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Ethnic-Specific Normative Reference Values for Echocardiographic LA and LV Size, LV Mass, and Systolic Function

The EchoNoRMAL Study

The EchoNoRMAL (Echocardiographic Normal Ranges Meta-Analysis of the Left Heart) Collaboration*

ABSTRACT

OBJECTIVES This study sought to derive age-, sex-, and ethnic-appropriate adult reference values for left atrial (LA) and left ventricular (LV) dimensions and volumes, LV mass, fractional shortening, and ejection fraction (EF) derived from geographically diverse population studies.

BACKGROUND The current recommended reference values for measurements from echocardiography may not be suitable to the diverse world population to which they are now applied.

METHODS Population-based datasets of echocardiographic measurements from 22,404 adults without clinical cardiovascular or renal disease, hypertension, or diabetes were combined in an individual person data meta-analysis. Quantile regression was used to derive reference values at the 95th percentile (upper reference value [URV]) and fifth percentile (lower reference value [LRV]) of each measurement against age (treated as linear), separately within sex and ethnic groups.

RESULTS The URVs for left ventricular end-diastolic volume (LVEDV), LV end-systolic volume, and LV stroke volume (SV) were highest in Europeans and lowest in South Asians. Important sex and ethnic differences remained after indexation by body surface area or height for these measurements, as well as for the LRV for SV. LVEDV and SV decreased with increasing age for all groups. Importantly, the LRV for EF differed by ethnicity; there was a clear apparent difference between Europeans and Asians. The URVs for LV end-diastolic diameter and LV end-systolic diameter were higher for Europeans than those for East Asian, South Asian, and African people, particularly among men. Similarly, the URVs for LA diameter and volume were highest for Europeans.

CONCLUSIONS Sex- and/or ethnic-appropriate echocardiographic reference values are indicated for many measurements of LA and LV size, LV mass, and EF. Reference values for LV volumes and mass also differ across the age range. (J Am Coll Cardiol Img 2015;8:656–65) © 2015 by the American College of Cardiology Foundation.

Reference values for echocardiographic chamber quantification were jointly published by the American Society of Echocardiography (ASE) and the European Association of Echocardiography (EAE) in 2005 (1), and revised recommendations have recently been released (2). The guidelines are an important advance in quantitative echocardiography; however, they may not be representative of the diverse world population to which they are applied. A systematic review of studies published up to 2009 found that values of left ventricular mass (LVM) in normal cohorts from around the world commonly fell outside the 2005 (and unchanged 2015) ASE/EAE reference ranges, whether they were indexed for body size or not (3). Body size is typically represented by height or body

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surface area (BSA), and it may be incorrect to assume that the relationship between cardiac size or structure and these surrogates of body size are the same across sex or different ethnic groups.

The EchoNoRMAL (Echocardiographic Normal Ranges Meta-Analysis of the Left Heart) collaboration was formed to develop contemporary normative reference ranges for standard echocardiographic measurements of the left heart (www.echonormal.org) (4). Such values are essential to guiding key clinical management decisions. Geographically diverse, population-based studies were sought to ensure reference values would be relevant to a "real world" population, with values derived from echocardiographic measurements acquired in adults without clinically evident cardiovascular (CV) disease or risk factors.

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The present study sought to derive age-, sex-, and ethnic-appropriate adult normative reference values for left atrial diameter (LAD), area, and left atrial volume (LAvol); left ventricular (LV) dimensions (left ventricular end-diastolic diameter [LVEDD] and left ventricular end-systolic diameter [LVESD]), volumes (left ventricular end-diastolic volume [LVEDV], left ventricular end-systolic volume [LVESV], and stroke volume [SV]), LVM, fractional shortening (FS), and ejection fraction (EF).

METHODS

STUDY COHORT. The development and methodology of the EchoNoRMAL individual person data meta-analysis has been described previously (4). In brief, population-based studies that reported echocardiographic measurements on adult volunteers were identified through comprehensive systematic reviews and personal communications. Investigators were asked to contribute individual person-level data to the EchoNoRMAL meta-analysis. Data on 51,222 subjects from 43 studies were received. Ethnicities defined in the original studies were categorized as African, American Black, East Asian, Australian Aboriginal, European, Middle Eastern, Pacific, or South Asian. After limiting the study population to people ages 18 to 80 years, subjects with clinically evident CV or renal disease, hypertension, or diabetes were excluded. Assessment for subclinical disease varied, and studies were not required to have performed more intensive screening of older subjects (although the same criteria for hypertension, diabetes, or renal disease were applied to all). After the exclusions, 22,404 subjects formed the EchoNoRMAL reference cohort from which reference values for standard echocardiographic measurements of the left heart were derived.

DEVELOPMENT OF REFERENCE VALUES. Data were combined from multiple studies in an individual person data meta-analysis. Quantile regression (5) of each echocardiographic measurement against age (treated as linear) was performed within sex- and ethnic-specific groups. Nonlinear relationships with age are possible; however, these were not suggested on scatterplots of each measurement. Initially, individual study was treated as a fixed effect. To investigate study-specific influences, the analysis of each measurement was repeated while treating the study as a random effect, with a study-specific intercept. Studies with ≤5 people per sex per ethnic group were excluded from the random effects model. The variance associated with each intercept was estimated using bootstrap re-sampling (1,000 samples). To identify potential outliers, the random intercepts of each study were ranked in ascending order. Because the distribution of the intercepts showed no clusters or other patterns of heterogeneity, the studies at either end of the range were examined. If there was no overlap in the 95% confidence intervals of 2 adjacent studies, the extreme study was identified as a potential outlier. A sensitivity analysis was then performed by removing the extreme study and repeating the fixed effect analysis. If there were important differences in the model after excluding the outlying study (defined as ≥5% difference in the intercept or coefficient of age), the study was excluded from developing the final reference values for that measurement. If the reference value was for a metric derived from other measurements (e.g., EF derived from LV volumes), the study was also excluded from reference values for the initial measurements (e.g., for LVEDV and LVESV, as well as EF). Because outlying data could be due to systematic measurement differences or real differences in the underlying population, sensitivity analyses were then performed for all other measurements, in which any study that had been excluded from the development of a reference range was excluded from every other measurement it contributed data to, and the fixed effect analysis repeated. Reference values derived from all studies, without exclusions, are presented as supplemental data (Online Appendix E). To further examine variability between studies, we selected

ABBREVIATIONS AND ACRONYMS

ASE = American Society of Echocardiography

BSA = body surface area

CV = cardiovascular

EAE/EACVI = European Association of Echocardiography/ European Association of Cardiovascular Imaging

HR = heart rate

FS = fractional shortening

LA = left atrial

LAD = left atrial diameter

LAvol = left atrial volume

LRV = lower reference value

LV = left ventricular

LVEF = left ventricular ejection fraction

LVEDD = left ventricular end-diastolic diameter

LVEDV = left ventricular end-diastolic volume

LVESD = left ventricular end-systolic diameter

LVESV = left ventricular end-systolic volume

LVM = left ventricular mass

SV = stroke volume

URV = upper reference value

wSD = weighted SD

the measurement of EF, and calculated a weighted variance of the predicted value for each study, with weights proportional to study size. Analyses were performed using R statistical software v3.0.2 (6), using the "quantreg" (7) package for fixed effects models and the "lqmm" (8) package for random effects models.

Upper reference values (URVs) were defined at the 95th percentile and lower reference values (LRVs) at the fifth percentile. In accordance with earlier recommendations (9), these values defined 90% of the population as normal, but they allowed for non-normal distributions. Reference values at ages 30, 50, and 70 years (where possible), and equations that allowed the URV or LRV to be calculated for any age, are provided in the Online Appendix. Reference values were not derived in a sex-specific ethnic group with <80 subjects (10). Values were derived for an age range of 18 to 80 years, where possible. When data were sparse for a subset of ages, the principle of Virtanen et al. (10) was generalized to require ≥1.3 subjects per year of age for the model to be extended over the area of sparse data. For example, if data on a measurement were available in 384 adults, of whom 368 were ages 18 to 70 years, the model would be developed up to 80 years because data on 16 people ages 70 to 80 years would adequately represent the remaining 10 years (1.6 people per year). If data on 12 people represented the remaining 10 years (1.2 people per year), the model would be limited to 18 to 70 years. In such cases (of sparse data), the model over the widest age range was compared with that developed over the limited age range. If they were the same, the wider age range was used; if not, the limited age range was used. When only 1 study contributed to a model, the model was limited to the ages in that study.

Reference values were derived for LA size (LAD, area, LAvol); LV diameters (LVEDD, LVESD), volumes (LVEDV, LVESV, SV), LVM, and function (FS, EF). In addition, reference values were derived for LA and LV diameters, volumes, and LVM after indexation (dividing) by BSA (11) and by height. LVM was estimated using the ASE recommended equation (12) whether measured from M-mode or 2-dimensional linear dimensions. Relative wall thickness (RWT) was calculated from the posterior wall dimension (PWD) as RWT = PWD*2/LVEDD.

RESULTS

COHORT. The EchoNoRMAL reference cohort is characterized in **Table 1**. Sufficient data for the development of reference values were available for each sex in the 5 largest ethnic groups (European, East Asian, South Asian, American Black, African). Because few data were available for American Blacks older than 65 years, reference values could only be derived for younger age groups. Robust reference values could not be derived for people of Australian Aboriginal, Pacific, or Middle Eastern descent because we received data on <80 subjects per sex in these groups.

REFERENCE VALUES. Data exclusions. One study had outlying data for LVEDV and LVESV, and 1 study had outlying data for EF. Sensitivity analyses showed that each of the studies had a significant influence on the reference values that were derived for these measurements; thus, they were excluded from the development of European reference values for LVEDV, LVESV, and EF (13,14). Reference values from the full data are presented in the Online Appendix. These 2 studies did not influence the equations for any other measurement.

Left ventricular volumes and ejection fraction. Age-specific URVs for LVEDV, LVESV, and SV, measured using Simpson's biplane method, are presented in **Tables 2 and 3** and also Online Tables A1a and A1b.

TABLE 1 Characteristics of the EchoNoRMAL Reference Cohort

	European (n = 14,042)	East Asian (n = 3,874)	South Asian (n = 1,751)	American Black (n = 1,708)	African (n = 676)	Australian Aboriginal (n = 118)	Pacific (n = 45)	Middle Eastern (n = 30)
Men	51	52	53	46	39	37	47	53
Age, yrs	47 (35-58)	53 (43-61)	50 (46-57)	29 (26-33)	49 (45-54)	32 (25-41)	29 (25-39)	33 (27-43)
Height, cm	170 (163-177)	160 (154-168)	164 (157-171)	170 (163-177)	165 (158-171)	165 (161-172)	170 (165-177)	168 (162-174)
Weight, kg	71 (62-81)	56 (50-64)	71 (62-80)	75 (64-88)	72 (62-83)	75 (64-87)	82 (67-102)	69 (65-82)
BSA, cm^2	1.8 (1.7-2.0)	1.6 (1.5-1.7)	1.8 (1.6-1.9)	1.9 (1.7-2.0)	1.8 (1.7-1.9)	1.9 (1.7-2.0)	2.0 (1.8-2.2)	1.8 (1.7-2.0)
BMI, kg/m^2	24 (22-27)	22 (20-24)	26 (24-29)	26 (23-30)	26 (23-29)	28 (23-31)	27 (25-33)	25 (24-28)
SBP, mm Hg	120 (110-129)	118 (110-126)*	122 (114-130)	108 (102-115)	124 (115-131)	116 (109-124)	123 (113-128)	110 (102-120)
DBP, mm Hg	74 (68-80)	70 (66-79)*	76 (71-81)	69 (63-75)	78 (72-82)	74 (69-80)	76 (70-80)	69 (60-75)
HR, beats/min	66 (60-74)	64 (58-71)*	73 (66-81)	68 (62-74)	67 (61-75)	74 (66-82)	67 (58-74)	65 (60-70)

Values are % or median (interquartile range). Ethnicity was not defined in 51 people. *Data were unavailable in >50% of subjects.
BMI = body mass index; BSA = body surface area; DBP = diastolic blood pressure; HR = heart rate; SBP = systolic blood pressure.

TABLE 2 Reference Values of Left Ventricular Volumes and Ejection Fraction for Men

Simpson's Biplane	European			East Asian			South Asian	
# of Subjects/# of Studies	1,107/10			523/6			329/5	
Age, yrs	30	50	70	30	50	70	50	70
LVEDV, ml	151 (3.8)	138 (1.9)	126 (3.3)	140 (3.0)	127 (1.9)	113 (3.4)	102 (3.1)	84 (4.5)
LVEDV/BSA, ml/m^2	72 (1.9)	66 (0.9)	61 (1.5)	72 (1.9)	71 (1.3)	69 (2.5)	52 (1.5)	46 (2.7)
LVEDV/height, ml/m	83 (2.0)	78 (1.1)	73 (2.0)	80 (2.2)	74 (1.5)	68 (2.8)	58 (2.0)	48 (2.5)
LVESV, cm	65 (2.0)	59 (1.0)	54 (1.7)	56 (1.3)	50 (1.1)	45 (2.2)	42 (1.6)	34 (4.0)
LVESV/BSA, ml/m^2	31 (0.8)	29 (0.4)	27 (0.8)	30 (0.6)	28 (0.7)	26 (1.3)	22 (0.5)	21 (1.6)
LVESV/height, ml/m	36 (0.8)	34 (0.5)	31 (1.0)	32 (0.8)	29 (0.6)	27 (1.1)	24 (0.7)	22 (1.8)
SV, ml	91 (2.8)	83 (1.3)	75 (1.7)	87 (0.9)	82 (1.8)	77 (3.4)	61 (2.1)	50 (1.3)
SV, ml*	39 (1.0)	37 (0.5)	35 (1.0)	43 (1.7)	39 (1.1)	36 (1.9)	26 (1.0)	24 (1.6)
SV/BSA, ml/m^2	44 (1.2)	41 (0.6)	37 (0.8)	46 (1.6)	46 (0.8)	47 (1.2)	32 (1.0)	28 (2.0)
SV/BSA, ml/m^2*	20 (0.8)	19 (0.4)	18 (0.7)	24 (1.0)	22 (0.7)	20 (1.2)	14 (0.5)	14 (0.7)
SV/height, ml/m	50 (1.8)	46 (0.9)	43 (1.0)	50 (1.1)	48 (0.9)	47 (1.8)	35 (1.3)	30 (0.8)
SV/height, ml/m*	23 (0.8)	21 (0.4)	20 (0.6)	24 (1.0)	23 (0.6)	21 (1.1)	16 (0.5)	15 (0.8)
EF, %*	49 (0.9)	50 (0.6)	50 (1.3)	55 (0.7)	56 (0.5)	56 (0.9)	52 (0.6)	52 (0.9)

Values are upper reference values (standard error) unless otherwise indicated. *Lower reference value. Ejection fraction (EF) was derived in 1,573 Europeans (13 studies), 524 East Asians (7 studies), and 361 South Asians (6 studies).

BSA = body surface area; LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end-systolic volume; SV = stroke volume.

LRVs for SV and EF are also presented. The URVs for LVEDV, LVESV, and SV were highest for Europeans and lowest for South Asians (**Figure 1**), and important sex and ethnic differences remained after indexation of LVEDV or LVESV by BSA or height. Indexation of SV by height reduced the apparent difference in URVs between Europeans and East Asians, but did not reduce the difference between these groups and South Asians. The difference in LVEDV and SV with increasing age was statistically significant for men and women of all 3 ethnic groups, except SV in South Asian women (Online Tables A2a and A2b).

Median heart rate (HR) was 7 beats/min higher among South Asians than Europeans (**Table 1**). Linear regression of LVEDV against HR in the whole cohort showed that LVEDV decreased by 0.64 ml per 1 beat/min increase in HR (data not shown); thus, a 7 beats/min increase in HR would be associated with a 4.5-ml reduction in LVEDV. Consistent with the URVs for LVEDV, median LVEDV for South Asian men was 37 ml lower than that of European men (68 ml vs. 105 ml) and 23 ml lower for South Asian women compared with European women (57 ml vs. 80 ml). Therefore, the ethnic-dependent differences in the distribution of LVEDV far exceed the influence of HR.

The LRV for EF differed by ethnicity (**Figure 2**). Among men and women aged 50 years, the LRV of EF for Europeans was an absolute 6% lower than that of East Asians and 2% lower than that of South Asians. The difference in LRV between Europeans and East Asians was statistically significant for both sexes.

Consistent with the lower LRV for Europeans, 97% of 386 people with an EF <50% were European. Mean LA volume was 50 ± 12.5 ml; however, LAvol was only available in 57 (18%) of these subjects (compared with 40% of Europeans with EFs ≥50%); therefore, this might represent a biased sample. LAD was available in 75% of Europeans with EFs <50%. Mean LAD was 3.4 ± 0.53 cm, which was less than the 3.5 ± 0.53 cm in Europeans with EFs ≥50% (Student *t* test for the difference, p = 0.025).

The difference in EF with increasing age was statistically significant for South Asian men only (Online Tables A2a and A2b).

Equations defining the LRVs for LV volumes are presented in Online Tables A3a and A3b.

Left ventricular dimensions and fractional shortening. Age-specific URVs for LVEDD and LVESD, from M-mode or 2-dimensional linear measurements, are presented in Online Tables B1a (men) and B1b (women). LRVs for FS are also presented. Insufficient data were available for younger African men to allow reference values to be developed over the whole age range; however, this was possible for African women. The URVs for LVEDD and LVESD at age 50 years were higher for Europeans than those for East Asian, South Asian, and African people. Values for American Blacks were limited to age 30 years, at which time the URVs were similar to Europeans at age 30 years (although these were measured from the parasternal short-axis view). Indexation of LVEDD by height appeared to reduce the difference in URVs between ethnic groups more than indexation by BSA.

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TABLE 3 Reference Values of Left Ventricular Volumes and Ejection Fraction for Women

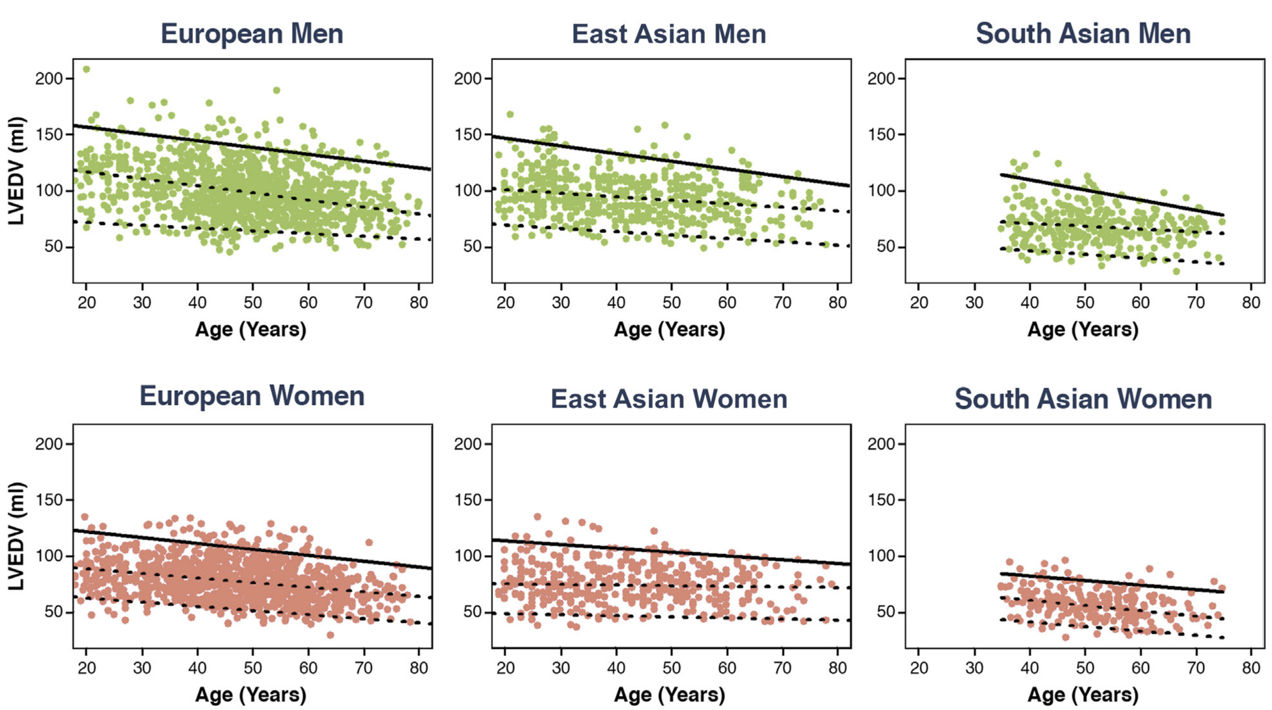
Simpson's Biplane	European			East Asian			South Asian	
# of Subjects/# of Studies	1,107/10			418/6			235/4	
Age, yrs	30	50	70	30	50	70	50	70
LVEDV, ml	116 (3.0)	106 (1.7)	95 (3.0)	109 (3.2)	103 (1.6)	96 (1.7)	80 (2.8)	73 (6.2)
LVEDV/BSA, ml/m^2	62 (0.9)	58 (0.6)	53 (1.3)	68 (1.5)	66 (1.2)	64 (2.3)	47 (1.2)	46 (2.4)
LVEDV/height, ml/m	68 (0.9)	63 (0.7)	59 (1.3)	67 (1.5)	65 (1.1)	62 (2.2)	50 (1.3)	46 (2.6)
LVESV, cm	48 (1.0)	44 (0.7)	41 (1.4)	40 (1.3)	38 (1.2)	36 (2.3)	35 (1.3)	27 (3.5)
LVESV/BSA, ml/m^2	26 (0.5)	24 (0.4)	23 (0.8)	25 (0.9)	24 (0.5)	23 (0.8)	20 (0.7)	17 (2.1)
LVESV/height, ml/m	28 (0.4)	27 (0.3)	25 (0.7)	24 (0.8)	24 (0.8)	23 (1.5)	22 (0.8)	17 (2.1)
SV, ml	72 (1.7)	66 (1.0)	60 (1.8)	72 (3.6)	67 (2.1)	63 (3.8)	48 (1.5)	46 (3.6)
SV, ml*	34 (0.7)	30 (0.5)	27 (1.0)	32 (1.7)	30 (1.2)	28 (2.3)	22 (1.3)	19 (0.9)
SV/BSA, ml/m^2	39 (0.9)	37 (0.5)	35 (0.9)	45 (1.6)	44 (0.9)	44 (1.4)	29 (0.6)	29 (1.3)
SV/BSA, ml/m^2*	20 (0.4)	17 (0.4)	15 (0.8)	21 (1.2)	20 (0.7)	18 (1.1)	14 (0.6)	12 (0.6)
SV/height, ml/m	42 (1.0)	39 (0.5)	37 (0.9)	45 (2.2)	42 (1.2)	40 (2.0)	30 (1.0)	29 (2.5)
SV/height, ml/m*	21 (0.5)	19 (0.3)	16 (0.7)	20 (1.1)	19 (0.8)	19 (1.5)	15 (0.7)	12 (0.3)
EF, %*	51 (0.5)	51 (0.5)	51 (1.0)	57 (0.8)	57 (0.6)	57 (1.2)	53 (1.0)	53 (3.1)

Values are upper reference values (standard error) unless otherwise indicated. *Lower reference value. EF was derived in 1,432 Europeans (13 studies), 422 East Asians (7 studies), and 270 South Asian (5 studies).

Abbreviations as in Table 2.

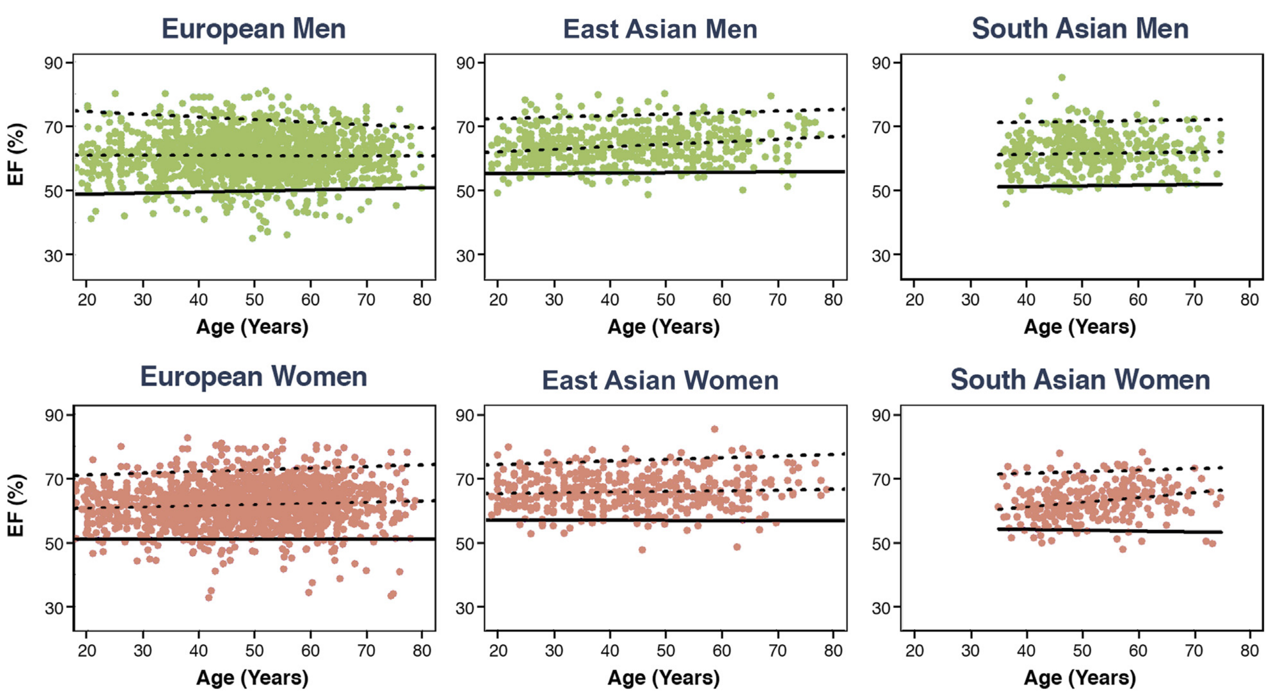
The change in the URVs of LVEDD with increasing age was minimal but statistically significant for M-mode measurements of East Asian men, East Asian women, and American Black women (over a limited age range), and for 2-dimensional linear measurements of East Asian men and European women (Online Tables B2a and B2b). Equations defining the LRVs for LV dimensions are presented in Online Tables B3a and B3b.

FIGURE 1 Left Ventricular End-Diastolic Volumes (Simpson's Biplane) Against Age



(Solid top line) The 95th percentiles are the upper reference values. **(Dotted central and bottom lines)** The 50th and fifth percentiles, respectively. LVEDV = left ventricular end-diastolic volume.

FIGURE 2 Ejection Fraction (Simpson's Biplane Volumes) Against Age



(Solid bottom line) The 5th percentiles are the lower reference values. **(Dotted central and top lines)** The 50th and 95th percentiles, respectively. EF = ejection fraction.

Left ventricular mass. Age-specific URVs for LVM, which were estimated from M-mode, 2-dimensional linear, or 2-dimensional area methods, are presented in Online Tables C1a (men) and C1b (women). The URVs for relative wall thickness from linear measurements are also presented. The URVs for LVM were higher for Europeans than that of East Asians, regardless of the measurement method. Among men, the differences between these groups remained after indexation by BSA or height. As seen for M-mode dimensions, the URVs for M-mode LVM were similar for Europeans and American Blacks at age 30 years. The change in the URVs of LVM with increasing age for men was statistically significant for M-mode-derived mass in European and American Black men and for 2-dimensional, linear-derived mass in European and South Asian men (Online Table C2a).

Among women, the URVs for LVM were similar for Europeans and South Asians; however, the reference for 30-year-old American Black women was higher than any other ethnic group (at that age, images were taken in the parasternal short-axis view). Indexation by BSA, and to a lesser degree, by height, appeared to reduce the difference in URVs among ethnic groups. The change in the URVs of LVM with increasing age was statistically significant for M-mode-derived mass in European and East Asian women, and for 2-dimensional, linear-derived mass in East Asian and South Asian women (Online Table C2b). Equations defining the LRVs for LVM are presented in Online Tables C3a and C3b.

Left atrial size. Age-specific URVs for LAD, area, and volume are presented in Online Tables D1a (men) and D1b (women). The URVs for LAD were highest for Europeans and American Blacks (at age 30 years) and were lowest for South Asians and Africans. The URVs for LAvol were also higher for Europeans than East Asians, although the difference was less pronounced among women. Among men, differences in the URVs of LAD and LAvol remained after indexation by BSA or height.

The change in the URVs of LAD with increasing age was statistically significant for European, African, and American Black men, and it varied for women depending on the method of measurement. The difference in LAvol with increasing age was not statistically significant for men, but was significant for European women (Online Tables D2a and D2b). Equations defining the LRVs for LA size are presented in Online Tables D3a and D3b.

Between-study variation. The predicted value of EF at age 50 years was used to examine between-study variation. In a random effects model of the fifth percentile of EF, the predicted values for European women at age 50 years from 13 studies ranged from -3.9% to +4.8% around the final predicted value. The weighted standard deviation (wSD) was 3.1% (Figure 3). The predicted values for East Asian women (5 studies) ranged from -3.3% to +1.1% around the final predicted value (wSD 0.8%), and for South Asian women (4 studies), the predicted values ranged from -1.6% to +1.4% around the final predicted value (wSD 0.5%).

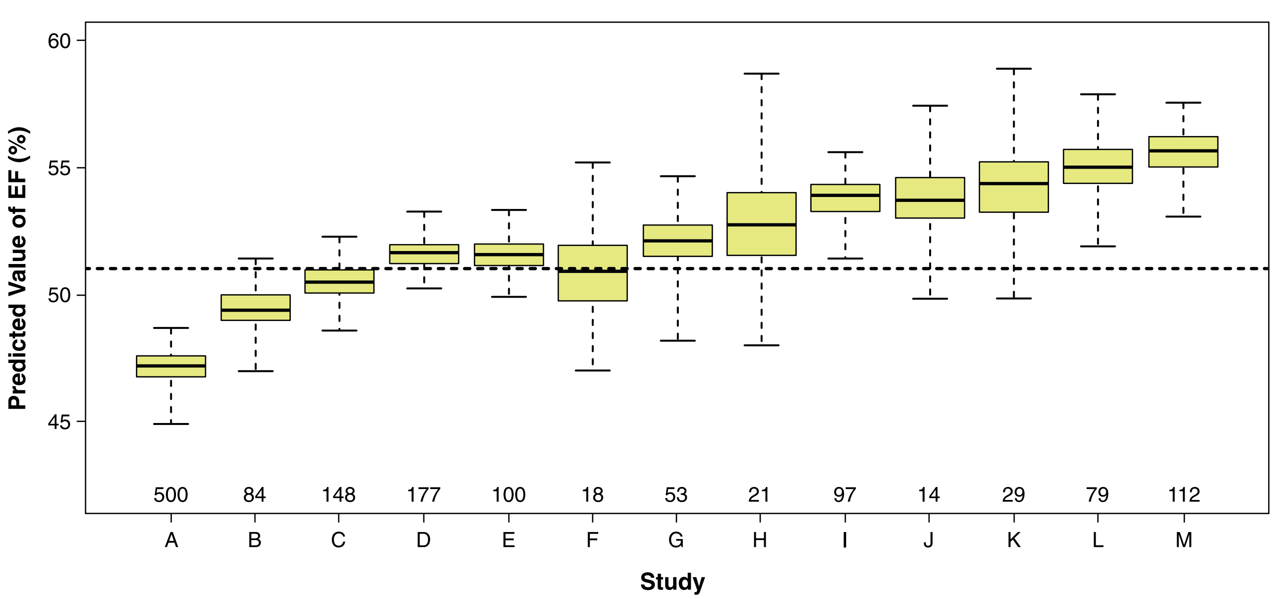
A similar pattern was seen among men. The predicted values for European men at age 50 years from each of 12 studies (1 study that had 4 European men was not included in the random effects model) ranged from -5.0% to +3.7% around the final predicted value (wSD 2.7%); for East Asian men (5 studies), the predicted value ranged from -1.9% to +2.4% around the final predicted value (wSD 0.7%), and for South Asian men (5 studies), the predicted valued ranged from -0.7% to +3.2% around the final predicted value (wSD 0.8%).

DISCUSSION

Quantitative echocardiography depends on reliable normative reference ranges that describe the distribution of values in a "healthy" referent population. It is well known that LV size differs for men and women (15,16). However, ethnic-based differences in LV size are less well recognized, and reference values that allow for variations in cardiac size and structure resulting from ethnic-based differences in body composition are lacking. We have shown that although simple indexation of LV size reduces sex- or ethnic-based differences, ethnic-appropriate reference values are still required for many measurements of the left heart. By collating echocardiographic measurements from population-based studies from around the world, this study has enabled age-, sex- and ethnic-appropriate adult reference values to be derived for nonindexed and indexed left heart dimensions, volumes, and mass, and nonindexed FS and EF.

Our findings support the current ASE/European Association of Cardiovascular Imaging (EACVI) recommendations for chamber quantification by sex, but they also challenge the use of values that ignore ethnicity. For example, the current ASE/EACVI recommendations advocate upper thresholds for LVEDD of 5.8 cm for men and 5.2 cm for women based on data from predominantly white European and American adults (2). The URVs for LVEDD derived for European men in the present study were similar to this threshold; however, the URVs derived for East Asian, South Asian, and African men were substantially lower than those for Europeans and lower than those of the ASE/EACVI recommendations. Among women,

FIGURE 3 Predicted Values of the Fifth Percentile of Ejection Fraction per Study Among 50-Year-Old European Women



Number of women per study along the x-axis. Abbreviation as in Figure 2.

the URVs for LVEDD were similarly higher for Europeans than other ethnic groups; however, the ASE/EACVI threshold was more compatible with the non-European groups. Similar disparities were seen between the current recommendations and the URVs derived in this study for LA size and LV volumes. East Asian and South Asian men in particular would be disadvantaged if European reference values were applied, because significant LV dilatation would need to occur before being viewed as a pathological change. This and other differences in reference values between ethnic groups could have significant implications for the under- and over-diagnosis of CV abnormalities in these populations.

Basic indexation of LV diameters by BSA or height removed much of the disparities in reference values between sex and ethnic groups, but they did not have this effect on LV volumes. The disparities that remained for indexed SV in particular might have implications in the management of "low flow" aortic stenosis. Standardization by a metric of body size should not be expected to account for all variations in heart size, even in health, and a persistent difference in indexed LV volumes between Europeans and East Asians was also found in the MESA (Multi-Ethic Study of Atherosclerosis) study (17). One explanation for the differing impact of indexation on diameters compared with volumes might be based on the differing geometry of the measurements involved. LV diameter and height are both 1-dimensional measurements; therefore, a simple ratiometric association between them is geometrically consistent. LV volume is a 3-dimensional measure; therefore, the relationship with height (1-dimensional) or BSA (2-dimensional) is not linear and might necessitate a more complex association (18). The ratiometric and allometric relationships of measurements with height, weight, and BSA are being investigated by the EchoNoRMAL collaboration but are beyond the scope of the present paper.

Our findings suggest that static thresholds may not be appropriate for many measurements. In contrast to the relatively constant URVs of LV diameters across age, the URVs of LV volumes decreased with increasing age. Because biplane volume includes length, and is measured in orthogonal planes, the change in volume may represent a change in geometry with increasing age that is not captured by the 1-dimensional measurement of diameter. An important caveat to these findings is that normative reference values define the boundaries of a reference cohort and are not related to the risk of an outcome. A change in the "normal" value with age does not necessarily mean a value is normal, and may not infer low risk of an adverse event.

The URV for SV also decreased with increasing age. Although the reduction in volume per year of age is proportionally greater (compared with the intercept) for LVESV than LVEDV, the reduction in absolute volume is greater for LVEDV, leading to its greater contribution to the reduction in SV. The trend with age for the URV of LVM was variable, depending on sex, ethnic group, and method of measurement. Previous studies (19,20) have found that LVM increases with increasing age. This may be a direct influence of age, but may also be an influence of long-term exposure to other factors, such as increased blood pressure (although this was within the normotensive range for all subjects in this study).

To the best of our knowledge, an ethnic-specific difference in EF among healthy subjects has not been demonstrated before. The reference values resulted from modeling in the tails of the distribution at each age, so they may be sensitive to studies that systematically measure lower values. When the study was permitted to vary as a random effect in quantile regression models, 1 study was defined as having outlying low values for EF that affected the reference values for EF in Europeans, and another study had similarly important outlying values of larger LV volumes (Online Tables E1a to E3b). After excluding these 2 studies from the analysis of EF, the predicted values for Europeans remained significantly lower than those for East Asians. Proportionally, 10 times more Europeans than East Asians had an EF <50% (4.3% Europeans, 0.4% East Asians). Unfortunately, there were insufficient data to investigate the difference in LAvol among subjects with a low EF; however, among Europeans, LAD was lower when EF was <50% compared with ≥50%. Thus, our data suggest, that even with the inherent variability in operator-dependent measurements from a range of centers around the world, the distribution of EF differs by ethnic group. Future work may determine whether these differences have prognostic or therapeutic implications, which are currently based on a universal cutpoint of EF.

A low EF may be expected in people that are not entirely "normal," whether due to disease or other factors (e.g., athletic training, sustained living at altitude, dietary or drinking habits). Subjects with known risk factors for CV disease were excluded from the EchoNoRMAL reference cohort, and values of blood pressure or glucose for people with EFs <50% were similar to those of people with EFs ≥50% and were not weighted toward the thresholds for hypertension or diabetes (data not shown). Similarly, studies recruited from athletic cohorts were not included in the EchoNoRMAL meta-analysis. Athletic individuals may well remain in the reference cohort; however, it was unlikely that they would represent all subjects in the lower end of the European distribution of EF.

STUDY LIMITATIONS. This study incorporated echocardiographic measurements from a wide range of cohorts from around the world. However, many populations remain under-represented, and we were unable to develop robust reference values for Australian Aboriginal, Pacific (Pacific Island or Māori), and Middle Eastern groups. In addition, the adult age range could not always be adequately represented (e.g., American Blacks), and insufficient data to derive reference values of 3-dimensional images were received. There is a need for further prospective studies to allow comprehensive ethnic-appropriate reference values to be derived. These may include cohorts with disease to allow the severity of abnormalities (e.g., LV hypertrophy) to be appropriately defined. There may also be a role for prognostic reference values to be developed, which relate a measurement to the risk of a future event. These may be of particular relevance to the elderly, in whom cardiac size and function may not be normal, and in whom the more relevant question is the impact of a given cardiac size or function on their risk of a future event.

Individual studies collected data prospectively according to individual protocols; therefore, some variation may have occurred in image capture and measurement. Sources of variability have been identified (4), but a pre-defined image acquisition and measurement protocol did not exist. Furthermore, any comparison of reference values obtained by different measurement modes or echocardiographic views was limited because very few subjects had measurements repeated from more than 1 mode or view. However, the individual studies were planned and performed as research protocols, and so heterogeneity among studies represented the real world in clinical and academic centers, and the variability was thus likely to be less than might be observed across different clinical echocardiography laboratories.

Importantly, the statistical methods required to develop reference ranges did not support a discussion about the biological influences on the similarities or differences between sex and ethnic groups. These aspects will be explored in subsequent analyses from the EchoNoRMAL collaboration.

CONCLUSIONS

New echocardiographic reference values for left heart size and systolic function have been derived from a large international cohort of subjects without CV disease or risk factors. Indexation of LV diameters may reduce the need for ethnic-appropriate reference values (within sex); however, this cannot be achieved with simple indexation of LV volumes or LVM by height or BSA. Importantly, ethnic-appropriate reference values for EF should be utilized. Important differences by sex, ethnicity, and age have been demonstrated and support the need for more comprehensive reference values to be applied to patients undergoing echocardiography.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Many echocardiographic measurements of cardiac size and function differ by sex, ethnicity, and age. Failure to take these factors into account could have significant implications for the under- and over-diagnosis of cardiovascular abnormalities in different populations and appropriate reference values should be used.

TRANSLATIONAL OUTLOOK: The impact of this information on diagnosis in non-European populations should be evaluated in prospective studies.

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APPENDIX For supplemental tables, please see the online version of this article.