Similarities and Differences in Left Ventricular Size and Function among Races and Nationalities: Results of the World Alliance Societies of Echocardiography Normal Values Study

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Background: The World Alliance Societies of Echocardiography (WASE) Normal Values Study evaluates individuals from multiple countries and races with the aim of describing normative values that could be applied to the global community worldwide and to determine differences and similarities among people from different countries and races. The present report focuses specifically on two-dimensional (2D) left ventricular (LV) dimensions, volumes, and systolic function.

Methods: The WASE Normal Values Study is a multicenter international, observational, prospective, cross-sectional study of healthy adult individuals. Participants recruited in each country were evenly distributed among six predetermined subgroups according to age and gender. Comprehensive 2D transthoracic echocardiograms were acquired and analyzed following strict protocols based on recent American Society of Echocardiography and European Association of Cardiovascular Imaging guidelines. Analysis was performed at the WASE 2D core laboratory and included 2D LV dimensions, LV volumes, and LV ejection fraction (LVEF) by the biplane Simpson method and global longitudinal strain (GLS).

Results: Two thousand eight subjects were enrolled in 15 countries. The median age was 45 years (interquartile range, 32–65 years), 42.8% were white, 41.8% were Asian, and 9.7% were black. LV dimensions and volumes were larger in male subjects, while LVEF and GLS were higher in female subjects. Global

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WASE normal ranges for LV dimensions were smaller than those in the guidelines, but the upper limits of normal for LV volumes and the lower limits of normal for LVEF were higher in the WASE study. Significant intercountry variation was identified for all LV parameters reflecting LV size (dimensions, mass, and volumes) even after indexing to body surface area, with LV end-diastolic and end-systolic volumes having the highest variation. The largest volumes were noted in Australia, while the smallest were measured in India for both genders. This finding suggests that in addition to gender and body surface area, specific country should be considered when evaluating LV volumes. Intercountry variation for LVEF and GLS was smaller but still statistically significant ($P < .05$ for all).

Conclusions: LV dimensions and volumes are larger in men, while LVEF and GLS are higher in women. Current guideline-recommended normal ranges for LV volumes and LVEF should be adjusted. Intercountry variability is significant for LV volumes, and therefore nationality should be considered for defining ranges of normality. (J Am Soc Echocardiogr 2019;32:1396-406.)

Keywords: Normal values, Echocardiography, WASE, Left ventricle, International, Multiracial

The recent American Society of Echocardiography (ASE) and European Association of Cardiovascular Imaging (EACVI) updated recommendations for chamber quantification define ranges of normative values for the general population using data obtained from well-designed population-based studies.[1] Although these normative values are used as a reference worldwide, they are derived from data obtained in the United States[2] or specific regions in Europe,[3-7] thereby reflecting a predominantly white population that is not representative of patients from other races or areas of the world. Importantly, recent reports from China,[8] Japan,[9] and Iran[10] suggest that "normal" hearts in those nations are smaller compared with those reported in American and European studies. However, each of these studies followed different methodologies, therefore no direct comparisons with standardized image acquisition and analysis have been performed to date. Accordingly, the World Alliance Societies of Echocardiography (WASE) Normal Values Study was designed with the following aims: (1) to prospectively establish normal echocardiographic values for parameters of chamber size and function across different nationalities, races, and ethnicities worldwide in a multinational study and (2) to describe and characterize similarities and differences among these groups using standardized protocols for image acquisition, modern echocardiographic machines, and centralized readings to ensure uniform, high-quality measurements. The goals of the present report are to establish global and regional normative values (lower limit of normal [LLN] and upper limit of normal [ULN]) for the evaluation of left ventricular (LV) size and function using two-dimensional (2D) echocardiography and strain imaging and to characterize similarities and differences among healthy adults from different nationalities and races.

METHODS

Study Design and Population

The rationale and design of the WASE Normal Values Study have been described in detail elsewhere.[11] Briefly, WASE is a multicenter international, observational, prospective, cross-sectional study of healthy adult individuals. The ASE invited representatives of member societies of the ASE International Alliance Partners (as of March 2016) to participate in this study by enrolling 100 "normal" local healthy adult volunteers. A "normal" subject was defined as one without a history or clinical evidence of heart, lung, or kidney disease. Detailed inclusion and exclusion criteria are listed in Supplemental Table 1.

Individuals recruited in each country were evenly distributed among six predetermined subgroups according to age (young, 18–40 years; middle-aged, 41–65 years; and elder adults, >65 years) and gender, to allow adequate intercountry comparisons. A single encounter with each patient was required for the collection of basic demographic information and acquisition of a comprehensive transthoracic echocardiogram. Body surface area (BSA) was calculated using the Mosteller formula. For the purpose of the WASE study, the definitions of race and ethnicity were adapted from those proposed for the 2020 US census, the US Food and Drug Administration, and the 2011 UK census.[12-14]

The study was approved by the local ethics committees, and subjects provided consent as mandated by each of the enrolling center's institutional review boards or ethics committees.

Echocardiographic Image Acquisition and Analysis Protocol

A comprehensive transthoracic echocardiogram was acquired following a study-specific standardized acquisition protocol created by the WASE core laboratories (MedStar Health Research Institute and the University of Chicago) and on the basis of recent ASE recommendations.[1,15] Ultrasound machines used for data acquisition could be from any vendor but had to be able to acquire 2D, Doppler, and three-dimensional images using uniform settings. Digital Imaging and Communications in Medicine and raw-format images were transferred to the echocardiography core laboratories for analysis. All 2D and strain data analysis were performed by the core laboratory at MedStar Health Research Institute (Washington, DC) using a vendor-neutral workstation (Image Arena; TomTec, Unterschleissheim, Germany), following ASE/EACVI guidelines.[1] LV and LV wall linear dimensions were measured on 2D images at end-diastole from the parasternal long-axis view, at the tips of the opened mitral valve leaflets and perpendicular to the long axis of the left ventricle. LV mass was calculated with the cube formula. LV volumes and LV ejection fraction (LVEF) were calculated from the apical views, using the biplane Simpson rule. All LV dimensions and volumes were also indexed to BSA. Endocardial LV global longitudinal strain (GLS) was calculated from 2D images using a speckle-tracking technique, from the apical two-, four-, and three-chamber views.

Statistical Analysis

Normal ranges for each echocardiographic parameter were defined as those that would include 95% of the population. Three different approaches were used in generating normal ranges on the basis of normality of data distribution, which was tested using the Kolmogorov-Smirnov test: (1) If data distribution was normal, range was calculated as mean ± SD × 1.96. (2) If data distribution was not

Abbreviations

2D = Two-dimensional

ASE = American Society of Echocardiography

BSA = Body surface area

EACVI = European Association of Cardiovascular Imaging

GLS = Global longitudinal strain

LLN = Lower limit of normal

LV = Left ventricular

LVEDV = Left ventricular end-diastolic volume

LVEF = Left ventricular ejection fraction

TTE = Transthoracic Echocardiogram

ULN = Upper limit of normal

WASE = World Alliance of Societies of Echocardiography

normal, log transformation was performed and the data were re-tested for normality. If log-transformed data were normal, range was obtained using mean ± SD × 1.96 of lognormal variable and transformed back using antilog. (3) If lognormal variable did not show normal distribution, normal range was obtained as the range between the 2.5th percentile and 97.5th percentile. This approach was applied to each subgroup of the sample for which the normal range was calculated. Comparisons between men and women were conducted using two-sample *t* tests when the normality assumption was satisfied and the nonparametric Wilcoxon rank-sum test when data were not normal. An intercept-only random-effect model was specified to measure variation among countries by specifying intercept as a random effect at the country level. This model partitions total variance around the mean into variance that occurs among countries and variance that occurs among subjects within countries. The *P* value for testing if variance among countries is equal to zero is provided along with the percentage of variation among countries (by intraclass correlation coefficient). A higher percentage of variation implies more similarity between subject within a country than between countries. GLS was considered negative for the definition of reference values and positive (GLS magnitude or absolute value) in all statistical comparisons. Statistical significance was defined as $P < .05$. All statistical analysis was performed using SAS version 9.4 (SAS Institute, Cary, NC)

RESULTS

From September 2016 to January 2019, 2,262 individuals were enrolled at 19 centers in 15 countries, representing six continents (Supplemental Figure 1). A total of 2,008 subjects formed the final population of the 2D analysis for the WASE study (distribution per enrolling center is presented in Supplemental Table 2), after the exclusion of 254 subjects who either did not meet inclusion or exclusion criteria (age, cardiac disease, age or gender group already fulfilled, etc.) or had incomplete echocardiograms missing critical views. Feasibility of LV data analysis was excellent: the biplane Simpson method for LV volumes and LVEF was suitable in 1,994 subjects (99%), while 2D LV dimensions were obtained in all but one subject; LV GLS, using all three apical views, was obtained in 1,882 subjects (93.7%).

Basic demographic characteristics of the study population, including race and ethnicity, are described in Table 1. The median age was 45 years (interquartile range, 32–65 years; range, 18–98 years), evenly distributed among age and gender and nationality groups, by protocol design. Most individuals were of white or Asian race (42.8% and 41.8%, respectively), while a minority were black or mixed or other (9.7% and 5.7%, respectively). Mixed-race individuals were almost exclusively a mix of white and Native American, recruited in Mexico. Among the 501 individuals enrolled in the elder group, 36 (7%) had comorbidities that were considered exclusion criteria for the other age groups (19 had medically controlled hypertension, 12 had medically controlled hyperlipidemia, and five had both).

Table 1 Demographic characteristics

Variable	Value
Age, y	45 (32–65)
Age group, y	
18–40	854 (42.5)
41–65	653 (32.5)
>65	501 (25.0)
Sex, male	1,033 (51.4)
Height, cm	167 (160–174)
Weight, kg	67 (58–77)
BSA, m^2	1.76 (1.62–1.92)
Heart rate, beats/min	68 (60–75)
SBP, mm Hg	120 (110–130)
DBP, mm Hg	74 (69–80)
Race	
White	860 (42.8)
Black	194 (9.7)
Asian	840 (41.8)
Other, mixed + others	114 (5.7)
Ethnicity	
White, North America, Europe	605 (30.1)
White, Middle Eastern	162 (8.1)
Black	196 (9.8)
Asian	839 (41.8)
Hispanic	202 (10.1)
Other	4 (0.2)

DBP, Diastolic blood pressure; *SBP*, systolic blood pressure.
Data are expressed as median (interquartile range) or as number (percentage).

Global LV Normal Ranges

Table 2 describes the nonindexed and indexed normal ranges for LV chamber dimensions and functional parameters by gender on the basis of the global WASE population, together with those proposed by the 2015 ASE/EACVI guidelines.[1] Normal values for LV volumes, defined from the global WASE population, were significantly larger for male than for female subjects, even after indexing to BSA. Although LV internal dimensions at end-systole and end-diastole were larger for men, this difference was reversed after indexing to BSA (larger for women). On the other hand, LVEF and GLS were higher in absolute value for women. All these gender differences were significant ($P < .0001$).

Compared with guideline recommendations, ranges of normality were slightly wider in the WASE population with regard to LV volumes and dimensions. The ULN for LV dimensions and LV mass index were lower in WASE, but those of LV end-diastolic volume (LVEDV; 165 and 122 mL for male and female subjects) and indexed LVEDV (80 and 70 mL/m^2, respectively) were higher than those proposed by the

HIGHLIGHTS

- LV dimensions and volumes are larger in males, while LVEF and GLS are higher in females.
- Current guidelines-recommended normal ranges for LV volumes and EF should be revised.
- Due to inter-country variability, nationality should be considered for defining ranges of normality for LV volumes.
- Dimensions and volumes are similar for people of White and Black race, while smaller for Asians and Mexicans (mixed white/native American race).
- Given national variations within same race, adjustments of normal ranges by nationalities seem more appropriate than by race.

guidelines for both genders. However, with regard to LVEF, ranges were narrower, with the LLN being higher in WASE than those proposed in the guidelines (57% vs 52%, respectively, for men and 58% vs 54% for women). The LLNs for LV GLS in WASE were −17% and −18% for men and women, respectively.

Comparison among Countries

Description of normal ranges according to country for both genders is presented in Table 3. When comparing all countries, significant intercountry variation was identified for all LV parameters reflecting LV size (dimensions, mass, and volumes), with LVEDV and LV end-systolic volume having the highest percentage of variation, even after indexing to BSA. Figure 1 represents a graphic intercountry comparison of the mean indexed LVEDV. The intercountry variations for LVEF and GLS were small but still statistically significant ($P < .05$ for all). In the male subjects, the ULNs for LVEDV indexed to BSA, the best indicator of LV size, were smallest in all Asian countries (ULNs were 76 mL/m^2 or lower in all of them) and in Mexico (ULN = 67 mL/m^2), while they were >76 mL/m^2 in all other countries, being largest in the United States, Argentina, Italy, and Australia. In the female population, subjects from Mexico, India, the Philippines, Brazil, and Canada had the smallest ULNs for indexed LVEDV, while Argentina, the United States, and Australia had the largest. The LLNs for LVEF in male individuals were between 56% and 58% for all countries except Korea (60%), while in women LLNs were between 58% and 60% for all countries except Australia and Nigeria (55% in both). LLNs for GLS were −17% to −19% in all cases, except for men from Korea (in whom it was −16%).

Individual Countries Compared with Current Guidelines

Figure 2 represents the mean and ranges of normality (95% of the population) for each country and their comparison with the global ranges of normality proposed by the 2015 ASE/EACVI guidelines and to the overall WASE population. For LVEF, subjects from all countries in WASE fell within the guideline range, and almost no subjects came close to the proposed LLN. Accordingly, the guidelines' ranges appear to be too wide for the global and country-specific populations. Normal ranges for GLS were similar in all countries, but they could not be properly compared with guidelines (no specific values were provided). On evaluation of indexed LV volumes and dimensions, multiple countries have >10% or 20% of their cases falling outside of the guidelines' ranges (marked with single and double *asterisks* in the figure, respectively). Importantly, this was observed more frequently for diastolic than systolic measurements. Although most of these cases fall above the ULN for volumes, they fall under the LLN for dimensions and LV mass index.

Comparison among Races

Description of normal ranges according to race and gender are presented in Table 4. After indexing to BSA, individuals of white and black race have larger LV volumes and dimensions than those of Asian race and larger volumes than those of mixed race. However, there are no differences between people of white and black races.

Table 2 Normal ranges for the global WASE population by gender and its comparison with 2015 ASE/EACVI guidelines

Variable	WASE, LLN to ULN			Guidelines	
	Male	Female	*P*	Male	Female
LVIDd, mm	36 to 56	33 to 51	<.0001	42 to 58	38 to 52
Indexed LVIDd, mm/m^2	19 to 30	20 to 31	<.0001	22 to 30	23 to 31
LVIDs, mm	22 to 37	21 to 34	<.0001	25 to 40	22 to 35
Indexed LVIDs, mm/m^2	12 to 20	12 to 21	<.0001	13 to 21	13 to 21
IVSd, mm	6 to 12	5 to 10	<.0001	6 to 10	6 to 9
LVPWd, mm	6 to 11	5 to 10	<.0001	6 to 10	6 to 9
LV mass, g	74 to 204	55 to 148	<.0001	88 to 224	67 to 162
LV mass index, g/m^2	42 to 101	36 to 85	<.0001	49 to 115	43 to 95
LVEDV, mL	61 to165	47 to 122	<.0001	62 to 150	46 to 106
LVEDVI, mL/m^2	34 to 80	31 to 70	<.0001	34 to 74	29 to 61
LVESV, mL	21 to 65	17 to 47	<.0001	21 to 61	14 to 42
LVESVI, mL/m^2	12 to 32	11 to 28	<.0001	11 to 31	8 to 24
LVEF, %	57 to 68	58 to 69	<.0001	52 to 72	54 to 74
LV GLS, %	−17 to −24	−18 to −26	<.0001	NA	NA

IVSd, Interventricular septal dimension in diastole; *LVEDVI*, LVEDV index; *LVESV*, LV end-systolic volume; *LVESVI*, LVESV index; *LVIDd*, LV internal dimension at end-diastole; *LVIDs*, LV internal dimension at end-systole; *LVPWd*, LV posterior wall dimension in diastole; *NA*, not applicable.

Table 3 Normal ranges by country and gender

Country	LVIDd, mm	Indexed LVIDd, mm/m^2	LVIDs, mm	Indexed LVIDs, mm/m^2	IVSd, mm	LVPWd, mm	LV Mass, g	LV Mass Index, g/m^2	LVEDV, mL	LVEDVI, mL/m^2	LVESV, mL	LVESVI, mL/m^2	LVEF, %	GLS, %
Male														
ARG	36 to 57	18 to 30	22 to 38	11 to 20	5 to 11	6 to 11	52 to 197	28 to 98	49 to 166	25 to 84	17 to 65	9 to 33	56 to 68	−18 to −25
AUS	38 to 60	19 to 29	25 to 39	12 to 19	6 to 11	6 to 12	81 to 236	43 to 108	67 to 181	38 to 83	25 to 72	14 to 33	57 to 66	−17 to −24
BRA	36 to 54	17 to 28	22 to 36	11 to 19	5 to 11	7 to 11	66 to 176	36 to 88	59 to 153	30 to 78	20 to 60	11 to 30	57 to 67	−17 to −25
CAN	36 to 59	19 to 30	23 to 39	12 to 20	5 to 12	6 to 11	66 to 200	37 to 100	64 to 163	36 to 80	22 to 64	12 to 32	57 to 68	−17 to −23
CHI	37 to 53	20 to 30	22 to 35	12 to 20	5 to 10	6 to 11	66 to 164	38 to 89	60 to 135	35 to 73	20 to 50	11 to 28	58 to 69	−17 to −25
IN	34 to 52	18 to 31	22 to 34	12 to 20	5 to 11	6 to 11	64 to 169	40 to 88	47 to 113	29 to 62	18 to 46	10 to 24	58 to 69	−17 to −25
IRA	37 to 55	19 to 29	23 to 37	12 to 19	5 to 11	6 to 11	79 to 188	38 to 90	61 to 147	32 to 75	20 to 58	11 to 30	58 to 67	−17 to −24
ITA	36 to 56	19 to 29	23 to 37	12 to 19	5 to 12	6 to 11	64 to 201	36 to 101	71 to 167	39 to 83	21 to 64	13 to 34	57 to 68	−18 to −24
JAP	35 to 54	21 to 31	21 to 36	12 to 20	6 to 11	6 to 11	65 to 183	40 to 101	66 to 144	36 to 76	22 to 58	13 to 32	56 to 69	−17 to −24
KOR	37 to 56	20 to 29	24 to 36	13 to 19	6 to 12	7 to 12	95 to 212	53 to 109	58 to 142	35 to 72	19 to 54	12 to 27	60 to 69	−16 to −23
MEX	36 to 55	19 to 30	23 to 36	13 to 19	5 to 10	6 to 10	73 to 170	37 to 85	60 to 130	35 to 67	20 to 51	12 to 26	58 to 67	−19 to −24
NIG	31 to 52	19 to 28	21 to 37	12 to 19	6 to 11	6 to 12	71 to 203	42 to 95	48 to 166	32 to 80	14 to 66	10 to 32	56 to 69	−17 to −24
PHI	39 to 54	20 to 31	23 to 36	13 to 20	6 to 11	6 to 12	76 to 189	48 to 100	63 to 140	33 to 70	20 to 56	11 to 28	57 to 68	−17 to −23
UK	40 to 59	20 to 29	24 to 39	12 to 19	5 to 11	6 to 11	81 to 205	42 to 100	61 to 161	33 to 77	24 to 68	11 to 30	56 to 69	−17 to −25
USA	36 to 55	18 to 30	23 to 38	11 to 20	5 to 11	7 to 11	80 to 198	44 to 93	70 to 175	37 to 84	25 to 66	13 to 32	58 to 68	−17 to −24
% of variation	9.41	5.52	8.33	3.17	3.97	6.16	10.73	8.86	18.83	10.52	17.7	9.94	3.28	6.04
P	.011	.017	.011	.035	.033	.017	.009	.012	.006	.008	.006	.009	.038	.020
Female														
ARG	33 to 53	20 to 31	20 to 35	12 to 21	4 to 11	5 to 10	44 to 162	28 to 93	42 to 133	24 to 80	18 to 53	11 to 32	58 to 68	−17 to −26
AUS	36 to 54	20 to 31	23 to 36	13 to 21	5 to 10	6 to 10	65 to 149	37 to 85	65 to 134	39 to 73	22 to 54	13 to 30	55 to 68	−17 to −25
BRA	33 to 50	20 to 30	22 to 32	13 to 19	5 to 10	5 to 10	51 to 138	32 to 77	50 to 117	31 to 65	17 to 44	11 to 25	59 to 68	−18 to −26
CAN	35 to 52	21 to 31	22 to 35	13 to 20	5 to 10	5 to 10	56 to 131	39 to 76	51 to 118	34 to 65	17 to 45	11 to 25	59 to 72	−17 to −25
CHI	32 to 49	19 to 32	20 to 32	12 to 21	4 to 10	5 to 10	48 to 139	28 to 78	44 to 103	28 to 66	14 to 38	9 to 24	59 to 70	−18 to −25
IN	32 to 49	20 to 32	20 to 32	12 to 21	5 to 10	5 to 10	48 to 125	37 to 78	40 to 91	26 to 58	14 to 35	9 to 22	58 to 68	−18 to −26
IRA	35 to 50	20 to 30	22 to 33	12 to 20	4 to 10	5 to 10	56 to 140	34 to 81	51 to 115	32 to 67	19 to 47	10 to 26	59 to 68	−19 to −26
ITA	33 to 50	20 to 31	21 to 33	12 to 21	4 to 11	5 to 10	47 to 134	31 to 79	47 to 113	30 to 67	16 to 42	10 to 25	59 to 70	−18 to −27
JAP	33 to 49	22 to 32	21 to 31	14 to 20	4 to 10	5 to 10	51 to 142	31 to 85	49 to 105	34 to 67	17 to 38	12 to 24	59 to 69	−18 to −27
KOR	34 to 51	23 to 32	21 to 34	14 to 21	4 to 11	6 to 11	60 to 164	41 to 100	47 to 110	32 to 69	15 to 40	11 to 25	60 to 69	−17 to −26
MEX	32 to 50	20 to 31	20 to 32	13 to 20	5 to 9	5 to 9	52 to 110	34 to 67	38 to 99	26 to 60	13 to 36	9 to 22	60 to 68	−19 to −26
NIG	34 to 51	19 to 31	20 to 35	11 to 21	4 to 10	5 to 10	52 to 129	32 to 75	52 to 121	31 to 71	19 to 52	11 to 31	55 to 70	−18 to −26
PHI	34 to 49	20 to 32	21 to 33	13 to 21	5 to 12	5 to 11	60 to 161	39 to 99	47 to 105	30 to 65	15 to 40	9 to 25	59 to 70	−17 to −24
UK	33 to 53	20 to 32	21 to 35	12 to 21	4 to 10	5 to 10	56 to 141	38 to 75	50 to 126	30 to 72	18 to 47	11 to 27	58 to 68	−18 to −26
USA	35 to 52	19 to 30	21 to 35	11 to 20	5 to 10	6 to 10	57 to 146	35 to 78	52 to 132	29 to 75	17 to 50	9 to 28	58 to 69	−18 to −26
% of variation	7.72	6.41	8.3	3.38	4.57	3.2	9.12	8.06	20.62	10.76	20.38	10.91	6.78	4.78
P	.014	.015	.013	.033	.029	.044	.012	.015	.006	.010	.007	.010	.017	.026

ARG, Argentina; *AUS*, Australia; *BRA*, Brazil; *CAN*, Canada; *CHI*, China; *IN*, India; *IRA*, Iran; *ITA*, Italy; *IVSd*, interventricular septal dimension in diastole; *JAP*, Japan; *KOR*, South Korea; *LVEDVI*, LVEDV index; *LVESV*, LV end-systolic volume; *LVESVI*, LV end-systolic volume index; *LVIDd*, LV internal dimension at end-diastole; *LVIDs*, LV internal dimension at end-systole; *LVPWd*, LV posterior wall dimension in diastole; *MEX*, Mexico; *NIG*, Nigeria; *PHI*, Philippines; *UK*, United Kingdom; *USA*, United States of America.
Comparison of all countries for each parameter is described as percentage of variation, and its statistical significance expressed as a *P* value.

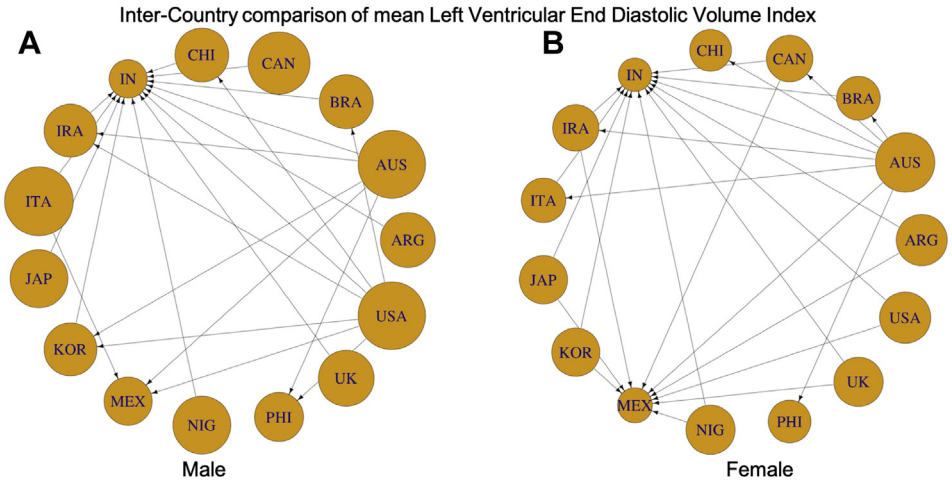

Figure 1 Intercountry comparisons of mean indexed LVEDV, divided by gender: **(A)** male and **(B)** female. *Arrows* represent statistically significant differences ($P < .05$), and the direction of the *arrows* represents larger to smaller mean indexed LVEDV. The sizes of the *circles* are proportional to the mean indexed LVEDV per country. *ARG*, Argentina; *AUS*, Australia; *BRA*, Brazil; *CAN*, Canada; *CHI*, China; *IN*, India; *IRA*, Iran; *ITA*, Italy; *JAP*, Japan; *KOR*, South Korea; *MEX*, Mexico; *NIG*, Nigeria; *PHI*, Philippines; *UK*, United Kingdom; *USA*, United States.

Normal ranges by race in WASE compared with those proposed in the guidelines are presented in Figure 3. Importantly, there is intercountry variation within each race (e.g., between Indians and Chinese, Australians and Italians).

DISCUSSION

The WASE Normal Values Study is unique in that it provides normal reference values of echocardiographic parameters in adults across a wide range of ages, races, ethnicities, and countries. In contrast to previous studies, this study included head-to-head comparisons, in which all technical differences in data acquisition between regions were minimized and standardized by using state-of-the-art equipment and strictly following ASE/EACVI recommendations. In addition, data analysis and interpretation were conducted uniformly by a core laboratory. The main findings of this study are as follows: (1) universal normal values for parameters of LV size and function, including GLS, were established and showed small differences among races and countries, with the exception of LV volumes; (2) these normal ranges differ from those published in the 2015 ASE/EACVI guidelines, suggesting that adjustments are needed, including country-specific LV volume data; (3) the normal range of LVEF is narrower, indicating that the lower abnormality cutoff should be adjusted upward for both genders and that the lower normality cutoff of the indexed dimensions and mass should be adjusted downward for both genders; and (4) our findings confirmed the previously reported small gender differences in LV function indices (higher LVEF and GLS in women).

Rationale for the WASE Study

The ASE/EACVI chamber quantification recommendations published in 2015 made significant progress relative to the previous 2005 version by including normal values and ranges for a variety of 2D chamber measurements.[1,16] These reference values have been obtained by meta-analysis from population-based studies,[2,4,7] which have several limitations. First, the majority of subjects were white, while few individuals of black race, Latinos, or Asians were included, because all studies were conducted in the United States or Europe. Second, the overall population of these studies predominantly reflected middle-aged adults, with limited representation of healthy elderly populations. Third, each study followed its own unique protocol, resulting in heterogeneous image acquisition and reported measurements; consequently, the normal values of each parameter were derived from different data sets. Even the largest, most recent meta-analysis conducted to provide global normal reference values,[17,18] representing a total of 22,404 subjects, has many of the same limitations. Nevertheless, this study suggested that differences may exist in LV size among ethnic groups, creating the need for additional studies aimed at answering this question.

In an attempt to standardize image acquisition and interpretation, the Normal Reference Ranges for Echocardiography study was performed as the first large multicenter European effort involving EACVI-accredited echocardiography laboratories, in which image acquisition followed the European guidelines and interpretation was performed in a centralized core laboratory.[3] Nevertheless, the main limitation of that study was that it still predominantly represented a white European population. Although studies from countries such as Brazil, Iran, Japan, China, Nepal, and individual European countries have been reported,[2,4,7-10,19,20] each of these studies used different imaging protocols and reported normal values of different parameters. Given these methodologic heterogeneities in individual studies, it is impossible to determine with certainty whether the findings reported in these populations are due to technical reasons or represent real differences in cardiac size and function. Accordingly, the need for reliable normative data in different populations led the ASE and its alliance partners to conduct the WASE study for a direct comparison of cardiac size and function from multiple regions in the world using standardized protocols that strictly follow guideline recommendations and a core laboratory.[21,22]

Linear LV Dimensions and Mass Measurements

We found that race- and country-related differences in average BSA-indexed LV linear dimensions were small in both systole and diastole, in both genders (within 2 mm/m^2). Interestingly, compared with the guidelines, average LV dimensions were smaller across genders, races,

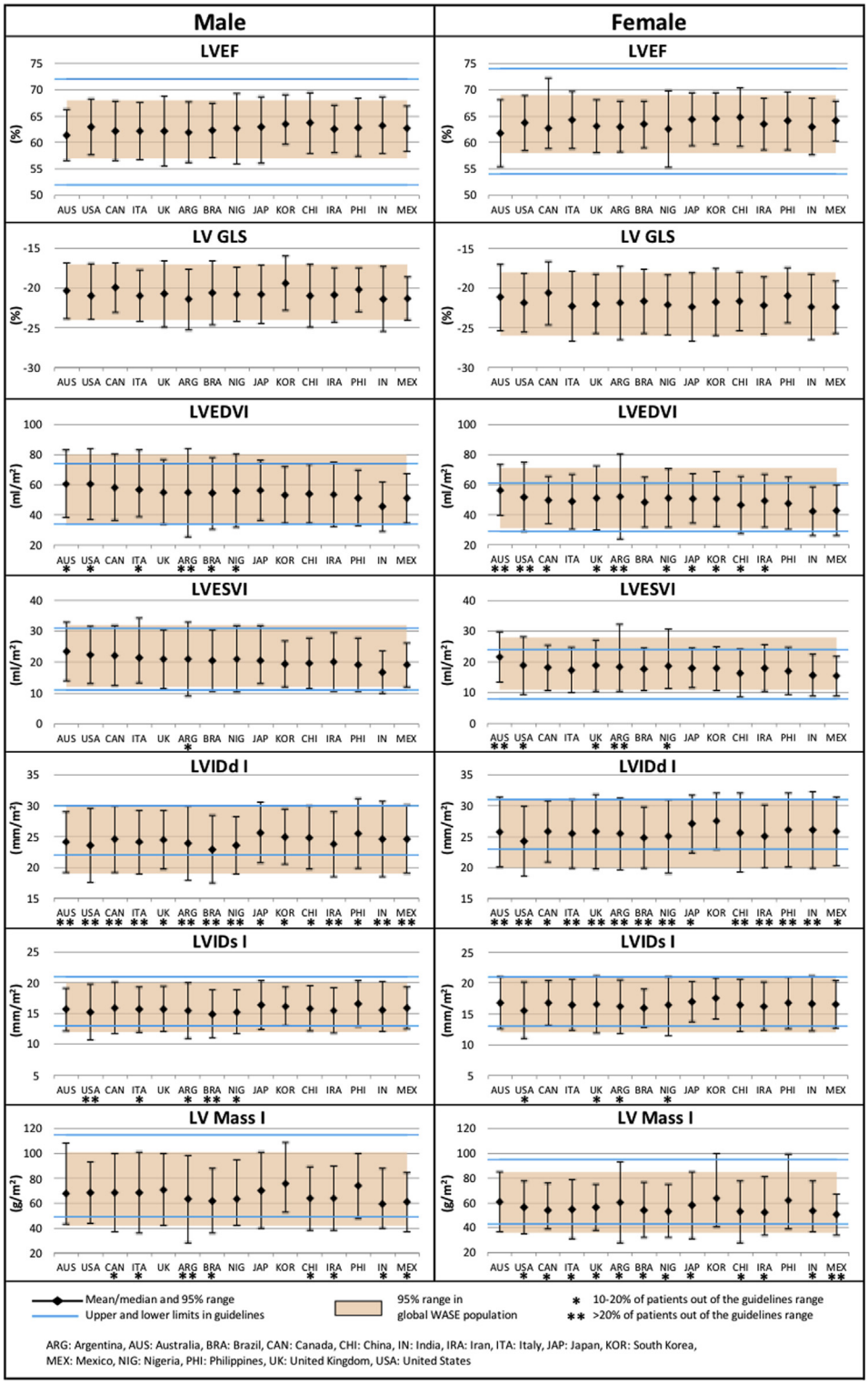

Figure 2 Normal ranges by country, compared with overall WASE and guideline-proposed ranges. Mean and ranges of normality (95% of the population) for each country and their relationship to the global ranges of normality proposed by the 2015 ASE/EACVI guidelines (ULN and LLN are presented as *horizontal blue lines*) and to the overall WASE population *(shaded horizontal bars)*. In each plot, countries are organized by predominant race (from *left* to *right*, white, black, Asian, and mixed). *Single asterisks* represent groups in which 10% to 20% of the cases fall outside of the guideline-proposed normal range; *double asterisks* represent groups in which >20% of the cases fall outside of the guideline-proposed normal range. *LVEDVI*, LVEDV index; *LVESVI*, LV end-systolic volume index, *LVIDd I*, LV internal dimension at end-diastole, indexed; *LVIDs I*, LV internal dimension at end-systole, indexed (mm/m^2); *LV mass I*, LV mass index.

Table 4 Normal ranges by race and gender

Race	Indexed LVIDd, mm/m-	Indexed LVIDs, mm/m^2	IVSd, mm	LVPWd, mm/m^2	LV Mass Index, g/m^2	LVEDVI, mL/m^2	LVESVI, mL/m^2	LVEF, %	GLS, %
Male									
White	19 to 29*	12 to 19*	6 to 12	6 to 11†	41 to 102	33 to 81*,†	11 to 32*,†	57 to 68*	−17 to −24
Black	18 to 29*	11 to 19*	6 to 11	7 to 12*,†	45 to 96	33 to 81*,†	13 to 33*	57 to 69	−17 to −25
Asian	20 to 30	13 to 20	6 to 12	6 to 11	43 to 102	31 to 72	12 to 29	58 to 69	−17 to −25
Other	19 to 30	13 to 19	5 to 11	6 to 10*	37 to 86*	34 to 68	12 to 27	58 to 67	−18 to −24
Female									
White	20 to 31*	12 to 20*	5 to 11†	6 to 10†	36 to 85†	32 to 76*,†	11 to 29*,†	58 to 69*	−18 to −26
Black	19 to 30*	11 to 21*	4 to 10	6 to 10†	33 to 76	32 to 69*,†	12 to 29*,†	56 to 68*	−18 to −26
Asian	21 to 31	13 to 21	5 to 11	5 to 11	36 to 89	29 to 66	10 to 24	59 to 69	−18 to −26
Other	20 to 31	13 to 20	5 to 9	5 to 9*	35 to 67*	26 to 62*	9 to 23	60 to 68	−19 to −25

IVSd, Interventricular septum dimension in diastole; *LVEDVI*, LVEDV index; *LVESVI*, LV end-systolic volume index; *LVIDd*, LV internal dimension at end-diastole; *LVIDs*, LV internal dimension at end-systole; *LVPWd*, LV posterior wall dimension in diastole.
The comparison between black and white was significantly different only for LVPWd in men.
*Significant difference ($P < .05$) between Asian and white, black, or other (mixed) races.
†Significant difference ($P < .05$) between other races (mixed) and white, black, or Asian.

and countries. Although the upper normal limits were similar in our study and in the guidelines, our lower limits are consistently lower than previously reported. As a result, in all countries, ≥10% of the study subjects, and in most countries >20%, fell below the guidelines recommended ranges. This finding was more pronounced for end-diastolic compared with end-systolic dimensions. A possible explanation for these findings is that the guideline-recommended normal values of linear dimensions were obtained from a mix of parasternal short- and long-axis views, as well as M-mode images, in which oblique cross-sections might have resulted in overestimated dimensions. In contrast, in our study, all linear dimensions were obtained from 2D parasternal long-axis views, in which particular care was taken to identify the dimension perpendicular to the long axis of the ventricle at the tip of the mitral valve leaflets. Such differences between WASE results and the guidelines propagated into LV mass measurements, which resulted in lower normal ranges. As a result, for both genders and most races and countries, ≥10% of the study subjects fell below the guideline-recommended ranges of LV mass. Despite the small differences, adjusting the reference ranges for LV dimensions and mass in the guidelines seems to be needed.

Two-Dimensional Volume Measurements

Interestingly, the race- and country-related differences in LV volumes were larger in both systole and diastole, especially for the upper limits of normal, with the country-related variability in volumes being as high as 20% and in indexed volumes >10% in both genders. This is potentially clinically important for the detection of ventricular enlargement in different countries, because these differences are not negligible. The largest volumes were noted in Australia, while the smallest volumes were measured in India for both genders. For example, the ULN LVEDV for women in India is 91 mL, whereas in Australia it is considerably higher at 134 mL. This finding suggests that in addition to gender and BSA, the specific country should be considered when evaluating normality of LV volumes.

However, unlike the linear dimensions, average LV volumes were larger across genders, races, and countries compared with the guidelines. Although the lower normal limits are similar between our results and the guidelines, the upper limits are consistently higher. As a result, in most countries ≥10% of the study subjects, and >20% in some countries, fell above the guideline-recommended ranges. This finding was more pronounced in women than men. These differences in normal values of LV volumes between our results and the guidelines can probably be explained by a few technical issues enforced in our study: (1) special emphasis was placed on avoiding foreshortening when acquiring apical views, and (2) the core laboratory traced the endocardial boundaries at the interface between the trabeculae and the compacted myocardium, in order to better reproduce cardiac magnetic resonance volume measurements, as previously suggested.[1,23] This is as opposed to the earlier studies, in which a number of apical views were foreshortened and endocardial boundaries were likely traced along the blood-trabeculae interface, resulting in smaller volume measurements. These differences were less pronounced at end-systole, when the trabeculae are compressed and the interface between the compacted and noncompacted myocardium is more difficult to identify. Given the significant differences, current guidelines should be revised to better describe ULNs for LV volumes and to consider country-specific ranges.

Ventricular Function

In both genders, average LVEF values were similar among races and countries, with small variations of the order of magnitude of 1% to 2%. Similar to the guidelines, normal LVEF values were slightly higher in women than in men. Of note, however, the entire normal range of LVEF was considerably narrower in both genders, across races and countries. This is likely a result of the uniformity in data acquisition and interpretation methodology, as well as the larger sample size. These results suggest that the LLN of LVEF should be adjusted upward from the previously recommended cutoff values.

Although the guidelines did not provide normal ranges for LV GLS, because of insufficient data, but only suggested a consensus-based abnormality cutoff value of −20%, the present study provides normal ranges across genders, races, and countries. Interestingly, the lower normal limits for GLS are considerably lower and stand at −17% for men and −18% for women. These data, however, should be interpreted with caution, as strain analysis to date is vendor dependent.

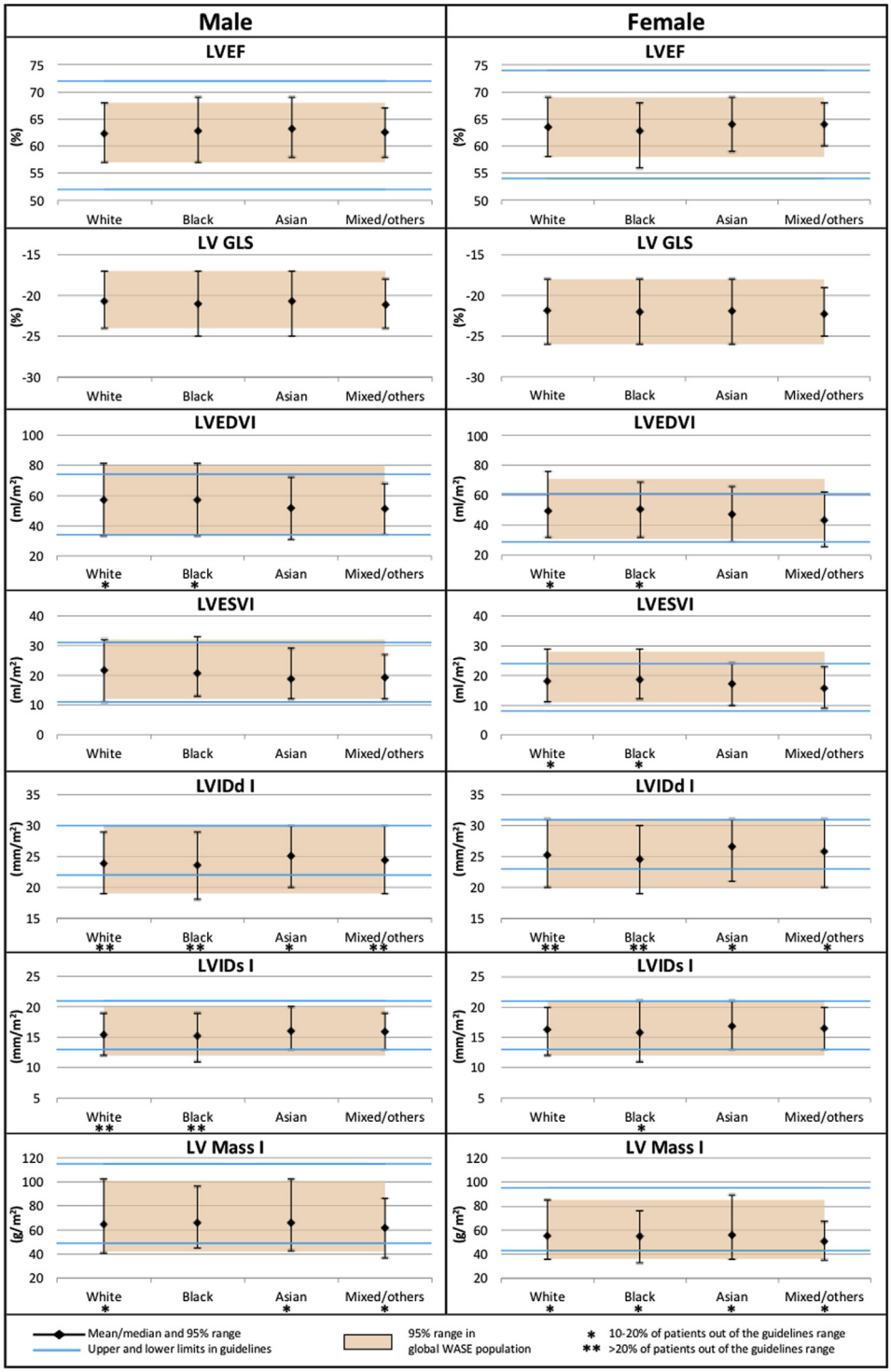

Figure 3 Normal ranges by race, compared with overall WASE and guideline-proposed ranges. Mean and ranges of normality (95% of the population) for each race and their relationship to the global ranges of normality proposed by the 2015 ASE/EACVI guidelines (ULN and LLN are presented as *horizontal blue lines*) and to the overall WASE population *(shaded horizontal bars)*. Mixed race is almost exclusively Mexicans, mixed between white and Native American. *Single asterisks* represent groups in which 10% to 20% of the cases fall outside of the guideline-proposed normal range; *double asterisks* represent groups in which >20% of the cases fall outside of the guideline-proposed normal range. *LVEDVI*, LVEDV index; *LVESVI*, LV end-systolic volume index, *LVIDd I*, LV internal dimension at end-diastole, indexed; *LVIDs I*, LV internal dimension at end-systole, indexed (mm/m^2); *LV mass I*, LV mass index.

Differences among Races

With regard to race, there were no significant differences between white and black people, while they both were larger (volumes and dimensions) than Asians and Mexicans (mixed). However, considering that there are intercountry differences within Asians and whites, it seems more reasonable to consider nationalities rather than race when determining LV normality or enlargement for a given individual.

Limitations

In the WASE study an attempt was made to be inclusive in order to represent multiple regions around the world, but certain areas remain underrepresented. Arguably, the number of individuals enrolled in each country could have been larger, an issue particularly relevant to address ethnic diversity within a country. However, in planning the sample size, we had to find the proper balance between inclusivity of the global international echocardiographic community and feasibility with the available resources. On the basis of the findings of this study, intercountry differences in LV volumes should spark additional, larger regional studies to establish even more statistically sound specific normality cutoffs or ranges for countries not included in the study (although countries not included may be better represented by individual WASE countries than by the current guidelines). In this context, a limitation of our study is that US census racial definitions were used, ignoring intraracial phenotypic differences. Also, in our study, the "mixed/other" race sample consisted almost exclusively of Mexican subjects, and thus our normal values for this racial category cannot be extrapolated to other mixed-race populations. In addition, multiple regional variations could be hypothesized to explain the described differences: climate, latitude, season of echocardiographic acquisition, dietary differences, and level of education, to mention just a few, none of which could be directly addressed in this study. Furthermore, in view of the widely reported intervendor variability in GLS measurements, our findings should be interpreted considering that images were acquired using multivendor equipment and analyzed using vendor-independent software. Accordingly, although our data are strong in detecting similarities or differences among subgroups, the hereby reported normal values may not be directly transferrable to measurements made using vendor-specific software. Finally, it is important to note that although higher volumes would be expected with the use of ultrasound-enhancing (contrast) agents, their use was not allowed in this study, so the normal range for the contrast-enhanced left ventricle cannot be answered with the WASE data.

CONCLUSION

The WASE Normal Values Study provides a unique and important set of normal reference values for LV size and functional parameters across genders, races, and countries, obtained using standardized methodology. We found small differences in normal values in most parameters among subjects of different races and in different countries, which achieved statistical significance but are unlikely to be clinically relevant. This suggests that the hereby reported normal values are nearly universal, with the exception of LV volumes, assessment of which needs to take into consideration race and country in addition to gender and body size. Importantly, these new normal values differ significantly from the ASE/EACVI guidelines, suggesting that the lower abnormality cutoff of LVEF should be adjusted upward and those of the indexed dimensions and mass should be adjusted downward for both genders. Also, the newly established normal ranges of GLS indicate different cutoff values than suggested by the guidelines. Although the normal values obtained in this study add confidence in defining abnormalities in LV size and function, the gender-, race-, and country-specific data may aid in the characterization of diverse populations around the world and their similarities and differences.

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SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.echo.2019.08.012.

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APPENDIX

REGIONAL PRINCIPAL INVESTIGATORS AND THEIR RESPECTIVE ENROLLING INSTITUTION

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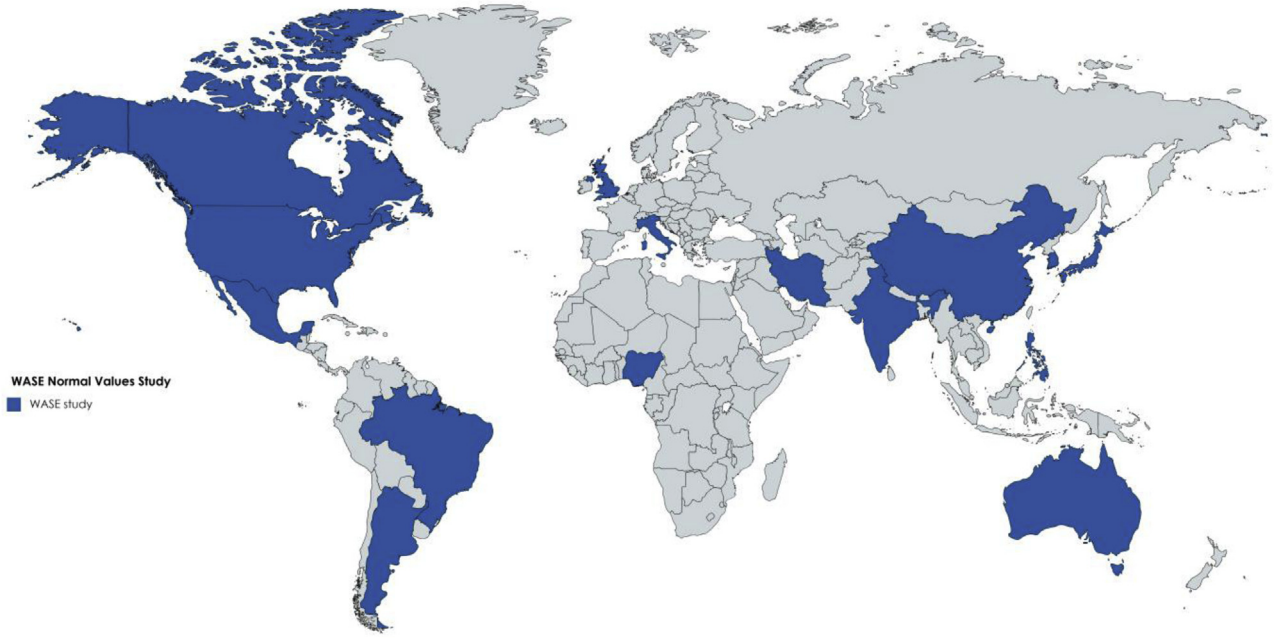

Supplemental Figure 1 WASE world map depicting countries that completed enrollment in the WASE Normal Values Study.

Supplemental Table 1 WASE inclusion and exclusion criteria

Inclusion criteria
≥18 years of age
No previous cardiac disease
No previous lung disease
No previous kidney disease
No history of (or receiving drugs for)
Hypertension*
Dyslipidemia*
Diabetes
Blood pressure < 140/90 mm Hg
Body mass index 20–30 kg/m^2†
Mild or less valvular disease
Exclusion criteria
Pregnant women
Competitive athletes
History of alcoholism
Significant renal insufficiency (blood creatinine > 2 mg/dL or 177 μmol/L)

*In June 2017, a protocol amendment was approved for allowing, only in the groups >65 years of age, a history of hypertension or hyperlipidemia as long as blood pressure and hyperlipidemia were well controlled with not more than two medications and there was no evidence of LV hypertrophy on echocardiography. This was decided on the basis of difficulty identifying elderly patients with no history of hypertension and hyperlipidemia. By the time of study completion, only 36 subjects were enrolled under these conditions.

†A body mass index of 18 to 30 kg/m^2 was allowed in countries with smaller body habitus, as perceived to be normal by the regional principal investigator (Japan).

Supplemental Table 2 Enrolling centers by country and number of enrolled subjects in WASE study

Country (Center)	*n*
Australia	101
China	131
Japan east (Tokyo)	141
Japan west (Kitakyushu)	89
Korea	102
Philippines	100
India south (Madurai)	126
India north (Medanta)	101
Iran	159
Argentina	101
Brazil	112
Nigeria	107
Canada	103
United States (Chicago)	74
United States (Seattle)	98
Mexico	102
Italy north (Padua)	97
Italy south (Salerno)	81
United Kingdom	83