-0.33 (-0.06, -0.61)		2.47 (1.03, 3.91)
ACE inhibitor therapy					0.76 (0.29, 1.24)
ARB therapy		1.35 (0.21, 2.50)			
CCB therapy	8.88 (5.60, 12.17)	3.73 (2.47, 4.99)	0.30 (0.08, 0.51)		0.80 (0.32, 1.28)
Beta-blocker therapy		-2.06 (-0.89, -3.23)	-0.74 (-0.50, -0.99)	-0.30 (-0.05, -0.54)	1.73 (1.19, 2.27)
Statin therapy					
Warfarin therapy	13.91 (6.88, 20.93)	-6.15 (-2.07, -10.23)	-1.23 (-0.62, -1.83)		
Digoxin therapy				1.19 (0.29, 2.10)	
Loop diuretic therapy				0.85 (0.18, 1.53)	
Mineralocorticoid antagonist therapy			-1.63 (-0.07, -3.19)		-3.25 (-1.72, -4.77)
NSAID therapy			-0.39 (-0.07, -0.71)		6.38 (2.44, 10.32)

Data shown as mean [95% confidence interval (CI)]. Predictors of gradient from mixed model analysis (Model 2) as described by Eng *et al.*<sup>20</sup>; all analyses adjusted for age at baseline, gender, and the respective baseline echocardiographic parameter value. These data are from Tables S13, S16, S20, S22, and S23.

**Figure 4** Diagrammatic summary of multivariable predictors of more rapid increase in left ventricular mass indexed to body surface area (LVMI), more rapid decrease in left ventricular end-diastolic volume indexed to body surface area (LVEDVI), more rapid decrease in peak systolic mitral annular velocity ( $S'$ ), more rapid decrease in average peak early diastolic mitral annular velocity ( $e'$ ), and more rapid increase in peak early diastolic mitral velocity to average peak early diastolic mitral annular velocity ratio ( $E/e'$ ). ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; BMI, body mass index; CCB, calcium channel blocker; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDLC, high-density lipoprotein cholesterol; HT, hypertension; MI, myocardial infarction; MinAntag, mineralocorticoid antagonist; NSAID, non-steroidal anti-inflammatory drug; OSA, obstructive sleep apnoea; Plat, platelet; PP, pulse pressure; SBP, systolic blood pressure; TG, triglyceride. Data from *Table 5*. Shown in parentheses are univariate predictors associated with the multivariable predictors (from *Tables S1, S4, S8, S10, and S11*).



Although LV volumes are usually described as ‘normal’ in HF with preserved ejection fraction (HFpEF),<sup>35</sup> age-associated decrease in LVEDVI, together with increase in LV wall thickness and its increased stiffness,<sup>36</sup> would be accompanied by an impaired ability of the LV to fill during diastole, such that a normal or increased LVEF may fail to ensure a cardiac output sufficient to meet metabolic needs. The age-associated decrease in LV volumes, increase in LVMI, increase in LVEF and deterioration in diastolic function resemble what might be expected to occur during the evolution of HFpEF. These data contribute to understanding of age-associated change in cardiac structure and function and the relative contribution of age-specific mechanisms and CVD risk factors to these changes. Therapies aimed at attenuation of age-associated change in cardiac structure and function, and HF evolution, likely need to address multiple risk factors.

Longitudinal changes in echocardiographic parameters exceeded the cross-sectional change, except for  $TR_{V_{max}}$ , and prediction of longitudinal change by age and CVD risk factors

differed from their prediction of baseline echocardiographic parameters. Longitudinal studies are superior to cross-sectional studies in revealing age-associated change in cardiac structure and function because cross-sectional analyses are affected by the cohort effect.<sup>37</sup> Potential contributors to the cohort effect in this study included changing smoking prevalence, better treatment of hypertension and hyperlipidaemia, and increasing use of coronary interventions that attenuate MI risk and size that may impact differentially on individuals of different ages. Individuals with a more extreme change in cardiac structure and/or function may be less likely to survive to older ages.

The SCREEN-HF cohort was of similar age to the Multi-Ethnic Study of Atherosclerosis (MESA) cohort.<sup>20</sup> Both cohorts included participants with CVD risk factors, although the MESA cohort was free of clinical CVD, whereas the SCREEN-HF cohort included participants with known MI and IHD. In agreement with Eng *et al.*,<sup>20</sup> we excluded participants with HF at baseline and participants who experienced MI or

HF between the baseline and follow-up echocardiographic examinations. However, other studies of longitudinal change in cardiac structure and function included participants with incident HF.<sup>17, 18</sup>

Our findings for LVMI in men and LV volumes in men and women were similar to those reported by Eng *et al.* in the MESA cohort, where LVM and LV volumes were measured by magnetic resonance imaging.<sup>20</sup> Whereas Eng *et al.* reported a longitudinal decrease in LVM in women, we observed an increase in LVMI in both men and women, in agreement with previous reports.<sup>16, 18</sup> Our observation of longitudinal increase in LVEF was in agreement with Kane *et al.*,<sup>17</sup> although Cauwenberghs *et al.* reported LVEF to decrease with age.<sup>21</sup> We also confirmed previous reports of age-associated deterioration in diastolic function.<sup>17, 19, 21</sup>

## The aging heart

The age-associated increase in LVMI and deterioration in diastolic function observed in this study were consistent with an age-associated increase in HF risk, as shown by our demonstration that stage B HF and diastolic abnormality at the time of the baseline echocardiographic examination predicted HF in this cohort.<sup>25</sup> Both cellular and molecular mechanisms have been proposed to account for the changes in cardiac structure and function that accompany aging,<sup>38</sup> and the association of aging with HF.<sup>39</sup> These include increased myocardial stiffness that may result from hypertensive LV remodelling, inflammation, microvascular dysfunction and rarefaction, fibrosis, oxidative stress, and cardiomyocyte remodelling, and dysfunction.<sup>35, 40</sup> We previously reported in a cross-sectional study that diastolic dysfunction of aging was independent of myocardial fibrosis, microvascular density, and cardiomyocyte size but was associated with plasma advanced glycation end-product levels.<sup>41</sup>

## Clinical implications

In addition to demonstrating age was an independent determinant of longitudinal change in cardiac structure and function, our data confirm the potential for risk factor modification to attenuate age-associated change in cardiac structure and function. Eng *et al.*<sup>20</sup> reported that SBP and BMI were univariate predictors of more rapid increase in LVM and that DBP, smoking, BMI, and impaired fasting glucose level were univariate predictors of more rapid decrease in LVEDV. In agreement with these observations, we found that SBP and waist circumference predicted more rapid increase in LVMI and that hypertension and BMI predicted more rapid increase in LVM/EDV ratio and RWT in multivariable analysis. HbA1c, BMI, physical inactivity, and triglyceride level predicted lower baseline LV volumes; and obstructive

sleep apnoea, alcohol intake, digoxin therapy, triglyceride level, and impaired renal function predicted more rapid decrease in LV volumes. In addition to the potential for reduction in BP, BMI, and waist circumference to attenuate age-associated increase in LVMI, LVM/EDV ratio, and RWT, our data indicate that BP reduction, prevention of obesity and diabetes, promotion of physical activity, prevention and/or treatment of obstructive sleep apnoea, reduction of alcohol intake, and prevention or attenuation of age-associated decline in renal function may also contribute to the reduction of age-associated decline in LV volumes.

The significance of CVD risk factor-associated longitudinal change in cardiac structure and function in this study was reinforced by our observation that many of the same risk factors predicted HF in the SCREEN-HF cohort<sup>24</sup> and were in agreement with strategies shown to reduce HF incidence and improve diastolic function. Antihypertensive therapy reduces LVMI and myocardial fibrosis,<sup>42–44</sup> improves diastolic dysfunction,<sup>42–45</sup> and prevents HF.<sup>46–48</sup> Moreover, weight reduction in obesity reduces LVM and improves diastolic function,<sup>49–51</sup> and physical activity increases LVEDV, reduces LV stiffness,<sup>52</sup> and is associated with reduced HF incidence.<sup>53, 54</sup>

## Limitations

Our study had a number of limitations. Participants were aged  $\geq 60$  years, but they represented the age range with increased HF incidence.<sup>24</sup> The inclusion criteria with respect to age and CVD risk factors, together with the SCREEN-HF cohort comprising volunteers (possible healthy volunteer bias) who were predominantly members of a health fund, may be cause for caution in the generalization of our findings to the general community. However, the SCREEN-HF cohort was not that dissimilar to the general Australian population aged  $\geq 60$  years; of Australians aged 65–74 years, 70% have hypertension,<sup>55</sup> 17% have diabetes,<sup>56</sup> 38.2% of men and 32.7% of women are obese,<sup>57</sup> 5% have AF,<sup>58</sup> and 53% have CVD.<sup>59</sup> Our findings are therefore likely to be applicable to the general Australian community. An advantage of enrolling participants with known IHD was that we were able to examine its prediction of age-associated change in cardiac structure and function.

Our inability to measure every echocardiographic parameter in every participant at both examinations reflected the practicalities of a community-based study where body habitus, such as increased BMI, may compromise image quality. A potential bias was that those attending the second examination may have been healthier than those who failed to attend.

A strength of our study was the number of CVD risk factors studied, including medications, although we did not adjust for change in risk factors during follow-up, apart from age. We

attempted to control for type 1 error in detection of statistically significant associations by conducting multivariable analysis. Some predictors may be missing because of limitations in data collection, and we do not presume causality. Nevertheless, our data show consistency across risk factors in their association with related echocardiographic parameters, thereby increasing confidence in the associations reported. For many risk factors, their associations with longitudinal change in echocardiographic parameters were similar to those we previously reported to predict HF,<sup>24</sup> and previous studies show that modification of many of these risk factors improves cardiac structure and function and reduces HF incidence.<sup>42–51, 53, 54</sup>

## Conclusions

In this community-based cohort, age was associated with longitudinal increase in LVMI, decrease in LV volumes, increase in LVEF, decrease in  $S'$ , and deterioration in diastolic function. Whereas the increase in LVMI with age was explained by CVD risk factors alone, age, together with risk factors, independently predicted longitudinal change in all other echocardiographic parameters, providing evidence for age-specific mechanisms of change in cardiac structure and function as people age. Age-associated change in LV volumes, LVMI, and diastolic function resembled what might be expected for the evolution of HFpEF. CVD risk factors were differentially associated with longitudinal change in different echocardiographic parameters, and therapies aimed at attenuation of age-associated change in cardiac structure and function, and HF evolution, will likely need to address multiple risk factors.

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## Conflict of interest

Bupa Australia was involved in the study design, recruitment of participants, and funding but was not involved in the data collection, analysis or interpretation, or writing of the article. Bupa Australia had no control or influence over the decision to submit the final manuscript for publication. Boffa was an employee of Bupa Australia. Liew received honoraria from Pfizer, Sanofi, Astra-Zeneca, Abbott, Bayer, MSD, GSK, Novartis, and Nycomed. Stewart received unrestricted educational grants from Schering Plough and Boehringer Ingelheim

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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.** Univariate predictors of baseline left ventricular mass indexed to body surface area (LVMI) and LVMI gradient (change per decade)

**Table S2.** Univariate predictors of baseline left ventricular mass/end-diastolic volume ratio (LVM/EDV ratio) and LVM/EDV ratio gradient (change per decade)

**Table S3.** Univariate predictors of baseline left ventricular relative wall thickness (RWT) and RWT gradient (change per decade)

**Table S4.** Univariate predictors of baseline left ventricular end-diastolic volume indexed to body surface area (LVEDVI) and LVEDVI gradient (change per decade)

**Table S5.** Univariate predictors of baseline left ventricular end-systolic volume indexed to body surface area (LVESVI) and LVESVI gradient (change per decade)

**Table S6.** Univariate predictors of baseline left ventricular stroke volume indexed to body surface area (LVSVI) and LVSVI gradient (change per decade)

**Table S7.** Univariate predictors of baseline left ventricular ejection fraction (LVEF) and LVEF gradient (change per decade)

**Table S8.** Univariate predictors of baseline peak systolic mitral annular velocity ( $S'$ ) and  $S'$  gradient (change per decade)

**Table S9.** Univariate predictors of baseline left atrial volume

indexed to body surface area (LAVI) and LAVI gradient (change per decade)

**Table S10.** Univariate predictors of baseline average peak early diastolic mitral annular velocity ( $e'$ ) and  $e'$  gradient (change per decade)

**Table S11.** Univariate predictors of baseline peak early diastolic mitral velocity to average peak early diastolic mitral annular velocity ratio ( $E/e'$  ratio) and  $E/e'$  ratio gradient (change per decade)

**Table S12.** Univariate predictors of baseline tricuspid maximum regurgitant velocity ( $TR_{Vmax}$ ) and  $TR_{Vmax}$  gradient (change per decade)

**Table S13.** Multivariable predictors of baseline left ventricular mass indexed to body surface area (LVMI) and LVMI gradient (change per decade)

**Table S14.** Multivariable predictors of baseline left ventricular mass/end-diastolic volume ratio (LVM/EDV ratio) and LVM/EDV ratio gradient (change per decade)

**Table S15.** Multivariable predictors of baseline left ventricular relative wall thickness (RWT) and RWT gradient (change per decade)

**Table S16.** Multivariable predictors of baseline left ventricular end-diastolic volume indexed to body surface area (LVEDVI) and LVEDVI gradient (change per decade)

**Table S17.** Multivariable predictors of baseline left ventricular end-systolic volume indexed to body surface area (LVESVI) and LVESVI gradient (change per decade)

**Table S18.** Multivariable predictors of baseline left ventricular stroke volume indexed to body surface area (LVSVI) and LVSVI gradient (change per decade)

**Table S19.** Multivariable predictors of baseline left ventricular ejection fraction (LVEF) and LVEF gradient (change per

decade)

**Table S20.** Multivariable predictors of baseline peak systolic mitral annular velocity ( $S'$ ) and  $S'$  gradient (change per decade)

**Table S21.** Multivariable predictors of baseline left atrial volume indexed to body surface area (LAVI) and LAVI gradient (change per decade)

**Table S22.** Multivariable predictors of baseline average peak early diastolic mitral annular velocity ( $e'$ ) and  $e'$  gradient (change per decade)

**Table S23.** Multivariable predictors of baseline peak early diastolic mitral velocity to average peak early diastolic mitral annular velocity ratio ( $E/e'$  ratio) and  $E/e'$  ratio gradient (change per decade)

**Table S24.** Multivariable predictors of baseline tricuspid maximum regurgitant velocity ( $TR_{Vmax}$ ) and  $TR_{Vmax}$  gradient (change per decade)

**Table S25.** Multivariable predictors of higher (shown in red) or lower (shown in blue) baseline echocardiographic parameter values.

**Table S26.** Multivariable predictors of longitudinal change (gradient) in echocardiographic parameters per decade of follow-up. Predictors of more rapid increase (or less rapid decrease) are shown in red, whereas predictors of more rapid decrease (or less rapid increase) are shown in blue.

**Figure S1.** Flow chart of numbers of individuals invited to participate in the SCReening Evaluation of the Evolution of New Heart Failure (SCREEN-HF) study who were subsequently enrolled and attended baseline and follow-up echocardiographic examinations.

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