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Impact of age and sex on left ventricular function determined by coronary computed tomographic angiography: results from the prospective multicentre CONFIRM study

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Background Left ventricular (LV) volumetric and functional parameters measured with cardiac computed tomography (cardiac CT) augment risk prediction and discrimination for future mortality. Gender- and age-specific standard values for LV dimensions and systolic function obtained by 64-slice cardiac CT are lacking.

Methods and results 1155 patients from the Coronary CT Angiography EvaluatioN For Clinical Outcomes: An InteRnational Multicenter registry (54.5% males, mean age 53.1 ± 12.4 years, range: 18–92 years) without known coronary artery disease (CAD), structural heart disease, diabetes, or hypertension who underwent cardiac CT for various indications were categorized according to age and sex. A cardiac CT data acquisition protocol was used that allowed volumetric measuring of LV function. Image interpretation was performed at each site. Patients with significant CAD (>50% stenosis) on cardiac CT were excluded from the analysis. Overall, mean left ventricular ejection fraction (LVEF) was higher in women when compared with men (66.6 ± 7.7% vs. 64.6 ± 8.1%, $P < 0.001$). This gender-difference in overall LVEF was caused by a significantly higher LVEF in women ≥70 years when compared with men ≥70 years (69.95 ± 8.89% vs. 65.50 ± 9.42%, $P = 0.004$). Accordingly, a significant increase in LVEF was observed with age ($P = 0.005$ for males and $P < 0.001$ for females), which was more pronounced in females (5.21%) than in males

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(2.6%). LV end-diastolic volume decreased in females from 122.48 ± 27.87 (<40 years) to 95.56 ± 23.17 (>70 years; $P < 0.001$) and in males from 155.22 ± 35.07 (<40 years) to 130.26 ± 27.18 (>70 years; $P < 0.001$).

Conclusion Our findings indicate that the LV undergoes a lifelong remodelling and highlight the need for age and gender adjusted reference values.

Keywords Cardiac computed tomography • Left ventricular ejection fraction

Introduction

Left ventricular (LV) function and diameters are important predictors of morbidity and mortality in various cardiovascular diseases. Cardiac computed tomography (cardiac CT) has proved high accuracy and reproducibility in the evaluation of LV morphology and function, and cardiac CT measures of left ventricular ejection fraction (LVEF) have recently been shown to improve risk stratification and discrimination for future cardiac events in patients with coronary artery disease (CAD).[1–3] Thus, given the widespread use of high-resolution cardiac CT for non-invasive evaluation of CAD and the incremental prognostic value of concomitant assessment of cardiac function, accurate determination of LV parameters obtained by cardiac CT is fundamental for risk stratification and appropriate decision making in CAD.

Starting from the observation that women with heart failure present with a clinical profile different from that of men and that women show poorer cardiovascular outcomes compared with males, the varied predisposition to LV dysfunction between men and women came recently into light.[4,5] Indeed, the risk of cardiovascular events has been shown to start at higher LVEF indices in women when compared with men, indicating that thresholds to pathologic state are gender dependent.[6] In addition, in view of the continuously growing elderly population in most countries, it becomes increasingly important to distinguish normal age-related changes in LV size and function from pathologic findings. However, despite growing awareness of gender- and age-related differences in diagnostic approaches, gender- and age-specific standard values for LV dimensions and systolic function obtained by 64-slice cardiac CT are lacking. Indeed, inconsistent data derived from small populations have been reported, indicating that LVEF decreases or remains unchanged with age and is not influenced by gender.[7,8] Knowledge of these parameters, however, is crucial in order to stratify risk and guide therapy of patients with CAD. Thus, given the prognostic importance of LV function and its routine use in clinical decision making, the aim of this study was to assess age- and gender-specific changes of LV dimensions and systolic function by 64-slice cardiac CT in a large international multicenter cohort.

Methods

Study population

1155 patients (54.5% males, mean age 53.1 ± 12.4 years, range: 18–92) from the CONFIRM (Coronary CT Angiography EvaluatioN For Clinical Outcomes: an InteRnational Multicenter Registry) registry who underwent gated cardiac CT with quantitative LV measurements for evaluation of possible CAD were included in the present analysis. CONFIRM, an international, multicenter, observational cohort study, prospectively enrolled 27 170 consecutive patients >18 years of age between 2005 and 2009 who underwent least 64-detector row cardiac CT for suspected CAD at 12 centers in 6 countries (Canada, Germany, Italy, Korea, Switzerland, and the USA). Details of the CONFIRM registry design and data elements have been described previously.[9–12] Among 27 125 patients, those free of previously diagnosed CAD, structural heart disease including cardiomyopathies, diabetes, hypertension, or ventricular hypertrophy was included in the present analysis. Information on the presence or absence of these conditions was prospectively collected in each individual. Patients whose cardiac CT images revealed obstructive CAD (>50% luminal narrowing), structural heart disease, or patients with incomplete data on LV function and studies with technical problems were excluded. Patients with non-obstructive CAD (<50% luminal narrowing) were not excluded from the study. Therefore, 1155 remaining individuals were included for the final analyses. The following risk factors for CAD were systematically determined: dyslipidaemia, family history of premature CAD, smoking, and obesity. Patients were neither included nor excluded on the basis of quantitative analysis of global LV function from the gated cardiac CT images. Five age groups by decade were established for both genders: ≤40 years, between >40 and ≤50 years, >50 and ≤60 years, >60 and <70 years, and ≥70 years. The study complies with the Declaration of Helsinki and patient consent or a waiver of informed consent (as per recommendations of each institutional review board) was obtained at each site in keeping with sites-specific regulations.

Data acquisition, image reconstruction, and cardiac CT analysis

Cardiac CT scanners used in the CONFIRM registry and data acquisition for cardiac CT have been previously described.[9] For coronary artery analysis, each site performed per-segment analysis for individual coronary artery segments by using a 16-segment model. CAD was defined as the presence of any plaque. Coronary atherosclerotic lesions were quantified for lumen diameter stenosis by visual estimation and graded as none (0% luminal stenosis), mild (1–49%), moderate (50–69%), or severe (>70%). A coronary lesion compromising the lumen by >50% was defined as obstructive. All patients were in normal sinus rhythm and were capable of the breath hold needed for cardiac CT. Patients with heart rates >70 beats/min were given oral or intravenous metoprolol as per local site protocol. During cardiac CT 80–140 mL of iodinated contrast material was used and timing of contrast material administration was chosen to optimize uniform contrast enhancement of the coronary arteries. Scanning parameters were as follows: collimation, 64 × 0.625/0.750 mm; tube voltage, 100 or 120 mV; effective 400–650 mA; gantry rotation time/2, 83–350 ms. Dose reduction strategies were used when available. Multiphase reconstructions were performed for each dataset and based on these datasets, multiplanar reconstructions permitting assessment of LV function were created.

LVEF was measured volumetrically (excluding papillary muscles) with post-processing by using 10–20 phases of the cardiac cycle (temporal resolution, 83–175 ms).[13] LVEF was automatically calculated using end-diastolic (EDV) and end-systolic (ESV) volumes. Indexed values were obtained by normalizing EDV and ESV to body surface area (BSA). Image interpretation was uniformly performed at each site according to Society of Cardiovascular Computed Tomography guidelines by level III-qualified readers with >3 years of experience in cardiac CT image interpretation.[14]

Statistical analysis

STATA version 14 (StataCorp LP, College Station, TX, USA) was used for all statistical analyses. Categorical variables are presented as frequencies and continuous variables as mean ± SD or median ± interquartile range (IQR). Variables were compared with χ^2 statistic for categorical variables and by Student's unpaired *t*-test, Mann–Whitney non-parametric test or median comparison test where appropriate for continuous variables. LVEF and LV volumes are indicated as model-estimated marginal means and SD. Differences in between stratified age groups for both genders were calculated using ANOVA *post hoc* tests. Normality of the data was assessed with the Kolmogorov–Smirnov test. LV volumes and LVEF were not normally distributed, and consequently, 95% confidence interval was used to define the limit of normality. General linear model analysis was performed to model the data, construct the reference range as mean and 95% CI, and assess the influence of age and gender on LV volumes and LVEF. Spearman or Pearson correlation coefficient was used to quantify relations. To determine whether our findings were independent of confounders, multivariable linear regression was performed (dependent variable LVEF, independent variables EDV, gender and age, covariates BMI). A two-tailed *P*-value of 0.05 was considered statistically significant.

Results

Patient characteristics

A total of 1155 subjects (629 (54.5%) males) without obstructive CAD as determined by cardiac CT were analysed. The demographic characteristics of the study population are listed in *Table 1*. Patients had been referred for cardiac CT for evaluation of chest pain or dyspnoea. Our study population included 19% obese subjects (body mass index [BMI] >30 kg/m^2), while patients with diabetes or hypertension were excluded from our analysis. Mean age of our study population was 54.3 ± 12.2 years for women and 52.1 ± 12.5 years for men ($P = 0.001$ for men vs. women). Age range was 18–87 years for women and 18–92 years for men. Our study population was normally distributed according to age (*Figure 1A*), thus, very young and very old patients comprised the smallest subgroups and were therefore summarized in patients <40 years and patients >70 years, respectively. Women were more often symptomatic ($P < 0.001$) and suffered less often from

Table 1 Characteristics of study population

Parameters ($n = 1155$)	Females ($n = 526$)	Males ($n = 629$)	*P*-value
Age (years, mean ± SD)	54.3 ± 12.2	52.1 ± 12.5	0.001
BMI all (kg/m^2, mean ± SD) (1142)	26.1 ± 5.8	26.9 ± 4.4	<0.001
≥30 kg/m^2, *n* (%) (1142)	106 (20.5)	116 (18.6)	0.41
BSA (m^2, mean ± SD) (1142)	1.7 ± 0.2	2.0 ± 0.2	<0.001
Current smoker, *n* (%)	69 (13.1)	91 (14.5)	0.51
FHx of CAD, *n* (%) (1147)	205 (39.2)	212 (34.0)	0.07
Dyslipidaemia, *n* (%) (1153)	192 (36.6)	256 (40.8)	0.15
Chest pain (1137)			<0.001
Asymptomatic, *n* (%)	207 (40.4)	357 (57.1)	
Non-anginal chest pain, *n* (%)	119 (23.2)	93 (14.9)	
Atypical chest pain, *n* (%)	107 (20.9)	118 (18.9)	
Typical chest pain, *n* (%)	79 (15.4)	57 (9.1)	
Shortness of breath, *n* (%)	161 (30.6)	133 (21.1)	<0.001
Ethnicity (376)			
Caucasian *n* (%)	154 (86.5)	152 (76.8)	0.02
Agatston calcium score, median, IQR (763)	33.7 ± 119.7 (0, 0–10)	90.4 ± 230.0 (1, 0–57)	<0.001
Small heart (ESV <20 mL), *n* (%)	23 (4.4)	4 (0.6)	<0.001
Pretest CAD likelihood (1135)			<0.001
Low (≤10%)	302 (59.2)	250 (40.0)	
Intermediate (11–89%)	181 (35.5)	344 (55.0)	
High (≥90%)	27 (5.3)	31 (5.0)	
Level of CAD (1152)			<0.001
Normal	345 (65.8)	312 (49.7)	
Non-obstructive (1–49%)	179 (34.2)	316 (50.3)	

BMI, body mass index; BSA, body surface area; FHx, family history; CAD, coronary artery disease; ESV, end-systolic volume; IQR, interquartile range.

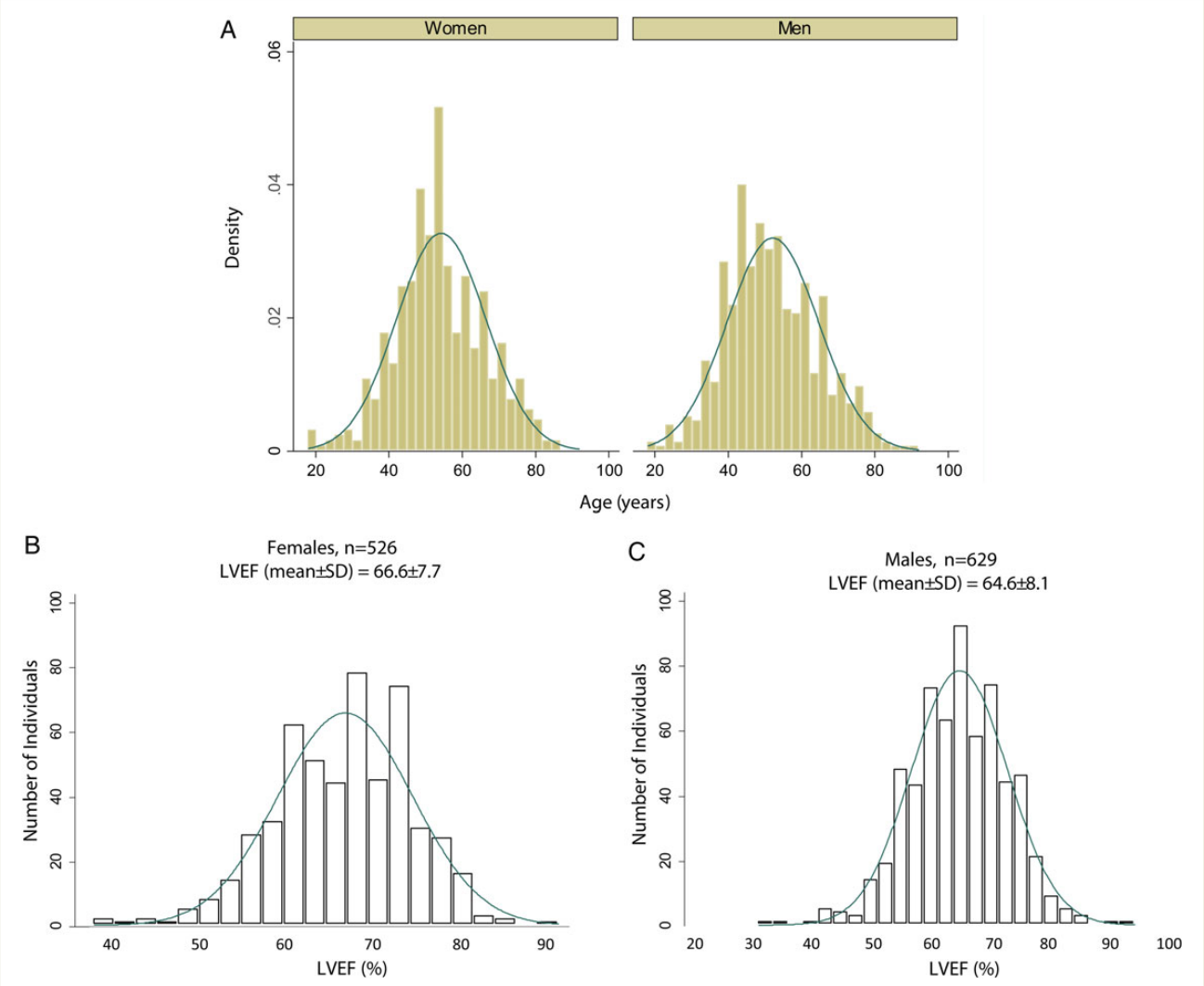

Figure 1 (*A*) Histograms of age distribution. Histogram showing distribution of LVEF for females (*B*) and males (*C*).

dyslipidaemia than men ($P = 0.15$) (*Table 1*). Women had a lower BMI and a lower BSA than men ($P < 0.001$, *Table 1*). Older male patients had a significantly lower BMI when compared with younger male patients ($P < 0.001$ for <40 years vs. ≥ 70 years), while no significant difference in BMI was observed between older and younger females ($P = 0.7$ for <40 years vs. ≥ 70, *Table 2*). Mean Agatston calcium score was lower in women than in men (33.7 ± 119.7 vs. 90.4 ± 230.0, $P < 0.001$, *Table 1*). Subjects were classified into six age groups: group 1 consisted of 149 subjects (54 women) aged <40 years, group 2 consisted of 315 subjects (127 women) aged 40–49 years, group 3 consisted of 361 subjects (183 women) aged 50–59 years, group 4 consisted of 205 subjects (99 women) aged 60–69 years, group 5 consisted of 125 subjects (63 women) aged ≥ 70 years (*Table 2*).

Influence of age and sex on LVEF

Mean LVEF for women ($n = 526$) was higher ($66.6 \pm 7.7\%$) than for men ($64.6 \pm 8.1\%$, $n = 629$; $P < 0.001$, *Figure 1B* and *C*). When subjects were stratified into age subgroups based on age in decades, a significant difference between sexes for LVEF in the age groups >70 years was seen, while no statistically significant difference between sexes was found for LVEF in subjects under 70 years of age (*Figure 2A*, *Table 2*). In addition, a strong and positive correlation of age and LVEF was found in females while a weaker correlation was observed in males (females: Pearson $r = 0.2$, $P < 0.001$; males: Pearson $r = 0.1$; $P = 0.005$; *Figure 3A*). Accordingly, a significant difference was seen between females ≥ 70 years and females <40 years ($P = 0.001$), but not in males ($P = 0.09$). Of note, when LVEF in women past menopausal age (51.4 years[15]) was compared with women at premenopausal age, a significant higher LVEF was found in those past menopausal age when compared with women below premenopausal age ($P < 0.001$). Multivariable regression analysis with LVEF being the dependent variable showed that age showed a stronger association with LVEF in females (*B*-coefficient $= 0.05$, $P < 0.001$) than in males (*B*-coefficient $= 0.01$, $P < 0.001$). In addition, the gender by age interaction term

Table 2 Gender-related differences in different age groups in LVEF and left ventricular volumes

	Age				
	<40	**40–49**	**50–59**	**60–69**	**≥70**
Variable	Males				
$N = 629$	95	188	178	106	62
LVEF (%)	62.9 ± 8.0	63.8 ± 7.1	65.3 ± 7.6	66.2 ± 9.3	65.5 ± 9.4
EDV (mL)	155.2 ± 35.1	144.33 ± 29.61	142.28 ± 34.37	135.54 ± 34.73	130.26 ± 27.18
ESV (mL)	57.2 ± 20.0	53.03 ± 17.14	49.67 ± 18.65	46.75 ± 19.09	45.34 ± 16.69
EDV/BSA (mL/m^2)	74.9 ± 14.6	71.13 ± 13.37	71.43 ± 16.04	68.02 ± 16.39	67.69 ± 14.54
ESV/BSA (mL/m^2)	27.6 ± 9.1	26.20 ± 8.19	24.90 ± 8.87	23.34 ± 9.04	23.65 ± 9.21
Small heart (%)	0	0	3 (1.69)	1 (1.94)	0
BMI (kg/m^2)	27.8 ± 4.8	27.77 ± 4.39	26.46 ± 4.70	26.37 ± 3.56	25.31 ± 2.89
Variable	Females				
$N = 526$	54	127	183	99	63
LVEF (%)	64.7 ± 7.0	65.3 ± 7.5	66.3 ± 7.3	68.0 ± 7.4	70.0 ± 8.9
EDV (mL)	122.5 ± 27.9	124.0 ± 26.2	116.5 ± 24.0	107.2 ± 23.8	95.6 ± 23.2
ESV (mL)	44.4 ± 17.2	43.2 ± 15.9	39.5 ± 13.7	34.3 ± 12.9	29.9 ± 14.0
EDV/BSA (mL/m^2)	71.5 ± 14.6	69.4 ± 13.0	66.1 ± 12.4	63.1 ± 12.0	58.3 ± 13.2
ESV/BSA (mL/m^2)	26.1 ± 9.9	24.4 ± 9.2	22.3 ± 7.2	20.2 ± 7.4	18.4 ± 8.6
Small heart (%)	1 (1.85)	0	6 (3.3)	6 (6.1)	10 (15.9)
BMI (kg/m^2)	25.3 ± 6.7	26.5 ± 5.6	27.1 ± 6.5	25.4 ± 4.5	24.7 ± 4.5
P-values for men vs. women at each age group					
LVEF (%)	0.21	0.08	0.17	0.10	0.004
EDV (mL)	<0.001	<0.001	<0.001	<0.001	<0.001
ESV (mL)	<0.001	<0.001	<0.001	<0.001	<0.001
EDV/BSA (mL/m^2)	0.08	0.15	<0.001	0.007	0.001
ESV/BSA (mL/m^2)	0.11	0.02	0.002	0.006	0.001
Small heart (%)	0.36	–	0.50	0.058	0.001
BMI (kg/m^2)	<0.001	0.002	0.89	0.019	0.20

A small heart was defined as ESV <20 mL. Values are all given as mean ± SD.
EDV, end-diastolic volume; ESV, end-systolic volume; EDV/BSA, EDV adjusted for BSA; ESV/BSA, ESV adjusted for BSA; BMI, body mass index.

was significantly associated with LVEF ($P = 0.044$), while only age ($P < 0.001$) but not gender ($P = 0.1$) was a statistically significant main effect variable for LVEF, indicating that gender and age show not a simple linear association with LVEF (*Table 3*). While BMI was not found to have significant independent influence on LVEF ($P = 0.9$), LVESV, and LVEDV both correlated significantly with LVEF ($P < 0.001$, *Table 3*), indicating that concomitant changes in both, LVESV and LVEDV, trigger the observed changes in LVEF with increasing age.

Influence of age on LV volumes

Men had significantly higher absolute and indexed LVEDV and LVESV values than women. This difference was more pronounced in older age groups (*Figure 2B* and *C*, *Table 2*). When LVESV was stratified by both gender and age, categorizing age in 10-year intervals, LVESV decreased with age in females from 44.4 ± 17.2 mL (<40 years) to 29.9 ± 14.0 mL (≥70 years; $P < 0.001$) and in males from 57.2 ± 20.0 mL (<40 years) to 45.3 ± 16.7 mL (≥70 years; $P < 0.001$) (*Figure 2*, *Table 2*). Accordingly, a significant negative association was found between age and LV volumes in both sexes; however, a stronger association between age and LV volumes was observed in women (Pearson $r = -0.4$, $P < 0.001$ for LVESV and $r = -0.7$, $P < 0.001$ for LVEDV, *Figure 3B* and *C*) than in men (Pearson $r = -0.3$, $P < 0.001$ for LVESV and $r = -0.6$, $P = 0.005$ for LVEDV, *Figure 3B* and *C*). As the ageing process *per se* is associated with a decrease in body size and since an association between an increase in BSA and an increase in chamber dimensions has been reported, we corrected chamber volumes for body size. Compared with uncorrected values, normalization of LV volumes (LVEDV/BSA and LVESV/BSA) cancelled out the significant difference in LV volumes between genders seen in younger age groups (<50 years, *Table 2*). In contrast, indexing for BSA did not change the gender-difference in older age groups (*Table 2*). As expected, women had smaller hearts than men (defined as ESV < 20 mL; 4.4% in females vs. 0.6% in males; $P < 0.001$, *Table 1*). The percentage of female patients with a small heart was higher in older age groups (1.9% for <40 year group, 15.9% for ≥70 year group; $P = 0.01$, *Table 2*). Multivariable regression analysis showed that age and gender were significant variables for LVEDV ($P < 0.001$ for age and $P = 0.04$ for gender), while only age ($P < 0.001$) but not gender was significantly

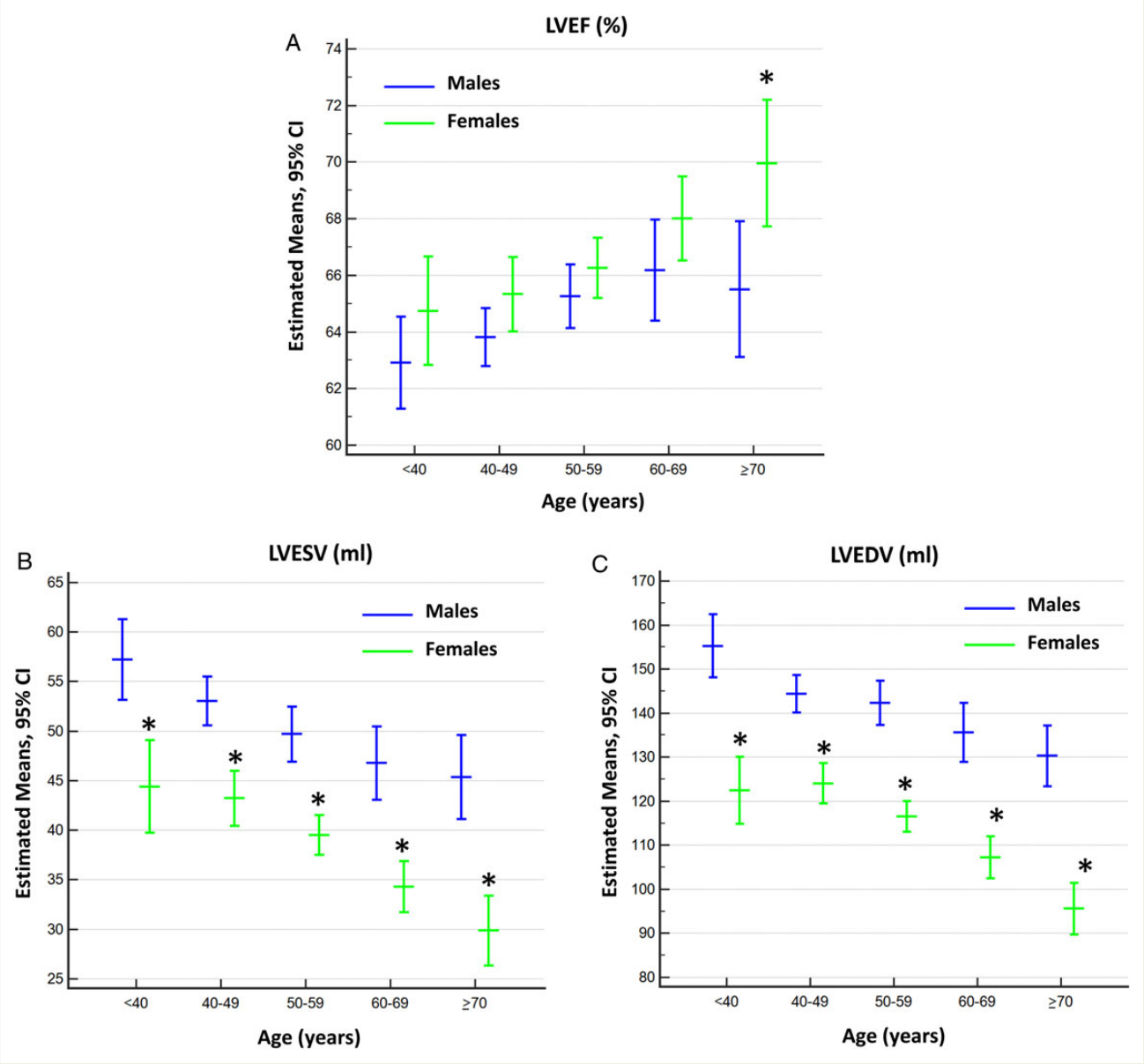

Figure 2 (*A*) Comparison of LVEF. Data are presented as estimated mean ± 95% CI. *$P < 0.05$ (male vs. female). (*B*) Comparison of LVESV. Data are presented as estimated mean ± 95% CI. *$P < 0.05$ (male vs. female). (*C*) Comparison of LVEDV. Data are presented as estimated mean ± 95% CI. *$P < 0.05$ (male vs. female).

associated with LVESV indicating that gender differences in LVEDV might trigger the observed differences in LVEF between elderly men and women.

Reference limits for LVEF

LVEF in our study population was not normally distributed, thus the 95% confidence limit was used to define cut-offs for abnormality. Given the marked gender differences in mean LVEF measurements, men and women were separated for these analyses. Mean LVEF was 66.65 (95% CI: 65.96–67.34) in women and 64.65 (95% CI: 64.03–65.27) in men. *Table 4* indicates mean and 95% confidence intervals of LVEF for each age group. For better visualization of the data, linear regression was applied to model the data (*Figure 4*). In patients ≥70 years, there was no overlap between the limits of the bootstrap 95% CI for women and men (63.26–67.74% for men, 67.84–72.06% for women, *Table 4*), indicating that different normal limits should be used for older women and men.

Discussion

We report here LVEF values obtained by cardiac CT in a large population free of hypertension, diabetes, structural heart disease, and obstructive CAD. Our findings indicate that women have a higher cut off value for normal LVEF than men due to smaller ventricular

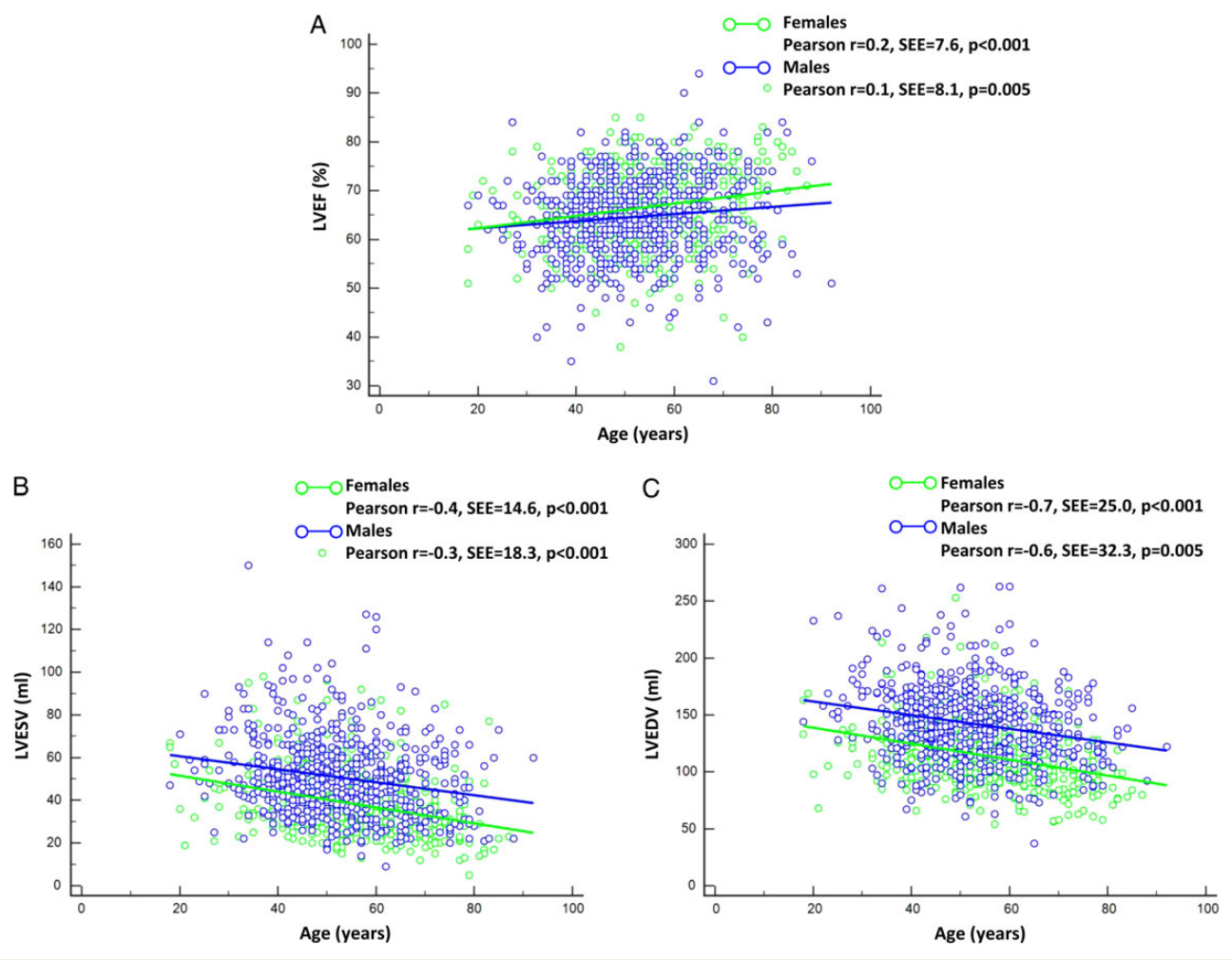

Figure 3 (*A*) Regression lines and scatter plots of relationship between LVEF and age in males and females. (*B*) Regression lines and scatter plots of relationship between LVESV and age in males and females. (*C*) Regression lines and scatter plots of relationship between LVEDV and age in males and females. SEE, standard error of estimates.

Table 3 Data output of multivariable regression analysis and test for interaction among independent variables (EDV, ESV, gender, and age)

Dependent variable: LVEF	Mean	SD	*B*-coefficient	*P*-value
Independent variable				
Age	53.1	12.4	0.05	<0.001
Male gender	–	–	1.65	0.114
LVESV	45.4	18.2	−0.59	<0.001
LVEDV	129.8	33.3	0.20	<0.001
Covariable: BMI	26.6	5.1	0.02	0.854
Interaction: Age × gender	–	–	−0.04	0.044

BMI was tested as covariate. Values are all given as mean ± SD.
LVEF, left ventricular ejection fraction; EDV, end-diastolic volume; ESV, end-systolic volume.

Table 4 Lower and upper limits of bootstrap (500 reps) 95% CI of the mean of LVEF based on gender and age

Age	LVEF (%)			
	Males		Females	
	95% CI		95% CI	
	Lower	Upper	Lower	Upper
<40	61.33	64.48	62.95	66.53
40–49	62.82	64.80	64.05	66.61
50–59	64.17	66.33	65.30	67.22
60–69	64.43	67.91	66.59	69.41
≥70	63.26	67.74	67.84	72.06

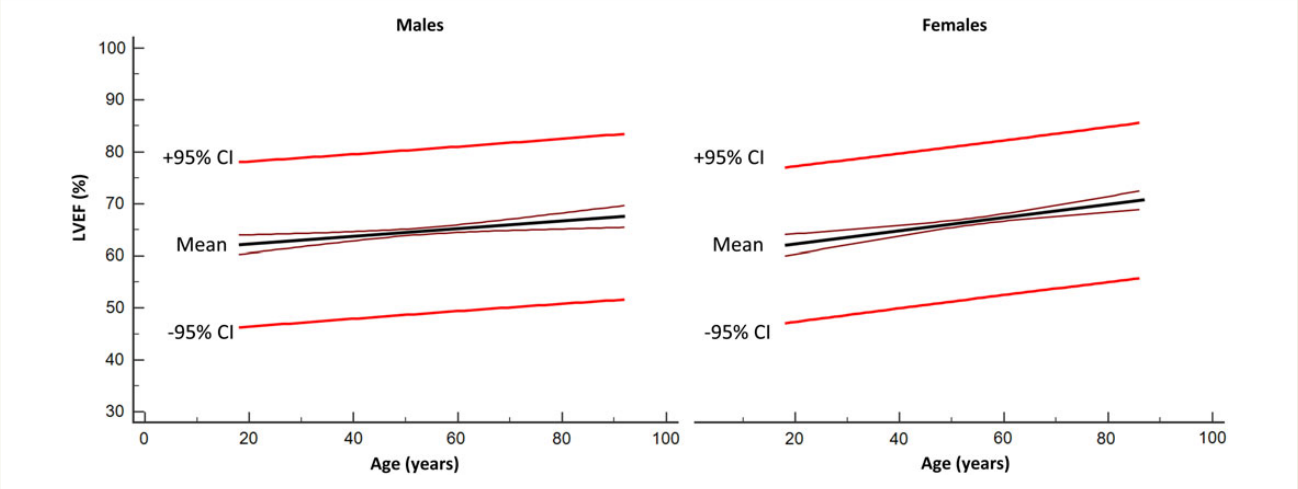

Figure 4 Age-adjusted values for LVEF for males and females. Linear regression was applied to model the data, which are presented as mean and 95% confidence intervals.

volumes and that LVEF increases with age in both genders. These age-dependent alterations are more pronounced in women than in men, indicating that age- and gender-adjusted LVEF reference values are needed.

Assessment of LV function and volumes is the cornerstone of cardiac diagnostics and numerous studies have highlighted its prognostic value in patients with CAD.[16–18] Heart failure is the most frequent complication observed in patients with CAD and while more men than women suffer from heart failure at younger ages, at the age of 75 the reverse is true.[19,20] Notably, heart failure is frequently underdiagnosed and established late in female patients,[21–23] which could be linked with the fact that the risk of cardiovascular events starts at higher LVEF indices in women when compared with men.[6] Thus, distinguishing impaired LV function from normal age- and gender-related changes is crucial, since the difference between these measurements may be the difference between whether a patient does, or does not, qualify for therapeutic intervention. During the last decade, cardiac CT has proved to provide excellent diagnostic information for the analysis of LV function and an additive prognostic value of cardiac CT-measured LV function was recently demonstrated.[24] Taking into account that modern cardiac CT equipment implements now permit to acquire cardiac CT datasets with a submillisievert fraction of effective radiation dose and given that LV measurements by cardiac CT show a high agreement with those obtained by other imaging modalities including echocardiography and cardiac magnetic resonance (CMR) imaging, cardiac CT offers a reliable alternative to assess LV function in patients with CAD.[25–27]

There is strong evidence showing that LV function is associated with traditional risk factors including diabetes mellitus, hypertension, smoking, and dyslipidaemia. Indeed, diabetes mellitus is considered a major contributor to the development of heart failure, even in the absence of CAD and hypertension,[28] while blood pressure is one of the most dominant variables predicting LV hypertrophy, thus, patients with diabetes mellitus and/or hypertension were excluded from the present analysis.[29] Smoking has been associated with decreased regional LV function in asymptomatic individuals[30] and dyslipidaemia has been shown to have an adverse effect on LV performance in patients with CAD.[31,32] Similarly, obesity has been found to be associated with increased LV mass and decreased LV volumes.[33] While no differences were detected regarding the prevalence of dyslipidaemia and smoking between males and females in our study, we observed that women had a lower BMI than men, and a significant decrease in BMI with increasing age was seen in males but not in females. However, BMI was not found to have significant independent influence on LVEF in our study, thus, the observed gender-specific changes in LV systolic function occurring with advancing age do not seem to depend on an increase in BMI. In addition, it is known that coronary artery calcification (CAC) is associated with the incidence of congestive heart failure and a correlation between CAC and LV diastolic dysfunction has recently been observed in elderly people.[34] Of note, in our study, males had significantly higher calcium scores than female subjects. However, considering the overall low calcium scores in our study population (33.7 in females and 90.3 in males) and given that an association between CAC and diastolic dysfunction was only observed in patients with high calcium scores >400,[34] it seems unlikely that CAC was a predictor of age-dependent LV remodelling in our population. Since our study was underpowered to assess the impact of CAC on LV function and volumes, further prospective studies will have to evaluate how CAC affects LV volumes in males and females at different ages.

Among the hypothesized mechanisms accounting for the stronger positive correlation between age and LVEF in women when compared with men, age-dependent changes in oestrogen/testosterone status are notable, as are gender-based lifestyle factors or differences in neurohumoral signalling. In fact, progressive myocyte loss occurring with increasing age in men but not in women was observed in an autopsy study and may explain why women show a stronger positive correlation between age and LVEF than men.[35]

Reduced testosterone levels and reduced physical activity in older men have been suggested to account for the enhanced myocyte apoptosis in elderly men.[8,35] Of note, while strong and negative correlations were found between age and LV volumes, the association between age and LVEF was much weaker, which further supports the notion that an extraneous variable, e.g. changes in LV mass and/or increased afterload, might influence age-dependent changes of the LV. However, data on myocardial mass and aortic compliance were not collected in our cohort, thus, we are unable to determine whether the higher LVEF in aged women was secondary to differences in contractile state or loading conditions. Interestingly, with increasing age, a higher prevalence of small hearts was detected in our female study population ($n = 1$ at age <40 years and $n = 6$ at age >70 years). Since we observed a correlation between LVESV and LVEF, it is likely that the augmented LVEF in elderly women is partially based upon women having smaller hearts than men which, in turn, raises the question whether the observed alterations of LV function in elderly women have a protective or detrimental impact on cardiovascular morbidity and mortality. Indeed, the differential predisposition to functional cardiac impairment in men and women at different ages is not yet understood, and, although heart failure is less common in women, overall mortality in females is higher.[36,37] Along that line, one could hypothesize that elderly women live under constant hyperdynamic conditions to compensate for the disadvantage of smaller ventricles and that the latter may predispose them to enhanced cardiac vulnerability in high-stress situations. Indeed, women have higher baseline sympathetic activity and excessive sympathetic discharge after acute myocardial infarction (MI) and during heart failure than men,[38,39] and lower testosterone levels in elderly men have been associated with decreased cardiac sympathetic nerve activity.[40] Of note, pathological cardiac conditions associated with sympathetic hyperactivity such as Takotsubo syndrome or cardiac syndrome X are highly prevalent in postmenopausal women.[41,42] However, whether higher regional cardiac sympathetic activity drives the adaption for a heart of smaller dimensions in elderly women warrants further investigation.

There are limitations to this study that should be pointed out. First, our study has the inherent limitations of an open-label, observational registry, including intersite variability in image acquisition and analysis. However, image interpretation was uniformly performed at all CONFIRM sites according to Society of Cardiovascular Computed Tomography guidelines by level III-qualified readers and the variety of sites included in the analysis ensures that our measures are clinically useful across different institutions, CT platforms, post-processing software, and independent of vendor. Second, the administration of β-blockers is essential in cardiac CT imaging since image quality is clearly improved at heart frequencies <70 bpm.[43] Since an influence of β-blocker administration on myocardial contractility cannot be excluded in our study, the generalizability of LV functional measurements obtained by cardiac CT to other imaging modalities might be limited. However, previous studies have demonstrated high accuracy and a tight concordance of LVEF values obtained by cardiac CT with those provided by CMR.[44,45] In addition, our results correlate well with previously published functional LV values for CMR and echocardiography.[46,47] Third, our results are based on a population that has been referred for cardiac CT. Patients with diabetes, hypertension, structural heart disease, and obstructive CAD were excluded, while patients with non-obstructive ($<50\%$ luminal narrowing) CAD were included in the analysis. This approach can be criticized since subjects referred for cardiac CT may have some reasons for the referral, which may not be found at the examination, indicating that they may not be representative of a healthy reference population. In addition, a previous meta-analysis in patients undergoing cardiac CT suggests that patients with non-obstructive CAD confer a greater incidence of major adverse cardiac events when compared with patients with entirely normal coronary arteries.[48] Further, abnormalities in diastolic function have recently been observed in a CMR study in women with non-obstructive CAD and symptoms of ischaemia.[49] However, in accordance with our data, in this recent CMR study, LVEF and LV volumes were similar between patients with non-obstructive CAD and normal coronary arteries, and given the high prevalence of non-obstructive CAD in the elderly population, applying very rigorous exclusion criteria may have led to a reference population that represents a 'too healthy' part of the population. Thus, we believe that the inclusion and exclusion criteria in this study represent a reasonable balance in order to have a relevant reference population reflecting the real word for establishing normal limits.

In summary, in this large international multicentre study we observed a significant increase in LV systolic function with advancing age; these alterations are particularly pronounced in women. Our findings indicate that the LV undergoes a continuous lifelong remodelling and suggest that the risk of cardiovascular events might start at higher LVEF indices in women, thereby emphasizing the need for gender- and age-specific criteria in clinical decision making. Given the prognostic importance of LVEF, further studies will need to explore variables that modulate myocardial contractility and, thus, vulnerability to cardiac injury in aged individuals.

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