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ORIGINAL ARTICLE

Risk factors for asymptomatic echocardiographic abnormalities that predict symptomatic heart failure

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Abstract

Aims Risk factors for asymptomatic echocardiographic abnormalities that predict symptomatic heart failure (HF) may provide insight into early mechanisms of HF pathogenesis. We examined risk factors associated with asymptomatic echocardiographic structural, systolic, and diastolic abnormalities, separately and in combination, and interactions between risk factors, in the prospective community-based SCReening Evaluation of the Evolution of New HF (SCREEN-HF) Study cohort of 3190 participants at increased risk of cardiovascular disease.

Methods and results Inclusion criteria were age $\geq$ 60 years with one or more of hypertension, diabetes, ischaemic heart disease, valvular heart disease, abnormal heart rhythm, cerebrovascular disease, or renal impairment. Exclusion criteria were known HF, ejection fraction $<$ 50%, or $>$mild valve abnormality. Structural, systolic, and diastolic echocardiographic abnormalities were defined according to the Atherosclerosis Risk in Communities study criteria, and risk factors for asymptomatic structural, systolic, and diastolic abnormalities were identified using logistic regression analysis. In multivariable analysis, increased body mass index (BMI), non-steroidal anti-inflammatory drug therapy, and alcohol intake were risk factors for isolated structural abnormality, whereas male gender, increased heart rate, atrial fibrillation (AF), angiotensin-converting enzyme inhibitor therapy, and obstructive sleep apnoea were associated with a lower risk. Moreover, male gender, smoking, increased systolic blood pressure, and physical inactivity were risk factors for isolated systolic abnormality, whereas increased pulse pressure and antihypertensive therapy were associated with a lower risk. Furthermore, increased age, blood pressure, amino-terminal pro-B-type natriuretic peptide level, and warfarin therapy (associated with AF) were risk factors for isolated diastolic abnormality, whereas increased heart rate and triglyceride level (associated with BMI) were associated with a lower risk. The association of increased heart rate with lower risk of structural and diastolic abnormalities was independent of β-blocker therapy. Interactions between risk factors differed for structural, systolic, and diastolic abnormalities.

Conclusions The different risk factors for asymptomatic structural, systolic, and diastolic abnormalities that predict symptomatic HF, and the interactions between risk factors, illustrate how these structural, systolic, and diastolic abnormalities represent unique trajectories that lead to symptomatic HF. Improved understanding of these trajectories may assist in the design of HF prevention strategies.

Keywords Risk factors; Echocardiography; Structural abnormality; Systolic abnormality; Diastolic abnormality

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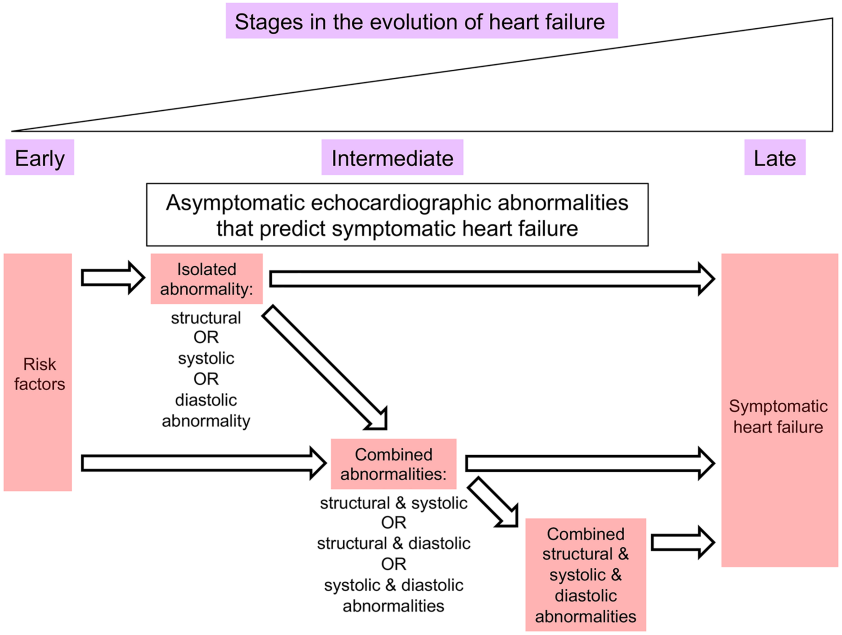
Introduction

Heart failure (HF) is a complex and progressive clinical syndrome that results from any structural or functional impairment of ventricular filling or ejection of blood,[1] with a lifetime risk of 20–46% among participants in the Chicago Heart Association Detection Project in Industry, the Atherosclerosis Risk in Communities (ARIC), and the Cardiovascular

Health Study cohorts.[2] HF may result from disorders of the pericardium, myocardium, endocardium, heart valves, great vessels, and/or metabolic abnormalities, but most patients with HF have symptoms due to impaired left ventricular (LV) myocardial function.[1] The American College of Cardiology Foundation and American Heart Association guideline describes four stages of HF; Stages A and B are asymptomatic whilst Stages C and D are symptomatic.[1] Stage A HF refers to asymptomatic individuals with cardiovascular disease (CVD) risk factors but without structural heart disease, whereas Stage B HF refers to asymptomatic individuals with structural heart disease, which may include any of LV dilatation, LV hypertrophy, reduced LV ejection fraction, wall motion abnormalities, and moderate or greater aortic or mitral stenosis or regurgitation.[3,4] Stage B HF predicts symptomatic HF,[3–5] and we recently reported that age-specific diastolic dysfunction, defined according to ARIC study criteria,[3] also predicts symptomatic HF and improves prediction of symptomatic HF by Stage B HF.[5]

Risk factors have played an important role in revealing underlying mechanisms of CVD. This includes delineating the role of hypertension, diabetes, smoking, and serum cholesterol in the pathogenesis of ischaemic heart disease.[6] Many risk factors for incident symptomatic HF have been identified,[7,8] and we previously identified key differences between risk factors for incident symptomatic HF with reduced (HFrEF) and preserved ejection fraction (HFpEF), and valvular HF in the SCReening Evaluation of the Evolution of New HF (SCREEN-HF) Study cohort, a community-based evaluation of the use of serum amino-terminal pro-B-type natriuretic peptide (NT-proBNP) to identify individuals with cardiac dysfunction (as assessed by echocardiography) and increased risk of symptomatic HF and other CVD events.[5,8–10] Asymptomatic echocardiographic structural, systolic, and diastolic abnormalities that predict symptomatic HF represent an early stage in the evolution of symptomatic HF. Moreover, asymptomatic isolated structural, systolic, and diastolic echocardiographic abnormalities that predict symptomatic HF may represent an earlier stage in the evolution of symptomatic HF than combined abnormalities (*Figure 1*). It was on this basis that we examined risk factors for these asymptomatic echocardiographic abnormalities that predict symptomatic HF, and their interactions, to obtain insight into early mechanisms of HF pathogenesis that may differentially impact on abnormalities of cardiac structure and function in the SCREEN-HF study cohort. We examined candidate risk factors we previously studied in our investigation of risk factors for incident symptomatic HFrEF, HFpEF and valvular HF in this cohort.[8] Our hypothesis was that asymptomatic echocardiographic structural, systolic, and diastolic abnormalities that predict symptomatic HF are associated with different risk factors, and these risk factors and their interactions may provide insight into differences in the pathogenesis of these asymptomatic structural, systolic, and diastolic abnormalities, and thereby insight into early mechanisms of HF pathogenesis.

Figure 1 Schematic of potential trajectories of evolution of symptomatic heart failure from risk factors for isolated asymptomatic echocardiographic structural, systolic, and diastolic abnormalities that predict heart failure, and for combinations of asymptomatic echocardiographic abnormalities.



Methods

Study design

The SCREEN-HF study, a prospective cohort study of men and women recruited from the community ≥60 years of age with CVD risk factors, but without symptomatic HF,[5,8–10] was approved by the Alfred Human Research Ethics Committee, 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.

Study cohort

A flow chart for participant recruitment is shown in Supporting Information, *Figure S1*. In summary, 44 000 members of private health fund Bupa, resident in Melbourne or Shepparton, Victoria, Australia, were invited to participate. Inclusion criteria were age ≥ 60 years with one or more of self-reported treatment for hypertension or diabetes for ≥2 years, myocardial infarction (MI) or other ischaemic heart disease, valvular heart disease, irregular or rapid heart rhythm, cerebrovascular disease, or renal impairment. We excluded individuals with previously diagnosed symptomatic HF and those with well-recognized HF risk such as previous valve surgery or documented valve abnormality graded >mild, LV ejection fraction < 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 clinical information and 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). Details of participant follow-up are shown in *Figure S1*. All participants with symptomatic HF at the time of echocardiography were identified and excluded from this analysis. The capture of incident HF has been described previously.[8] Participants were questioned for symptoms of HF and examined for signs of HF at the time of echocardiography. In order to capture all incident cases of HF, a participant was referred to their cardiologist or to a SCREEN-HF study cardiologist if he or she reported symptoms suggestive of HF or if signs suggestive of HF were detected during the study visit, and information was requested from the participant's primary care provider, physician, and cardiologist. All cases of symptomatic HF were adjudicated by two HF specialists, with differences in opinion adjudicated by a third HF specialist, according to European Society of Cardiology (ESC) criteria of 2012.[11] Excluding participants who developed symptomatic HF before Visit 2, 3190 participants had echocardiography at a median of 1.3 [interquartile range (IQR): 0.5, 1.9] years after enrolment (*Figure S1*). Diagnosis of atrial fibrillation (AF) was based on an electrocardiogram performed at the time of echocardiography (Visit 2), and other documentation from the participant's primary care provider, physician, and/or cardiologist.

Clinical assessment

Details of collection of baseline data are described elsewhere.[5,8–10] Clinical history and medication were updated and height, weight, waist circumference, and blood pressure (BP) and NT-proBNP level were measured at the time of echocardiography (Visit 2).

Echocardiographic assessment

Details of echocardiography, performed according to the American Society of Echocardiography and European Association of Cardiovascular Imaging (ASE/EACVI) guidelines,[12–15] have been previously reported.[5]

Definitions of structural, systolic, and diastolic abnormalities

Structural, systolic, and diastolic abnormalities were defined according to the age-specific criteria of the ARIC study, which derived 95th percentile limits from a healthy subgroup aged 67–91 years,[3] similar in age to SCREEN-HF participants, in contrast to ASE/EACVI guideline normal ranges based on populations with mean ages ranging from 37 to 50 years.[13]

ARIC criteria for structural abnormality were at least one of LV end-diastolic volume indexed to body surface area (LVEDVI) > 60.2 mL/m^2 (men) or >51.9 mL/m^2 (women), or LV mass/height$^{2.7}$ > 45 g/m$^{2.7}$ (men) or >41.5 g/m$^{2.7}$ (women), linear method, or moderate or greater stenosis or regurgitation of the aortic or mitral valve. ARIC criteria for systolic abnormality were at least one of LV ejection fraction < 59% (men) or <57.4% (women), or wall motion abnormality. ARIC criteria for diastolic abnormality were at least one of septal e′ < 4.3 cm/s (men) or <4.1 cm/s (women), or septal E/e′ ratio > 14.8 (men) or >17.4 (women), or left atrial volume indexed to body surface area (LAVI) > 34.2 mL/m^2 (men) or >32.4 mL/m^2 (women).[3]

Table 1 Characteristics of SCREEN-HF participants at Visit 2, when echocardiography was performed

Characteristic	Men $n = 1762$	Women $n = 1428$
Age (years)	71 (67, 77)	71 (67, 77)
Bupa member	1744 (99%)	1413 (99%)
Systolic BP (mmHg)	140 (130, 150)	137 (126, 150)
Diastolic BP (mmHg)	77 (70, 83)	75 (69, 83)
Pulse pressure (mmHg)	63 (55, 72)	62 (53, 73)
Heart rate (b.p.m.)	67 (60, 75)	70 (63, 78)
BMI (kg/m^2)	28 (26, 31)	28 (25, 32)
Waist circumference (cm)	101 (95, 109)	92 (84, 102)
CVD risk factors		
Hypertension	1574 (89%)	1338 (94%)
Diabetes	344 (20%)	216 (15%)
Obesity (BMI $\geq$ 30 kg/m^2)	591 (34%)	530 (37%)
Overweight (25 $>$ BMI $<$ 30 kg/m^2)	863 (49%)	554 (39%)
eGFR $<$ 60 mL/min/1.73 m^2	329 (19%)	290 (20%)
Previous myocardial infarction	259 (14.7%)	74 (5.2%)
Coronary revascularization	410 (23.3%)	100 (7.0%)
Total ischaemic heart disease	540 (31%)	204 (14%)
Previous stroke or TIA	214 (12%)	149 (10%)
Peripheral vascular disease	91 (5.2%)	30 (2.1%)
Cardiovascular disease	713 (40%)	338 (24%)
Atrial fibrillation	246 (14.0%)	136 (9.5%)
Pacemaker	55 (3.1%)	21 (1.5%)
Obstructive sleep apnoea	183 (10.4%)	51 (3.6%)
Physical inactivity	1104 (63%)	994 (71%)
Tobacco use		
Current smoker	59 (3.3%)	40 (2.8%)
Former smoker	966 (55%)	491 (34%)
Non-smoker	737 (42%)	896 (63%)
Alcohol $>$2 drinks/day	520 (29.5%)	126 (8.8%)
Medication use		
β-Blocker	408 (23%)	336 (24%)
ACE inhibitor	597 (34%)	386 (27%)
ARB	815 (46%)	761 (53%)
ACE inhibitor or ARB	1351 (77%)	1107 (78%)
CCB	555 (31%)	425 (30%)
Statin therapy	1021 (58%)	736 (52%)
Thiazide diuretic	525 (30%)	514 (36%)
Loop diuretic	57 (3.2%)	66 (4.6%)
Mineralocorticoid antagonist	12 (0.7%)	13 (0.9%)
Digoxin therapy	63 (3.6%)	30 (2.1%)
Aspirin therapy	879 (50%)	543 (38%)
Clopidogrel therapy	139 (7.9%)	78 (5.4%)
Warfarin therapy	138 (7.8%)	58 (4.1%)
NSAID therapy	159 (9.0%)	171 (12.0%)
Insulin therapy	56 (3.2%)	39 (2.7%)
Oral anti-diabetic medication	249 (14%)	147 (10%)
Nitrate therapy	89 (5.1%)	68 (4.8%)
Biochemistry and haematology		
NT-proBNP (pmol/L)	10.7 (5.3, 24.1)	13.8 (7.5, 27.3)
Total cholesterol (mmol/L)	4.5 (3.8, 5.2)	5.2 (4.5, 5.9)
Triglyceride (mmol/L)	1.5 (1.1, 2.2)	1.5 (1.1, 2.0)
HDL cholesterol (mmol/L)	1.1 (0.9, 1.4)	1.4 (1.2, 1.7)
HbA1c (%)	5.6 (5.4, 5.9)	5.6 (5.4, 5.8)
Haemoglobin (g/dL)	14.6 (13.8, 15.3)	13.3 (12.7, 14.0)
WCC ($\times$ 10^9/L)	7.0 (6.1, 8.2)	7.1 (6.1, 8.3)
Platelets ($\times$ 10^9/L)	212 (182, 246)	249 (215, 288)
eGFR (mL/min/1.73 m^2)	76 (64, 86)	75 (63, 86)
Echocardiographic abnormality		
No abnormality	374 (21.2%)	354 (24.8%)
Isolated structural abnormality	120 (6.8%)	220 (15.4%)
Isolated systolic abnormality	231 (13.1%)	85 (6.0%)
Isolated diastolic abnormality	238 (13.5%)	236 (16.5%)
Combined structural and systolic abnormalities	120 (6.8%)	67 (4.7%)

(*Continues*)

Table 1 (continued)

Characteristic	Men $n = 1762$	Women $n = 1428$
Combined structural and diastolic abnormalities	211 (12.0%)	270 (18.9%)
Combined systolic and diastolic abnormalities	204 (11.6%)	78 (5.5%)
Combined structural, systolic, and diastolic abnormalities	264 (15.0%)	118 (8.3%)

ACE, angiotensin-converting enzyme; ARB, angiotensin II type 1 receptor blocker; BMI, body mass index; BP, blood pressure; CCB, calcium channel blocker; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation[19]; Hb, haemoglobin; HDL, high-density lipoprotein; NSAID, non-steroidal anti-inflammatory drug; NT-proBNP, amino-terminal pro-B-type natriuretic peptide; TIA, transient ischaemic attack; WCC, white cell count.
Summary statistics are median (interquartile range) or *n* (%). 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. Physical activity was assessed using the New York Heart Association questionnaire, and physical inactivity refers to participants who did not walk for, on average, ≥30 min/day and/or participate in, on average, ≥10 min/day of more vigorous exercise, including housework. Alcohol >2 drinks/day refers to consumption of more than 2 standard drinks on any day. Data for cardiovascular disease, diabetes, obstructive sleep apnoea, smoking, alcohol intake, and drug therapy were from self-report.
Heart rate data from 1759 men and 1428 women, BMI from 1761 men and 1428 women, NT-proBNP levels from 1706 men and 1354 women, haemoglobin and WCC from 1761 men and 1428 women, platelet counts from 1759 men and 1424 women, total cholesterol, triglyceride, and HDL cholesterol from 1706 men and 1352 women, HbA1c from 1628 men and 1283 women, and physical activity data from 1689 men and 1326 women.
Whereas data for eGFR, haemoglobin, WCC, and platelet count were from Visit 1, NT-proBNP, HbA1c, and lipid measurements were from Visit 2.

Statistical analysis

Of 3190 participants with echocardiographic data, risk factor data were missing for body mass index (BMI; *n* = 1), heart rate (*n* = 3), physical inactivity (*n* = 51), NT-proBNP (*n* = 130), total cholesterol, triglycerides (TG) and high-density lipoprotein (HDL) cholesterol (*n* = 132), HbA1c (*n* = 279), haemoglobin and white cell count (WCC; *n* = 1), and platelet count (*n* = 7). Multiple imputation was performed using the expectation–maximization with bootstrapping algorithm to produce five imputed datasets.[16] Logistic regression analyses of the five multiple-imputed datasets, with 'no echocardiographic abnormality' as the reference group, were combined, and confidence intervals (CIs) obtained from Rubin's degrees-of-freedom estimate.[17] Multivariable logistic regression analyses were performed using backward stepwise regression, and post hoc analysis of interactions between multivariable risk factors was performed by adding each two-way interaction separately to the multivariable model. Sensitivity analysis was performed by comparing analyses of multiple-imputed datasets with analyses restricted to complete cases.[18] The haemoglobin, WCC, and platelet count cut-points were the lower (for haemoglobin and platelet count) and upper (for WCC) limits of the normal range for the laboratory: low haemoglobin (<13 g/L, male; <12 g/L, female), high WCC (>11 × 10^9/L), and low platelet count (<150 × 10^9/L). Discrimination of structural, systolic, and diastolic abnormalities and their combination from no abnormality by serum NT-proBNP level was assessed by receiver-operating characteristic (ROC) curve analysis for individuals with NT-proBNP measurement. Continuous variables are presented as median (IQR) and compared with Mann–Whitney *U* test. Categorical variables are presented as *n* (%) and compared with χ^2 test. Statistical significance was interpreted as a two-tailed *P* value < 0.05. Analyses were conducted using Statview 5.0.1 (SAS Institute, Cary, NC, USA) and R Version 1.4.1103.

Results

Baseline clinical characteristics

Participant characteristics are shown in *Table 1*. The 3190 participants had a median age of 71 (IQR: 67, 77) years at the time of echocardiography, 55% were male, 91% had hypertension, 18% had diabetes, 35% were obese (BMI $\geq$ 30 kg/m^2), 44% were overweight (25 $<$ BMI $<$ 30 kg/m^2), 19% had an estimated glomerular filtration rate (eGFR) $<$ 60 mL/min/1.73 m^2, 10% had previous MI, 23% had a history of ischaemic heart disease, and 12% had AF. Participants were enrolled before direct acting anticoagulant therapies for AF were routine; thus, warfarin was prescribed to prevent thromboembolic events in AF.

Of the 3190 participants, 728 (23%) had no echocardiographic abnormality, 340 (11%) had isolated structural abnormality, 316 (10%) had isolated systolic abnormality, 474 (15.5%) had isolated diastolic abnormality, 187 (6%) had combined structural and systolic abnormalities, 481 (15%) had combined structural and diastolic abnormalities, 282 (9%) had combined systolic and diastolic abnormalities, and 382 (12%) had combined structural, systolic, and diastolic abnormalities.[5]

Univariate and multivariable analyses of risk factors for isolated structural, systolic, or diastolic abnormality, com-

Table 2 Summary of statistically significant univariate risk factors ($P < 0.05$) for echocardiographic abnormalities that predict symptomatic heart failure according to ARIC criteria, determined by unadjusted logistic regression of multiple-imputed data

Risk factor	Structural abnormality alone	Systolic abnormality alone	Diastolic abnormality alone	Structural and systolic abnormalities	Structural and diastolic abnormalities	Systolic and diastolic abnormalities	Structural, systolic, and diastolic abnormalities
Age (per decade)			1.87 (1.54, 2.26)		1.44 (1.19, 1.73)	2.38 (1.90, 2.98)	1.91 (1.56, 2.34)
Male gender	0.52 (0.40, 0.67)	2.57 (1.93, 3.43)		1.70 (1.22, 2.36)	0.74 (0.59, 0.93)	2.48 (1.84, 3.34)	2.12 (1.63, 2.75)
Hypertension		0.55 (0.36, 0.84)				0.51 (0.33, 0.78)	
Diabetes			0.72 (0.52, 1.00)				
Ischaemic heart disease		1.49 (1.10, 2.03)				2.00 (1.47, 2.72)	1.84 (1.38, 2.44)
Myocardial infarction		1.79 (1.16, 2.77)		2.15 (1.31, 3.52)		2.81 (1.86, 4.25)	2.37 (1.60, 3.51)
Atrial fibrillation	0.43 (0.22, 0.84)		2.25 (1.54, 3.29)		2.00 (1.36, 2.93)	3.82 (2.57, 5.67)	3.50 (2.41, 5.08)
BMI quintile	1.38 (1.25, 1.52)		0.83 (0.77, 0.91)	1.16 (1.03, 1.30)	1.12 (1.03, 1.22)		1.11 (1.02, 1.21)
Waist circumference quintile		1.17 (1.07, 1.29)	0.86 (0.80, 0.94)	1.15 (1.03, 1.29)			1.16 (1.06, 1.26)
Systolic BP quintile			1.18 (1.08, 1.28)		1.16 (1.07, 1.26)	1.14 (1.03, 1.26)	1.22 (1.11, 1.33)
Diastolic BP quintile		1.20 (1.09, 1.32)		1.15 (1.03, 1.29)		1.11 (1.01, 1.23)	1.10 (1.01, 1.20)
Pulse pressure quintile		0.86 (0.78, 0.95)	1.21 (1.11, 1.32)		1.23 (1.14, 1.34)		1.19 (1.09, 1.30)
Heart rate quintile	0.89 (0.81, 0.97)		0.76 (0.70, 0.83)		0.70 (0.64, 0.76)	0.79 (0.72, 0.87)	0.76 (0.69, 0.83)
Obstructive sleep apnoea	0.56 (0.32, 0.96)				0.60 (0.38, 0.97)		
Current or former smoker		1.46 (1.12, 1.90)		1.55 (1.12, 2.15)		1.42 (1.07, 1.87)	1.36 (1.06, 1.74)
Alcohol >2 glasses/day		1.74 (1.26, 2.38)		1.73 (1.18, 2.53)			1.46 (1.07, 1.98)
Physical inactivity							1.51 (1.15, 1.99)
NT-proBNP quintile			1.54 (1.40, 1.69)	1.23 (1.08, 1.40)	1.59 (1.44, 1.76)	2.06 (1.82, 2.34)	1.98 (1.77, 2.20)
Total cholesterol quintile		0.88 (0.80, 0.97)		0.89 (0.79, 1.00)		0.79 (0.71, 0.87)	0.89 (0.82, 0.97)
Triglyceride quintile			0.82 (0.76, 0.90)		0.82 (0.76, 0.89)	0.87 (0.79, 0.96)	0.92 (0.84, 1.01)
HDL cholesterol quintile		0.86 (0.78, 0.95)	1.20 (1.10, 1.30)		1.13 (1.04, 1.23)		
Low haemoglobin			1.60 (1.07, 2.40)		2.14 (1.46, 3.13)	1.72 (1.09, 2.73)	1.56 (1.02, 2.40)
Low platelet count				2.20 (1.07, 4.53)			2.15 (1.19, 3.89)
ACEI therapy	0.70 (0.52, 0.94)						
ARB therapy	1.31 (1.01, 1.70)					0.64 (0.49, 0.85)	
ACEI and/or ARB therapy		0.63 (0.46, 0.86)				0.51 (0.37, 0.70)	0.57 (0.43, 0.76)
CCB therapy		0.70 (0.51, 0.96)			1.39 (1.09, 1.79)		1.33 (1.02, 1.74)
β-Blocker therapy			1.75 (1.32, 2.33)		1.98 (1.49, 2.61)	2.40 (1.75, 3.30)	2.43 (1.82, 3.25)
Thiazide diuretic therapy		0.72 (0.54, 0.96)				0.67 (0.50, 0.91)	
Mineralocorticoid antagonist therapy						5.25 (1.30, 21.15)	
Statin therapy						1.33 (1.01, 1.76)	
Clopidogrel therapy			1.58 (1.00, 2.51)			1.95 (1.17, 3.23)	

(*Continues*)

Table 2 (continued)

Risk factor	Structural abnormality alone	Systolic abnormality alone	Diastolic abnormality alone	Structural and systolic abnormalities	Structural and diastolic abnormalities	Systolic and diastolic abnormalities	Structural, systolic, and diastolic abnormalities
Warfarin therapy		2.19 (1.02, 4.71)	2.96 (1.53, 5.73)		4.37 (2.34, 8.17)	9.18 (4.93, 17.07)	8.04 (4.39, 14.71)
Digoxin therapy			3.37 (1.36, 8.32)		3.54 (1.45, 8.68)	9.58 (4.08, 22.50)	7.52 (3.23, 17.50)
Nitrate therapy						1.87 (1.05, 3.33)	1.84 (1.08, 3.13)
NSAID therapy	1.76 (1.17, 2.66)			1.95 (1.20, 3.18)	1.68 (1.15, 2.45)		1.70 (1.14, 2.54)

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin type 1 receptor blocker; BMI, body mass index; BP, blood pressure; CCB, calcium channel blocker; HDL, high-density lipoprotein; NSAID, non-steroidal anti-inflammatory drug; NT-proBNP, amino-terminal pro-B-type natriuretic peptide.
Data shown as odds ratios (95% confidence interval); red shading indicates odds ratios > 1, and blue shading indicates odds ratios < 1. Low haemoglobin: <13 g/L (male); <12 g/L (female), low platelet count: $<150 \times 10^9$/L.

bined structural and systolic abnormalities, combined structural and diastolic abnormalities, combined systolic and diastolic abnormalities, and combined structural, systolic, and diastolic abnormalities are shown in *Tables S1–S7*. Summaries of statistically significant univariate risk factors are shown in *Table 2*, and multivariable risk factors are shown in *Figures 2* and *3*.

Risk factors for structural abnormality

Increased BMI and non-steroidal anti-inflammatory drug (NSAID) therapy were risk factors associated with isolated structural abnormality, and also for combined structural and systolic, and combined structural and diastolic abnormalities in multivariable analysis (*Figures 2* and *3*). In addition, alcohol intake was a multivariable risk factor for isolated structural abnormality, whereas male gender, increased heart rate, AF, angiotensin-converting enzyme inhibitor (ACEI) therapy, and obstructive sleep apnoea (OSA) were associated with lower risk for isolated structural abnormality. Moreover, increased waist circumference was associated with lower risk of isolated structural abnormality, and also of combined structural and diastolic abnormalities in multivariable, but not univariate analyses.

Risk factors for systolic abnormality

In contrast to isolated structural and isolated diastolic abnormalities, male gender was associated with isolated systolic abnormality, and also with combined structural and systolic, and combined systolic and diastolic abnormalities in multivariable analysis (*Figures 2* and *3*). Increased systolic BP and physical inactivity were also multivariable risk factors for isolated systolic abnormality, whereas increased pulse pressure, and ACEI and/or angiotensin type 1 receptor blocker (ARB) and calcium channel blocker (CCB) therapies were associated with lower risk of isolated systolic abnormality. Smoking was a risk factor for isolated systolic abnormality, and also combined structural and systolic abnormalities. Ischaemic heart disease, MI, increased diastolic BP, alcohol intake, and warfarin therapy were risk factors for isolated systolic abnormality, whereas increased total cholesterol, increased HDL cholesterol, and thiazide diuretic therapy were associated with lower risk of isolated systolic abnormality in univariate, but not multivariable analyses (*Table 2*, *Figure 2*).

Risk factors for diastolic abnormality

In contrast to isolated structural and isolated systolic abnormality, age, but not gender, was a risk factor for isolated diastolic abnormality, together with increased pulse pressure and increased diastolic BP, and increased age and diastolic

Figure 2 Forest plots showing odds ratios (95% confidence interval) for statistically significant risk factors for asymptomatic echocardiographic abnormalities that predict symptomatic heart failure according to ARIC criteria, determined by multivariable logistic regression analysis of multiple-imputed data. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin type 1 receptor blocker; BMI, body mass index; BP, blood pressure; CCB, calcium channel blocker; eGFR, estimated glomerular filtration rate calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation[19]; NSAID, non-steroidal anti-inflammatory drug; NT-proBNP, amino-terminal pro-B-type natriuretic peptide. Low haemoglobin: <13 g/L (male); <12 g/L (female).

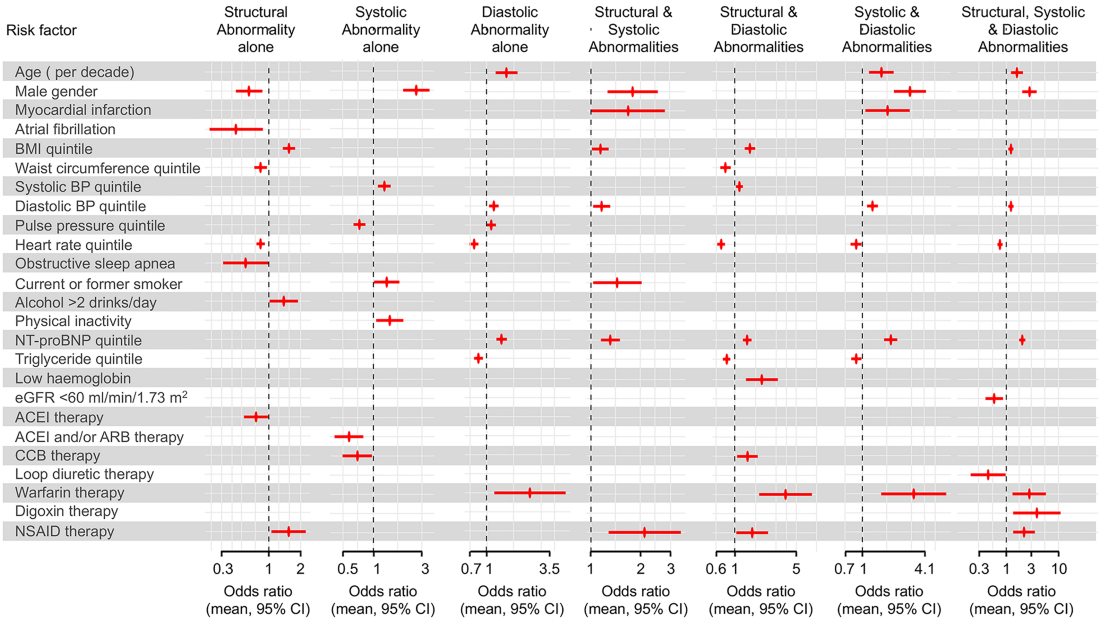
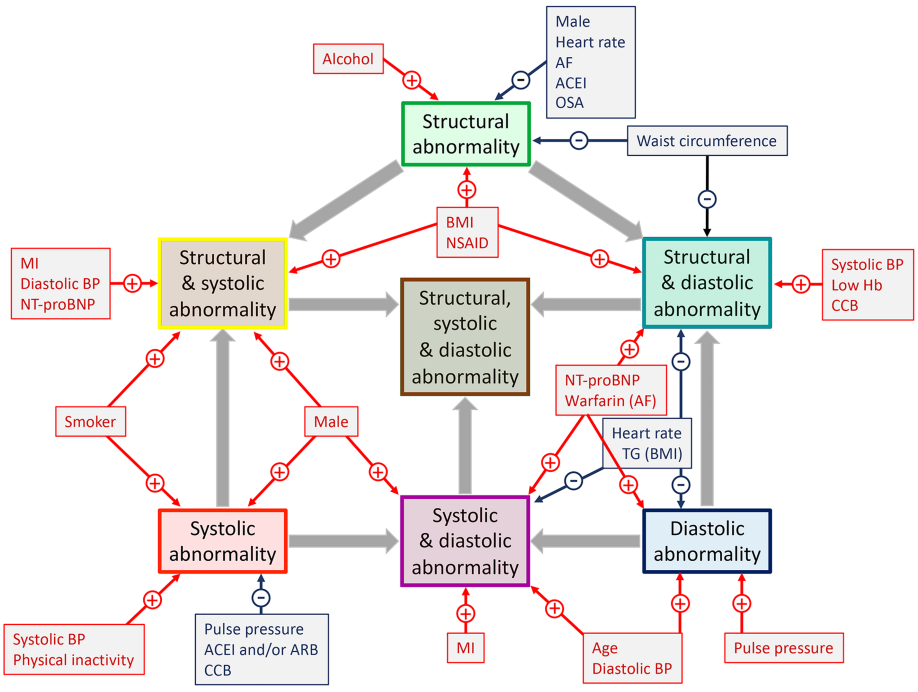


Figure 3 Summary of statistically significant multivariable risk factors for asymptomatic echocardiographic abnormalities that predict incident symptomatic HF. ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin type 1 receptor blocker; BMI, body mass index; BP, blood pressure; CCB, calcium channel blocker; Hb, haemoglobin; MI, myocardial infarction; NSAID, non-steroidal anti-inflammatory drug; NT-proBNP, amino-terminal pro-B-type natriuretic peptide; OSA, obstructive sleep apnoea; TG, triglyceride.



BP were also risk factors for combined systolic and diastolic abnormalities in multivariable analyses (*Figures 2* and *3*). Increased NT-proBNP level and warfarin therapy were also risk factors, whereas increased heart rate and increased TG level were associated with lower risk of isolated diastolic abnormality, in addition to combined structural and diastolic, and combined systolic and diastolic abnormalities in multivariable analysis. AF, increased systolic BP, increased HDL cholesterol, low haemoglobin, and β-blocker, clopidogrel, and digoxin therapies were risk factors for isolated diastolic abnormality, whereas diabetes, increased BMI, and increased waist circumference were associated with lower risk of isolated diastolic abnormality in univariate but not multivariable analyses (*Table 2*, *Figure 2*). The associations of AF and digoxin therapy with increased risk of isolated diastolic abnormality in univariate analyses were in agreement with warfarin therapy as a multivariate risk factor. Similarly, the association of β-blocker therapy with increased risk of isolated diastolic abnormality in univariate analysis was in agreement with the association of increased heart rate with lower risk of isolated diastolic abnormality in multivariable analysis. Moreover, the associations of diabetes, increased BMI, and increased waist circumference with lower risk of isolated diastolic abnormality in univariate analyses were in agreement with the association of increased TG level with lower risk for diastolic abnormality in multivariable analysis (*Table 2*, *Figure 2*).

Receiver-operating characteristic curve analysis confirmed prediction of isolated diastolic abnormality and its combination with structural or systolic abnormality by NT-proBNP, whereas NT-proBNP level did not predict isolated structural or systolic abnormality (*Figure S2*).

Heart rate and β-blocker therapy

We examined whether the association of increased heart rate with lower risk of structural and diastolic abnormalities was independent of β-blocker therapy. Participants receiving β-blocker therapy had lower heart rates (63.3 ± 0.4 b.p.m., mean ± SEM, n = 744) than participants not receiving β-blocker therapy (71.3 ± 0.2 b.p.m., n = 2446, $P < 0.0001$). Among participants not receiving β-blocker therapy, heart rate did not differ between participants receiving (71.8 ± 0.4 b.p.m., n = 757) and not receiving CCB therapy (71.1 ± 0.3 b.p.m., n = 1689, P = 0.16). Among participants not receiving β-blocker therapy, increased heart rate was associated with lower risk of isolated structural abnormality [odds ratio (OR): 0.85; 95% CI: 0.76, 0.95; P = 0.0033] and isolated diastolic abnormality (OR: 0.75; 95% CI: 0.68, 0.83; $P < 0.0001$), and also lower risk of combined structural and diastolic abnormalities (OR: 0.69; 95% CI: 0.62, 0.77; $P < 0.0001$), combined systolic and diastolic abnormalities (OR: 0.74; 95% CI: 0.65, 0.83; $P < 0.0001$), and combined structural, systolic, and diastolic abnormalities (OR: 0.74; 95% CI: 0.66, 0.83; $P < 0.0001$), but was not associated with risk of combined structural and systolic abnormalities (OR: 0.91; 95% CI: 0.80, 1.04; P = 0.18) in univariate analyses. In contrast, increased heart rate was a risk factor for isolated systolic abnormality (OR: 1.13; 95% CI: 1.01, 1.27; P = 0.039) in participants not receiving β-blocker therapy in univariate analysis.

Sensitivity analysis

Multivariable analyses of either multiple-imputed datasets or complete cases identified similar or identical multivariable associations of risk factors with isolated and combined structural, systolic, or diastolic abnormalities (*Tables S8–S14*).

Interaction between multivariable risk factors for isolated structural abnormality

Among the nine multivariable risk factors associated with isolated structural abnormality (*Table S1*, *Figures 2* and *3*), there were three interactions (*Table S15*): between BMI and heart rate, between waist circumference and heart rate, and between ACEI and NSAID therapies. Whereas the association of BMI with isolated structural abnormality was not modified by heart rate, the association of heart rate with lower risk of isolated structural abnormality was not evident at lower BMI quintiles. Moreover, waist circumference and heart rate modified the association of each other with isolated structural abnormality, with the association of waist circumference with lower risk of isolated structural abnormality not evident at lower heart rate, and the association of heart rate with lower risk of isolated structural abnormality not evident at lower waist circumference. NSAID therapy was associated with isolated structural abnormality in the presence (OR: 2.95; 95% CI: 1.39–6.30) but not in the absence (OR: 1.22; 95% CI: 0.71–2.10) of ACEI therapy, whereas ACEI therapy was associated with lower risk of isolated structural abnormality in the absence (OR: 0.64; 95% CI: 0.45–0.89) but not in the presence (OR: 1.44; 95% CI: 0.58–3.65) of NSAID therapy. Thus, the association of NSAID therapy with isolated structural abnormality was only evident in participants receiving ACEI therapy, and NSAID therapy blocked the association of ACEI therapy with lower risk of isolated structural abnormality.

Interaction between multivariable risk factors for isolated systolic abnormality

Among the seven multivariable risk factors associated with isolated systolic abnormality (*Table S2*, *Figures 2* and *3*),

there were two interactions (*Table S15*): between physical inactivity and smoking, and between physical inactivity and CCB therapy. Smoking was associated with isolated systolic abnormality in participants who were (OR: 1.74; 95% CI: 1.23–2.45) but not in those who were not (OR: 0.87; 95% CI: 0.52–1.43) physically inactive. Conversely, physical inactivity was associated with isolated systolic abnormality in participants who were (OR: 2.04; 95% CI: 1.33–3.12) but not in those who were not (OR: 1.04; 95% CI: 0.67–1.60) smokers. Thus, smoking and physical inactivity amplified the association of the other with isolated systolic abnormality. Moreover, CCB therapy was associated with lower risk of isolated systolic abnormality in participants who were not (OR: 0.38; 95% CI: 0.19–0.76) but not in those who were (OR 0.87; 95% CI: 0.59–1.29) physically inactive. Conversely, physical inactivity was associated with isolated systolic abnormality in participants who were (OR: 2.92; 95% CI: 1.41–6.06) but not in those who were not (OR 0.1.24; 95% CI: 0.89–1.74) receiving CCB therapy. Thus, physical inactivity blunted the association of CCB therapy with lower risk of isolated systolic abnormality, whereas CCB therapy amplified the association of physical inactivity with isolated systolic abnormality.

Interaction between multivariable risk factors for isolated diastolic abnormality

Among the seven multivariable risk factors associated with isolated diastolic abnormality (*Table S3*, *Figures 2* and *3*), there were four interactions (*Table S15*): between age and NT-proBNP, between age and pulse pressure, between heart rate and NT-proBNP, and between pulse pressure and warfarin therapy. The association of age with isolated diastolic abnormality was attenuated at lower NT-proBNP levels, whereas the association of NT-proBNP with isolated diastolic abnormality was attenuated at lower age. Moreover, the association of age with isolated diastolic abnormality was attenuated at lower pulse pressures, whereas the association of pulse pressure with isolated diastolic abnormality was attenuated at lower age. Furthermore, the association of NT-proBNP with isolated diastolic abnormality was attenuated at lower heart rates, whereas the association of heart rate with lower risk of isolated diastolic abnormality was not evident in participants with intermediate NT-proBNP levels (quintiles 3 and 4). The association of pulse pressure with isolated diastolic abnormality was evident in participants taking warfarin (OR: 2.22; 95% CI: 1.06–4.67), but not in participants not taking warfarin (OR: 1.08; 95% CI: 0.99–1.19), whereas the association of warfarin therapy with isolated diastolic abnormality was only evident in participants with mid-range pulse pressures.

Interaction between multivariable risk factors for combined structural and systolic abnormalities

Among the seven multivariable risk factors associated with combined structural and systolic abnormalities (*Table S4*, *Figures 2* and *3*), there was one interaction (*Table S15*): between MI and NT-proBNP. Whereas the association of NT-proBNP with combined structural and systolic abnormalities was similar for participants with (OR: 2.08; 95% CI: 1.36–3.19) and without MI (OR: 1.25; 95% CI: 1.08–1.44), the association of MI with combined structural and systolic abnormalities, which was of borderline statistical significance (P = 0.050; *Table S4*), was not statistically significant for individual NT-proBNP quintiles.

Interactions between multivariable risk factors for combined structural and diastolic abnormalities

Among the 10 multivariable risk factors associated with combined structural and diastolic abnormalities (*Table S5*, *Figures 2* and *3*), there were three interactions (*Table S15*): between waist circumference and NT-proBNP level, between heart rate and warfarin therapy, and between TG level and low haemoglobin. The association of NT-proBNP level with combined structural and diastolic abnormalities was attenuated at lower waist circumference, whereas the association of waist circumference with lower risk of combined structural and diastolic abnormalities was not evident at higher NT-proBNP levels. Moreover, the association of heart rate with lower risk of combined structural and diastolic abnormalities was similar for participants receiving (OR: 0.39; 95% CI: 0.16–0.97) and not receiving (OR: 0.71; 95% CI: 0.64–0.78) warfarin therapy, whereas the association of warfarin therapy with combined structural and diastolic abnormalities was attenuated at higher heart rate. Furthermore, the association of TG level with lower risk of combined structural and diastolic abnormalities was similar for participants with (OR: 0.60; 95% CI: 0.44–0.83) and without (OR: 0.83; 95% CI: 0.75–0.92) low haemoglobin level, whereas the association of low haemoglobin level with combined structural and diastolic abnormalities was attenuated at higher TG levels.

Interactions between multivariable risk factors for combined systolic and diastolic abnormalities

Among the eight multivariable risk factors associated with combined systolic and diastolic abnormalities (*Table S6*, *Figures 2* and *3*), there were two interactions (*Table S15*): between age and NT-proBNP level, and between MI and diastolic BP. As described for isolated diastolic abnormality, the association of age with combined systolic and diastolic

abnormalities was attenuated at lower NT-proBNP levels; however, the association of NT-proBNP with combined systolic and diastolic abnormalities was not modified by age. Moreover, the association of diastolic BP with combined systolic and diastolic abnormalities was evident in participants without MI (OR: 1.36; 95% CI: 1.19–1.55), but not in participants with MI (OR: 0.82; 95% CI: 0.53–1.27), whereas the association of MI with combined systolic and diastolic abnormalities was attenuated at higher diastolic BP.

Interactions between multivariable risk factors for combined structural, systolic, and diastolic abnormalities

Among the 11 multivariable risk factors associated with combined structural, systolic, and diastolic abnormalities (*Table S7*, *Figures 2* and *3*), there were four interactions (*Table S15*): between age and NT-proBNP, between BMI and heart rate, between BMI and NT-proBNP, and between eGFR and loop diuretic therapy. As described for isolated diastolic abnormality and combined systolic and diastolic abnormalities, the association of age with combined structural, systolic, and diastolic abnormalities was attenuated at lower NT-proBNP levels; however, as described for combined systolic and diastolic abnormalities, the association of NT-proBNP with combined structural, systolic, and diastolic abnormalities was not modified by age. Moreover, the association of BMI with combined structural, systolic, and diastolic abnormalities was attenuated at higher heart rate, whereas the association of heart rate with lower risk of combined structural, systolic, and diastolic abnormalities was not evident at lower BMI. Furthermore, the association of BMI with combined structural, systolic, and diastolic abnormalities was attenuated at higher NT-proBNP levels, whereas the association of NT-proBNP level with combined structural, systolic, and diastolic abnormalities was not modified by BMI. eGFR $<$ 60 mL/min/1.73 m^2 was associated with lower risk of combined structural, systolic, and diastolic abnormalities in participants not receiving loop diuretic therapy (OR: 0.55; 95% CI: 0.36–0.83), but not in those receiving this therapy (OR: 1.90; 95% CI: 0.32–11.41), whereas loop diuretic therapy was associated with lower risk of combined structural, systolic, and diastolic abnormalities in participants with eGFR $\geq$ 60 mL/min/1.73 m^2 (OR: 0.26; 95% CI 0.10–0.70) but not in those with eGFR $<$ 60 mL/min/1.73 m^2 (OR: 0.83; 95% CI: 0019–3.67).

Discussion

Although risk factors for symptomatic HF are well described,[7,8] early mechanisms of HF pathogenesis that may differentially impact cardiac structure and function are yet to be fully elucidated. We therefore investigated risk factors associated with isolated and combined asymptomatic echocardiographic structural, systolic, and diastolic abnormalities that predict symptomatic HF to gain insight into early mechanisms of the pathogenesis of symptomatic HF. We were particularly interested in identifying previously unrecognized risk factors associated with asymptomatic isolated structural, systolic, or diastolic abnormalities that may represent early stages of HF pathogenesis. Our data illustrate multiple trajectories of evolution of symptomatic HF that may develop from asymptomatic isolated structural, systolic, or diastolic abnormality, each with its own risk factors. Our findings also raise new questions about the mechanisms of association of risk factors with these asymptomatic echocardiographic abnormalities. Improved understanding of the pathogenesis of asymptomatic echocardiographic abnormalities that predict symptomatic HF may assist in the design of strategies to prevent HF.

The focus of this study was the evolution of symptomatic HF whereby risk factors precede asymptomatic echocardiographic structural, systolic, and diastolic abnormalities that precede symptomatic HF (*Figure 1*). We chose age-specific ARIC criteria for structural, systolic, and diastolic abnormalities derived from 95th percentile limits from a healthy subgroup aged 67–91 years,[3] similar in age to SCREEN-HF participants, and we previously showed that structural, systolic, and diastolic abnormalities defined by ARIC criteria provided superior prediction of HF than ASE/EACVI criteria.[5] Recent guidelines describe the potential for measurement of global longitudinal strain to improve characterization of the LV.[20] However, ARIC longitudinal strain criteria did not identify additional participants who developed symptomatic HF, in comparison with ARIC Stage B HF criteria, in the 1401 SCREEN-HF participants with global longitudinal strain measurement.[5] Alternative criteria for LV remodelling that predict composite endpoints have been described, but the risk factors for these alternative criteria remain to be identified.[21–23]

Age and gender

Age was a risk factor for isolated diastolic abnormality, but not for isolated structural or isolated systolic abnormality, suggesting that age-specific mechanisms did not contribute to isolated structural or isolated systolic abnormality. Moreover, male gender had opposite associations with isolated structural and systolic abnormalities, and gender was not associated with isolated diastolic abnormality. Male gender was associated with lower risk (female gender was a risk factor) of isolated structural abnormality, whereas male gender was a risk factor for systolic abnormality. The association of male gender with lower risk of isolated structural abnormality

was consistent with the higher cut-points for LVEDVI and LV mass/height$^{2.7}$ for men, in comparison with women, according to ARIC criteria.[3] Moreover, the multivariable association of male gender with systolic abnormality was consistent with the univariate associations of systolic abnormality with MI and ischaemic heart disease, together with smoking and alcohol intake, all of which were more prevalent in men than women.

Body mass index

Increased BMI, either alone or together with increased waist circumference and increased TG level, had opposite associations with structural and diastolic abnormalities, in that increased BMI was a risk factor for structural abnormality, whereas increased TG level (in association with increased BMI and increased waist circumference in univariate analyses) was associated with lower risk of diastolic abnormality. The association of increased BMI with structural abnormality was in agreement with the association of increased BMI with LV mass.[24–26] However, the associations of increased BMI, increased waist circumference, and increased TG level with lower risk of isolated diastolic abnormality were in contrast to the association of increased BMI with E/e′ ratio,[26,27] and the prediction of HFpEF by BMI.[7,8,28] The predominant echocardiographic criterion for diastolic abnormality in the SCREEN-HF cohort was increased LAVI in ~50% of participants, with reduced septal e′ and increased septal E/e′ ratio in $<$10% of participants.[5] We previously showed that BMI was associated with lower LAVI and lower e′ in univariate, but not multivariable, analyses of the SCREEN-HF cohort, whereas BMI was associated with higher E/e′ ratio in both univariate and multivariable analyses.[27] Thus, the associations of increased BMI, waist circumference, and TG level with a lower risk of diastolic abnormality were consistent with a lower risk of elevated LAVI and e′, although the mechanisms of these associations are unexplained.

Atrial fibrillation

Atrial fibrillation also had opposite associations with isolated structural and diastolic abnormalities, in that warfarin therapy was a multivariable risk factor, and warfarin and AF were univariate risk factors for diastolic abnormality, whereas AF was associated with lower risk of isolated structural abnormality. The associations of AF, warfarin, and digoxin therapies with diastolic abnormality in univariate analysis and with warfarin therapy in multivariable analysis in the SCREEN-HF cohort were in agreement with diastolic dysfunction sharing many risk factors with AF, including age, hypertension, obesity, and diabetes.[29] By causing left atrial dilatation, LV diastolic dysfunction may lead to AF.[30] However, the association of AF with lower risk of isolated structural abnormality is unexplained, given the association of AF with LV hypertrophy.[31,32] The predominant echocardiographic criterion for structural abnormality in the SCREEN-HF cohort was increased LV mass/height$^{2.7}$ in 43–50% of participants whereas 11–16% of participants had increased LVEDVI,[5] and we have shown that AF was associated with increased LV mass/height$^{2.7}$ in multivariable analysis of the whole SCREEN-HF cohort.[27] The association of AF with lower risk of isolated structural abnormality, but not combined structural and systolic or combined structural and diastolic abnormalities, was consistent with isolated structural abnormality occurring earlier in the evolution of symptomatic HF than combined abnormalities, as depicted in *Figure 1*.

Heart rate

Our finding that increased heart rate, independent of β-blocker therapy, was associated with lower risk of isolated structural and diastolic abnormalities was in agreement with our previous finding that increased heart rate was associated with a lower risk of incident total HF in the SCREEN-HF cohort in univariate, although not multivariable, analyses.[8] Moreover, Inoue *et al*. reported an inverse association between resting heart rate and the development of electrocardiographic LV hypertrophy.[33] However, we are unable to explain why these findings differ from the reported association of increased heart rate with increased CVD incidence, including HF incidence, and all-cause mortality.[7,34–36] The mechanisms by which increased heart rate was associated with a lower risk of isolated structural abnormality, and a lower risk of diastolic abnormality, despite the positive association between BP and diastolic abnormality, remain to be defined. Rather than heart rate impacting isolated structural and diastolic abnormalities, a slower heart rate may be a consequence of these abnormalities.

Blood pressure

Blood pressure was a risk factor for structural, systolic, and diastolic abnormalities, as shown by the lower risk of structural and systolic abnormalities with antihypertensive therapies, and the direct association of BP with systolic and diastolic abnormalities. These findings were in agreement with the well-established association of hypertension with LV hypertrophy and systolic and diastolic dysfunction.[37–39] Nevertheless, the contradictory associations of ACEI and ARB therapies with isolated structural abnormality in univariate analyses (*Table 2*) are difficult to explain and illustrate a limitation of our investigation of associations between risk factors and asymptomatic echocardiographic abnormalities

that predict symptomatic HF. The contradictory associations of ACEI and ARB therapies with isolated structural abnormality in univariate analyses may relate to the different pharmacology of ARB and ACEI therapies and may also relate to indication bias, in that clinicians may prescribe ACEI and ARB therapies according to different patient characteristics.

Amino-terminal pro-B-type natriuretic peptide

In contrast to the similar prediction of incident HFrEF, HFpEF, and valvular HF by NT-proBNP level in the SCREEN-HF cohort,[9] NT-proBNP level was a risk factor for only diastolic abnormality, and not for either structural or systolic abnormality. The association of NT-proBNP level with diastolic abnormality was consistent with increased LV filling pressures being a more potent stimulus to cardiomyocyte secretion of NT-proBNP than either structural or systolic abnormality,[40] and in agreement with the prediction of LV end-diastolic pressure by BNP.[41]

Non-steroidal anti-inflammatory drug therapy

The association of NSAID therapy with structural abnormality was in agreement with our finding that NSAID therapy was a risk factor for incident HFpEF in the SCREEN-HF cohort,[8] and the increased CVD risk and doubling of HF risk by NSAID therapy.[42,43] NSAID therapy increases BP[44]; however, the specific association of NSAID therapy with structural abnormality is unexplained and raises the possibility that NSAID therapy may impact cardiac structure by mechanisms additional to BP elevation.

Interactions

Our study revealed diverse interactions between multivariable risk factors for asymptomatic echocardiographic abnormalities that predict symptomatic HF. There were interactions between risk factors with co-linear associations with echocardiographic abnormality in the multivariable model, such as between age, NT-proBNP level, and isolated diastolic abnormality, and interactions between risk factors with opposite associations with echocardiographic abnormality, such as BMI, heart rate, and isolated structural abnormality. Additionally, there were interactions between therapies associated with echocardiographic abnormality. Each multivariable risk factor had an independent association with an echocardiographic abnormality and/or combination of abnormalities in the multivariable model without interaction terms. Moreover, our finding of an interaction between ACEI and NSAID therapies in their associations with isolated structural abnormality may have relevance to the mechanisms of pathogenesis of, and the impact of therapies on, structural abnormality.

Strengths and limitations of the study

Our study had a number of limitations. The SCREEN-HF cohort comprised volunteers (possible healthy volunteer bias) that, together with the inclusion criteria with respect to age $\geq$ 60 years and CVD risk factors, may be cause for caution in the generalization of our findings to the general community. However, the SCREEN-HF cohort was similar to the general Australian population aged $\geq$60 years with respect to the prevalence of hypertension,[45] diabetes,[46] obesity,[47] AF,[48] and CVD.[49] Our findings are therefore likely to be applicable to the general Australian community. Another limitation was the need to impute missing data, although sensitivity analysis showed that imputation did not compromise our findings.

Summary and conclusions

Our data illustrate multiple trajectories of the evolution of symptomatic HF that may develop from asymptomatic isolated structural, systolic, or diastolic abnormality, each with its own risk factors. Our findings also raise new questions about the mechanisms of association of risk factors with these asymptomatic echocardiographic abnormalities. With respect to HF prevention, whereas age and gender are not amenable to intervention, our data reinforce the association of BP with systolic and diastolic abnormalities, and of BMI and NSAID therapy with structural abnormality. Additionally, the associations of smoking and physical inactivity with systolic abnormality, and of AF with diastolic abnormality, indicate additional preventative measures. Moreover, the associations of AF and increased heart rate with lower risk of isolated structural abnormality, of increased heart rate, BMI, waist circumference, and TG level with lower risk of diastolic abnormality, and the specific association of NSAID therapy with structural abnormality, require further investigation to discover the mechanisms responsible for these associations. Improved understanding of the mechanisms responsible for these associations, and the pathogenesis of asymptomatic echocardiographic abnormalities that predict symptomatic HF, may assist in the design of HF prevention strategies.

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Conflict of interest

Bupa Australia was involved in study design, recruitment of participants, and funding, but was not involved in 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.

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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 and multivariable risk factors associated with isolated structural abnormality (*n* = 340) in relation to no abnormality (*n* = 728), defined according to ARIC criteria, determined by logistic regression analysis of multiple-imputed data.

Table S2. Univariate and multivariable risk factors associated with isolated systolic abnormality (*n* = 316) in relation to no abnormality (*n* = 728), defined according to ARIC criteria, determined by logistic regression analysis of multiple-imputed data.

Table S3. Univariate and multivariable risk factors associated with isolated diastolic abnormality (*n* = 474) in relation to no abnormality (*n* = 728), defined according to ARIC criteria, determined by logistic regression analysis of multiple-imputed data.

Table S4. Univariate and multivariable risk factors associated with combined structural and systolic abnormalities (*n* = 187) in relation to no abnormality (*n* = 728), defined according to ARIC criteria, determined by logistic regression analysis of multiple-imputed data.

Table S5. Univariate and multivariable risk factors associated with combined structural and diastolic abnormalities (*n* = 481) in relation to no abnormality (*n* = 728), defined according to ARIC criteria, determined by logistic regression analysis of multiple-imputed data.

Table S6. Univariate and multivariable risk factors associated with combined systolic and diastolic abnormalities (*n* = 282) in relation to no abnormality (*n* = 728), defined according to ARIC criteria, determined by logistic regression analysis of multiple-imputed data.

Table S7. Univariate and multivariable risk factors associated with combined structural, systolic and diastolic abnormalities (*n* = 382) in relation to no abnormality (*n* = 728), defined according to ARIC criteria, determined by logistic regression analysis of multiple-imputed data.

Table S8. Comparison of multivariable risk factors associated with isolated structural abnormality (*n* = 340) in relation to no abnormality (*n* = 728), defined according to ARIC criteria, determined by logistic regression analysis of complete cases and multiple-imputed data.

Table S9. Comparison of multivariable risk factors associated with isolated systolic abnormality (*n* = 316) in relation to no abnormality (*n* = 728), defined according to ARIC criteria, determined by logistic regression analysis of complete cases and multiple-imputed data.

Table S10. Comparison of multivariable risk factors associated with isolated diastolic abnormality (*n* = 474) in relation to no abnormality (*n* = 728), defined according to ARIC criteria, determined by logistic regression analysis of complete cases and multiple-imputed data.

Table S11. Comparison of multivariable risk factors associated with combined structural and systolic abnormalities (*n* = 187) in relation to no abnormality (*n* = 728), defined according to ARIC criteria, determined by logistic regression analysis of complete cases and multiple-imputed data.

Table S12. Comparison of multivariable risk factors associated with combined structural and diastolic abnormalities (*n* = 481) in relation to no abnormality (*n* = 728), defined according to ARIC criteria, determined by logistic regression analysis of complete cases and multiple-imputed data.

Table S13. Comparison of multivariable risk factors associated with combined systolic and diastolic abnormalities (*n* = 282) in relation to no abnormality (*n* = 728), de-

fined according to ARIC criteria, determined by logistic regression analysis of complete cases and multiple-imputed data.

Table S14. Comparison of multivariable risk factors associated with combined structural, systolic and diastolic abnormalities (n = 382) in relation to no abnormality (n = 728), defined according to ARIC criteria, determined by logistic regression analysis of complete cases and multiple-imputed data.

Table S15. Interactions between multivariable risk factors associated with asymptomatic echocardiographic abnormalities that predict symptomatic heart failure.

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 Visit 1 and subsequent echocardiography (Visit 2).

Figure S2. Receiver operating characteristic (ROC) curves for prediction of structural, systolic and diastolic abnormalities, and their combination, defined according to ARIC criteria, by amino-terminal pro-B-type natriuretic peptide (NT-proBNP) level in men and women with NT-proBNP measurement.

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