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A meta-analysis of echocardiographic measurements of the left heart for the development of normative reference ranges in a large international cohort: the EchoNoRMAL study

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

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Aim To develop age-, sex-, and ethnic-appropriate normative reference ranges for standard echocardiographic measurements of the left heart by combining echocardiographic measurements obtained from adult volunteers without clinical cardiovascular disease or significant cardiovascular risk factors, from multiple studies around the world.

Methods and results The Echocardiographic Normal Ranges Meta-Analysis of the Left heart (EchoNoRMAL) collaboration was established and population-based data sets of echocardiographic measurements combined to perform an individual person data meta-analysis. Data from 43 studies were received, representing 51 222 subjects, of which 22 404 adults aged 18–80 years were without clinical cardiovascular or renal disease, hypertension or diabetes. Quantile regression or an appropriate parametric regression method will be used to derive reference values at the 5th and 95th centile of each measurement against age.

Conclusion This unique data set represents a large, multi-ethnic cohort of subjects resident in a wide range of countries. The resultant reference ranges will have wide applicability for normative data based on age, sex, and ethnicity.

Keywords Echocardiography • Reference ranges • Meta-analysis

Background

The clinical value of echocardiography (echo), or any imaging modality, relies on its ability to detect abnormalities. However, the diagnosis of 'abnormal' depends on the definition of 'normal'. The most recent reference values for echo chamber quantification were jointly published by the American Society of Echocardiography (ASE) and European Association of Cardiovascular Imaging (EACVI) in 2006.[1] This report was an important advance in quantitative echo in terms of consensus; however, the reference ranges were based upon a mixture of expert opinion, published and unpublished data, and a range of approaches to define the reference values. As reference values are inherently dependent upon the individual subjects studied, the population from which they are drawn is critical. In the joint ASE/EACVI report,[1] the ranges presented for left ventricular (LV) quantification were typically developed from relatively small North American cohorts recruited in the 1970s–80s and therefore may not represent the diverse world population to which they are now applied.

In support of this concern, a systematic review of the literature[2] identified that LV mass varied between normal cohorts from around the world. Individual values commonly fell outside the ASE/EACVI reference ranges,[1] whether indexed for body size or not. Ideally, sex- and ethnic-specific reference ranges should be developed using geographically diverse and population-based echo studies. As this has never been done before, we recently established a global collaborative initiative and here describe the objectives and methods of this initiative.

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Study objective

Our primary objective is to develop age-, sex-, and ethnic-appropriate normative reference ranges for standard echo measurements of the left heart by combining echo measurements obtained from adult volunteers without clinical cardiovascular disease (CVD) or significant cardiovascular risk factors, resident in a wide range of countries. This will be achieved through an individual person data meta-analysis.

Study design

Identification of cohorts

Population-based cohorts with echo measurements were identified through comprehensive literature searches, a published research call,[3] and personal communication.

Two literature searches were performed. The first was undertaken to identify studies that used echo in healthy volunteers. The second identified population studies in which echo was used to document the prevalence of a disease but for which echo findings may not have been published.

Studies were identified by searching Medline, Embase, and Scopus databases. The primary search used the keywords: echo with or without: Doppler, colour, stress, three-dimensional, four-dimensional; reference: values, ranges, limits; normal: ranges, values; atrial: dimension, volume, structure, function; ventricular: dimension, volume, mass, structure, function. In addition, the population search used the keywords: epidemiology, cohort, cross-sectional, sample studies; mass screening, anonymous testing, multiphasic screening; and supplementary concept terms of population: based, study, studies. Where applicable, keywords were searched as the root and truncation symbol (e.g. ventric*). All searches were limited to humans and studies published between 1 January 1990 and 31 December 2011. The language of publication was not restricted; however, abstracts were required to be in English. The corresponding author was emailed with an invitation to submit individual person-level data and so collaborate in the EchoNoRMAL meta-analysis. All individual studies were approved by appropriate ethics committees, and the EchoNoRMAL protocol was approved by the University of Auckland Human Participants Ethics Committee (#7653).

Study inclusion criteria

Studies that recruited >50 volunteers aged ≥ 18 years were eligible for inclusion. Of these, studies of special populations such as athletes or pregnant women were excluded. Studies must have measured at least one of LV size or mass, left atrial size, mitral inflow or tissue Doppler, or pulmonary vein Doppler and used at least one measurement modality of M-mode, two- (2D), or three-dimensional (3D) echocardiography.

Studies that included patients referred for echo, but who were later judged to have been free of the disease of interest, were not eligible for inclusion. This exclusion was on the basis that the referral may have been due to cardiac symptoms or risk factors even if no disease was detected. Such cohorts may include patients extracted from an echo laboratory database and retrospectively deemed 'healthy normal'. However, studies containing patients referred to specialist cardiac services for routine asymptomatic reasons, such as screening for medical insurance or a 'healthy heart check' and found to be free of cardiovascular or other disease, were included.

The studies included in EchoNoRMAL are described in *Table 1* and Supplementary data online.

Data management

De-identified individual person data were sent to the central co-ordinating centre located in Auckland, New Zealand, and stored on a secure server. Each data set was reviewed for units and methods of measurement, range checks were performed to identify and exclude biologically implausible values, and summary statistics cross-checked against published results, where available. Variables were re-coded to a central legend to allow data amalgamation. Study investigators were contacted to clarify any uncertainty about the data or methods.

Additional variables were created to describe: the year or range of years in which echocardiograms were performed, the model of echo machine used, if echocardiograms were performed at a single centre or not, and if image measurements were performed by a single or multiple observers. For chamber dimensions, the measuring convention used (leading-edge-to-leading-edge, Penn, or 2D-linear), as well as the echocardiographic view (parasternal long axis, parasternal short axis, apical 4- or 2-chamber) was defined for each variable. LV volumes and mass were defined as being derived from dimensions or from areas traced from 2D images, and the equation used to estimate volume or mass was defined.

Ethnicity

To enable the reference ranges derived in this study to be applied in the clinical setting, the definition of race or ethnicity needs to be carefully considered. Race is viewed as having a biological basis, whereas ethnicity embodies one or more of the following: 'shared origins or social background; shared culture and traditions that are distinctive, maintained between generations, and lead to a sense of identify and group; and a common language or religious tradition'.[40]

A wide range of ethnic groups were described by individual studies, with definitions on the basis of self-identification (16 studies), ancestry (1 study), or by name and country of recruitment (1 study). Twenty-five studies did not state how ethnicity was defined. Race may be the more appropriate concept by which to discuss cardiac size and function in health; however, ethnicity is typically self-identified and therefore the most accessible definition in practice. The data available to the meta-analysis were centred on ethnicity. Consequently, the ethnic groups described by individual studies have been grouped as follows: **African:** African, African-Caribbean, Black (not American), Black African, Black British, Black Caribbean, Brazilian-Mulatto, Nigerian, Somali; **American Black:** African American, Black (American studies); **Asian:** Asian, Asiatic, Chinese, East Timorese, Filipino, Japanese, Korean, Malaysian, Taiwanese, Thai, Tibetan, or Vietnamese; **Australian Aboriginal**; **European:** white European or Caucasian described as American, Australian, Belgian, British, Bulgarian, Caucasian Jew, Croatian, Czech, Danish, French, Greek, Italian, Latin American, Maltese, New Zealander, Polish, Scandinavian, Serbian, South African, Spanish, or Turkish; **Middle Eastern:** Arab, Iranian; **Pacific:** Maori, Samoan; **South Asian:** Bangladeshi, British South Asian,

Table 1 EchoNoRMAL studies and investigators

Study	Investigators
Alberta HEART[a]	T. Anderson, J. Dyck, J. A. Ezekowitz
Asklepios[4]	J. A. Chirinos, M. L. De Buyzere, T. C. Gillebert, E. Rietzschel, P. Segers, C. M. Van Daele
Auckland[a]	R. N. Doughty, K. K. Poppe, H. A. Walsh, G. A. Whalley
Campania Salute[5]	R. Izzo, N. De Luca, B. Trimarco, G. de Simone
CARDIA[6]	Restricted public use data
CCCC[7]	P. -C. Chen, K. -L. Chien, H. -J. Lin, T. -C. Su
CCHS[8]	R. Mogelvang, J. Skov Jensen
Chadha[9]	D. S. Chadha, K. Goel, A. Misra
China California Heart Watch[10]	R. Detrano, www.chinacal.org
Christchurch Healthy Volunteers[a]	V. Cameron, A. M. Richards, R. Troughton
CHS[6]	Restricted public use data
Di Pasquale[11]	P. Di Pasquale, S. Paterna
Duzenli[12]	M. Akif Duzenli
ECHOES[13]	F. D. R. Hobbs, M. K. Davies, R. C. Davis, A. Roalfe
E-ECHOES[14]	M. Calvert, M. K. Davies, R. C. Davis, N. Freemantle, P. S. Gill, G. Y. H. Lip
FLEMENGHO[15]	T. Kuznetsova, J. A. Staessen
Glasgow MONICA[16]	H. J. Dargie, I. Ford, T. A. McDonagh, J. J. V. McMurray
Grossman[17]	E. Grossman
Harrow Heart Failure Watch[18]	G. Galasko, A. Lahiri, R. Senior
Heart of Soweto[19]	L. Blauwet, K. Sliwa, S. Stewart
Heart of the Heart[20]	A. Brown, M. Carrington, H. Krum, M. McGrady, S. Stewart, C. Zeitz
HUNT[21]	H. Dalen, H. E. Moelmen Hansen, A. Støylen, A. Thorstensen
JAMP[22]	M. Daimon, H. Watanabe, J. Yoshikawa
JAMP-3D[23]	S. Fukuda
Kim[24]	H. -K. Kim
Leung[25]	N. K. W. Leung
Linhart[26]	A. Linhart
LOLIPOP[27]	N. Chahal, J. C. Chambers, J. Kooner, R. Senior
NEAT[28]	J. Davies, I. Loke, L. Ng, I. B. Squire
NEST[29]	E. Aune, J. E. Otterstad
Ng[30]	D. Y. Leung, A. C. T. Ng
Ojji[31]	D. Ojji
OxVALVE[a]	L. Arnold, S. Coffey, J. d'Arcy, C. Hammond, C. Mabbett, C. Lima, M. Loudon, N. Pinheiro, B. Prendergast, R. Reynolds
Padua 3D Echo Normal[32]	L. P. Badano, D. Muraru, D. Peluso, L. Dal Bianco
Petrovic[33]	D. J. Petrovic, J. Petrovic
Schvartzman[34]	P. Schvartzman, F. D. Fuchs
Simova[a]	T. Katova, I. Simova
Takeuchi[35]	K. Kaku, M. Takeuchi
Thomas[36]	A. Boyd, L. Thomas
Thomas 2[a]	E. M. Chia, L. Thomas
Tromsø Study[37]	H. Schirmer
Vitoria Brazil[38]	L. C. Angelo, A. C. Pereira, J. E. Krieger, J. G. Mill, S. L. Rodrigues
Vobarno[39]	M. L. Muiesan, A. Paini, E. Agabiti Rosei, M. Salvetti

[a]Unpublished data.
CARDIA, Coronary Artery Risk Development in Adults; CCCC, Chin-Shan Community Cardiovascular Cohort study; CCHS, Copenhagen City Heart Study; CHS, Cardiovascular Health Study; ECHOES, Echocardiographic Heart of England Screening; E-ECHOES, Ethnic-Echocardiographic Heart of England Screening; FLEMENGHO, Flemish Study on Environment, Genes and Healthy Outcome; HUNT, Nord-Trøndelag Health Study; JAMP, Japanese normal values for echocardiographic Measurements Project; LOLIPOP, Life Sciences Prospective Population Study; NEAT, New and Emerging Applications of Technology; NEST, Normal Echo Study Tønsberg.

East African Asian, Fijian Indian, Indian, Mauritian, Pakistani, or Sri Lankan; **Other:** ethnicity was not defined in the original study.

Individual participant exclusions

A flowchart showing derivation of the reference cohort is in *Figure 1*.

Individual study design may have included or excluded participants on the basis of clinically manifest disease at the point of recruitment. For example, studies recruiting from the general population may have included participants with a variety of common medical conditions, and such participants cannot be included in the derivation of normative reference ranges. The initial definitions of CVD, diabetes, hypertension, renal disease, or pregnancy were those determined by the individual study investigators. Study-level definitions of CVD were ≥1 of: self-reported history including prior surgery or intervention for coronary artery or valvular disease, physical assessment, resting ECG, stress test, major echo findings, and permanent pacemaker [for either bradycardia, tachycardia (including ICD), or cardiac resynchronization therapy]. Excluded rhythms included atrial fibrillation or flutter, second- or third-degree atrioventricular block (AVB), LBBB, or the presence of Q waves. Subjects were not excluded on the basis of mild first-degree AVB, RBBB, non-specific ST/T wave changes, when such data were available. Study-level definitions of diabetes and hypertension were based on ≥1 of: self-report, medical record or medication use, glucose levels, or blood pressure (BP) at the time of echo. Most of the studies used a BP threshold of >140/90 mmHg to define hypertension. Two studies used >160/90,[18,29] two used >135/85,[22,23] and one used >130/85 mmHg.[9]

In addition to these investigator-defined exclusions, subjects with probable diabetes, hypertension, or renal disease were excluded based on current recommended thresholds of glucose or HbA1c, BP, or creatinine, where available (*Figure 1*). Lastly, five people with extreme outlying values of LV ejection fraction (EF < 20%) were excluded.

The remaining 22 404 subjects form the EchoNoRMAL Reference Cohort and will be used to develop reference values. The 28 818 subjects excluded from the reference cohort will be used in sub-analyses of the EchoNoRMAL study. Demographic and echo variables that are available are described in *Table 2*.

Analysis

Reference values will be derived using quantile regression[41] or an appropriate parametric regression method to model the relationship between age and pre-defined centiles of each measurement (5th and 95th centiles). Reference values will be derived from models that represent contributing studies as a fixed effect. Study will then be included as a random effect to assess the variation between studies (within gender and ethnic group).

Reference values will be defined for measurements on the basis of imaging modality used. For example, LV mass estimated from M-mode images will not be combined with mass from 2D images. A range of indexation methods will be investigated for measurements of atrial and ventricular size, and of LV mass. This includes assessment of the ratiometric and allometric relationships of each measurement to height, weight, and body surface area.

As reference values are derived from the margins of the distribution, they are sensitive to variability, and for age-dependent values, require sufficient data at each age to be representative. Therefore, these ranges cannot be derived in sub-groups in which only a small amount of data are available. In these cases, exploratory or descriptive analyses will be undertaken to represent the data that are

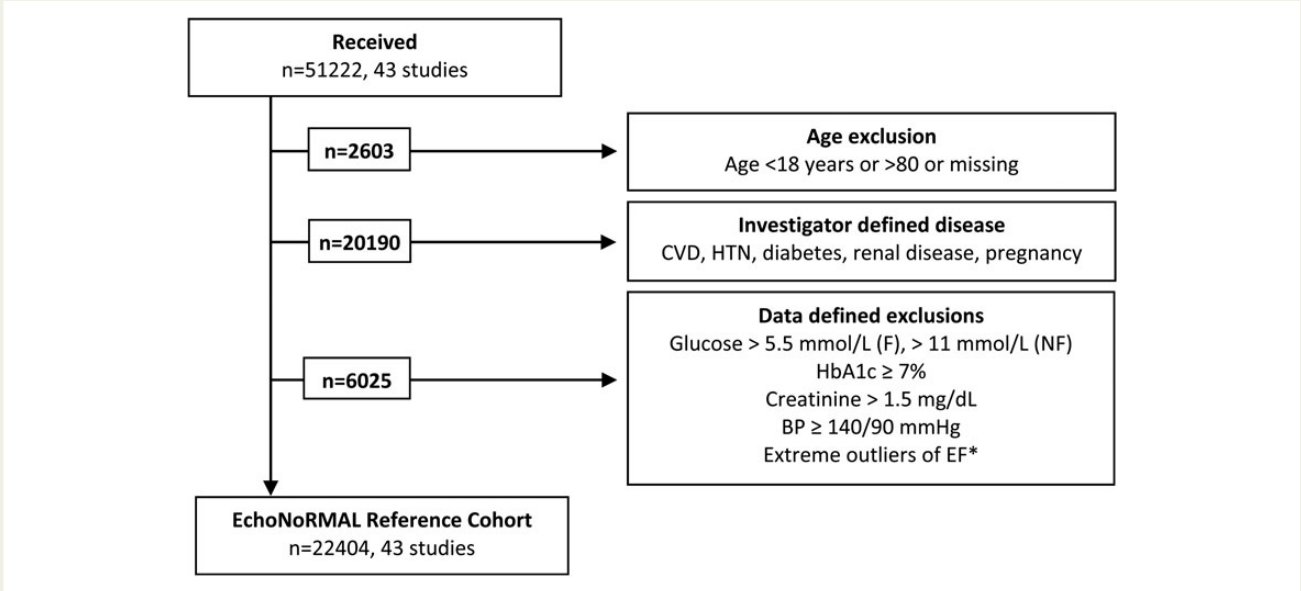

Figure 1 Development of the EchoNoRMAL reference cohort CVD, cardiovascular disease; HTN, hypertension; F, fasting; NF, non-fasting; HbA1c, glycosylated haemoglobin; BP, blood pressure; EF, left ventricular ejection fraction. *After excluding for disease, five subjects had EF of <20% that appeared to be erroneous values.

Table 2 Subject descriptors and echocardiographic measurements

Variable group	Variables
Descriptors	Age, sex, ethnicity, height, weight, BSA, BMI
Medical history	Cardiovascular disease, hypertension, diabetes, renal disease, current pregnancy
Clinical	Systolic BP, diastolic BP, cholesterol, glucose, creatinine
Aortic root	Dimension
Left atrium	Maximum and minimum: dimension, area, volume, 3D volume
Left ventricle	LV internal dimensions at end-diastole and end-systole, ventricular septal thickness at end-diastole, posterior wall thickness at end-diastole. Fractional shortening, EF(dimensions), LV mass, 2D and 3D LV volumes at end-diastole and end-systole. EF(volumes)
Mitral inflow Doppler	E and A wave peak velocity, A wave duration, E wave deceleration time, isovolumic relaxation time
Mitral annular tissue Doppler	e′, a′, and s′ peak velocities, and E/e′, at the medial and lateral annulus.
Pulmonary vein Doppler	Peak velocity of the S wave, D wave, A wave reversal, duration of A reversal
Right heart	Right ventricular dimension

BSA, body surface area; BMI, body mass index; BP, blood pressure; 3D, three-dimensional; LV, left ventricle; EF, ejection fraction; E, early filling wave of trans-mitral flow; A, late filling wave of trans-mitral flow; e′, tissue velocity during early filling; a′, tissue velocity during late filling; s′, tissue velocity during ventricular systole; E/e′, ratio of E wave to e′; S, systolic; D, diastolic; A, atrial contraction.

available, and these will highlight the need for further prospective studies in these groups.

Hypothesis-driven secondary analyses will also be undertaken. The approach to sub-analyses will be determined on a case-by-case basis.

Sources of variability

Multiple levels of random variation contribute to echo measurements. Factors at the level of the patient and the sonographer cannot be assessed in a meta-analysis of data obtained from the echo images; however, many sources of variability associated with image measurement can be identified and potentially incorporated into analyses (*Table 3*).

At the level of image measurement, human and methodological factors contribute to variability. Visual bias may lead to consistently larger or smaller measurements per operator, which may or may not be similar across multiple operators within a centre. For 2D images of the LV, for example, the selection of end-diastole and end-systole can differ, as can recognition and tracing of the endocardial surface. For Doppler images, the point of peak velocity within a bright or thickened flow profile, or in one with overshoot, is subjective. Measurement protocols also differ. Linear dimensions can be measured from M-mode images using the leading-edge-to-leading-edge convention,[50] or the Penn convention,[48] or they can be measured directly from 2D images. Left heart areas or volumes can be derived from single-plane or biplane 2D images, or from 3D images.

Table 3 Variables to represent sources of variability

Variable	Levels
Date of echo	Year
Machine used	As given
Centres	Single, multiple
Measurers	Single, multiple
LA dimension—method	M-mode leading-edge-to-leading-edge convention, M-mode Penn convention, 2D-linear
LA dimension—view	Parasternal long axis, parasternal short axis, apical 4-chamber, apical 2-chamber
LA area—view	Apical 4-chamber, apical 2-chamber, apical biplane
LA volume—method	Dimension-length,[42] area-length,[43] Simpson's biplane,[44] Simpson's single plane, 3D
LV dimension—method	M-mode leading-edge-to-leading-edge, M-mode Penn, 2D-linear
LV dimension—view	Parasternal long axis, parasternal short axis, apical 4-chamber, apical 2-chamber
LV volume—method (dimensions)	Teichholz[45]
LV volume—method (area)	Simpson's biplane, Simpson's single plane, area-length, [46] 3D
LV mass—method	M-mode, leading-edge-to-leading-edge,[47] 2D-linear dimensions, M-mode, Penn,[48] 2D-linear dimensions, Penn, area-length Reichek[49]

Only equations used in studies included in this meta-analysis are listed.

The conversion of measurements to estimates of area or volume requires equations based on assumptions about the geometry of each chamber. Different equations have been developed to allow specific measurements to be used (dimension, area) and allow for differing parameterizations of the measurements (*Table 3*).

Study organization

The EchoNoRMAL collaboration is structured into an Executive Group, Steering Group, Statistical Group, and a Co-ordinating Centre. The role of each of these groups is described in Supplementary data online. Communication within and between groups is facilitated via teleconferences and face-to-face meetings, and regular updates on study progress are provided to all members of the collaboration.

Limitations

As with any meta-analysis, the EchoNoRMAL study relies on the extent and quality of existing data, whether published or unpublished. Data may not be available for less-studied populations in the world and although this may limit the scope of the current study, it will serve to highlight areas that need further prospective investigation.

The derivation of a reference cohort for development of normative reference ranges is reliant on identification of clinically manifest CV or renal disease, hypertension, and diabetes. The focus of individual studies will differ and the extent and accuracy of screening for disease will vary. Similarly, the definition of disease will vary between studies. We have accounted for this by introducing a second tier of exclusion criteria based on continuous values of BP, blood glucose or HbA1c, and creatinine levels. However, these variables were not available in all studies, and some subjects with abnormal values may remain in the final reference cohort.

Variability is inherent in echo. Sources of variability have been identified and analyses stratified by method of measurement, where possible. However, we cannot account for the individual variation in image capture and measurement, which will lead to a degree of increased noise and variability around the measurements. Similarly, the type of machine is known; however, machine settings and the use of harmonic or fundamental imaging is not known. The ideal sampling strategy would be to gather data in a prospective manner after standardization of image collection and measurement.[51] However, the results of this study can be applied in a wide range of settings, the majority of which will not have such stringent controls. In this way, the EchoNoRMAL database may be a fair representation of 'real world' echocardiographic measurements.

Discussion

The EchoNoRMAL individual person data meta-analysis will provide population-based sex-, age-, and ethnic-specific normative reference values for commonly used echo measurements of the left heart. The inclusion of a wide range, and large number, of people should make these values widely applicable for use in everyday clinical practice.[52] Where possible, values will be derived that are relevant to a specific echo modality (M-mode, 2D, 3D), measurement convention, and other measurement-specific criteria.

Sex-specific reference ranges have been available for some time, but not for all measurements, and not in combination with age and ethnicity. For example, age-related changes in LV diastolic parameters were found to differ between Japanese men and women,[22] and LV mass differs in young American Blacks compared with American Whites,[6] but there are no large comparative studies of ethnic differences across the range of echo measurements. Few previous studies have been adequately powered, with adequate numbers of men and women, over a wide age range, to evaluate these factors.

In a previous systematic review,[2] there was sufficient variation in the range of LV mass in normal cohorts, defined by country of origin, for us to be confident that reference values for measurements of cardiac structure will vary by ethnicity. Many echo measurements are indexed to a measure of body size to account for differences in body size and composition. This study will explore different methods of indexation, the impact among men and women, and across ethnicity.

Reference ranges can be derived in a number of ways. A common method is to define the range as a number of standard deviations from the mean of a sample of measurements. This requires values to be normally distributed, or able to be transformed to be normally distributed, and values can only be reported per category of age. An advantage of a regression-based method, such as quantile regression, is that it allows continuous reference values to be derived across the range of one or more covariates. Such models require relatively large data sets compared with what is required for a fully parametric model; however, the size of the collaboration makes this approach possible. By fitting independent regression models to segments of the distribution (e.g. the 5th or 95th centile), quantile regression can also accommodate changes in variability and allow a greater understanding of how measurements behave across age. The European Respiratory Society Task Force has recently published multiethnic reference values for spirometry based on data from 33 countries.[53] They also elected to use a regression-based method as it allowed the changing trend in spirometry values from ages 3 to 95 years to be modelled.

The benefits of this study will not be limited to the reference values it produces. Given the marked diversity of the world population, it is likely that this study cannot find appropriate studies from all populations. This should identify areas where future prospective studies are necessary. There remains the possibility of updating the analyses if new normative echo data become available. This study has been limited to the left heart but could be extended to measurements of the right heart.

This is a unique international collaboration that has collated echo and clinical data on 22 404 individuals without clinical CVD to develop widely applicable reference ranges for use in echo laboratories around the world. It is hypothesized that there will be significant differences in the range of reference values across different ethnic groups, even when adjusted for sex and body size. If this hypothesis is proven correct, it could have significant implications for both the under- and over-diagnosis of CV abnormalities in different ethnic groups.

Supplementary data

Supplementary data are available at *European Heart Journal – Cardiovascular Imaging* online.

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Executive Group: R. N. Doughty, J. M. Gardin, F. D. R. Hobbs, J. J. V. McMurray, S. F. Nagueh, K. K. Poppe (Study Lead), R. Senior, L. Thomas, G. A. Whalley (PI). *Steering Group*: E. Aune, A. Brown, L. P. Badano, V. Cameron, D. S. Chadha, N. Chahal, K. L. Chien, M. Daimon, H. Dalen, R. Detrano, M. Akif Duzenli, J. Ezekowitz, G. de Simone, P. Di Pasquale, S. Fukuda, P. S. Gill, E. Grossman, F. D. R. Hobbs, H. –K. Kim, T. Kuznetsova, N. K. W. Leung, A. Linhart, T. A. McDonagh, M. McGrady, J. J. V. McMurray, J. G. Mill, R. Mogelvang, M. L. Muiesan, A. C. T. Ng, D. Ojji, J. E. Otterstad, D. J. Petrovic, K. K. Poppe, B. Prendergast, E. Rietzschel, H. Schirmer, P. Schvartzman, R. Senior, I. Simova, K. Sliwa, S. Stewart, I. B. Squire, M. Takeuchi, L. Thomas, G. A. Whalley. *Statistical Group*: D. Altman, R. Perera, K. K. Poppe, C. M. Triggs. *Coordinating Centre*: H. Au Yeung, G. A. Beans Picón, K. K. Poppe, G. A. Whalley, University of Auckland and Unitec Institute of Technology, New Zealand. echonormal@unitec.ac.nz. *Studies and Investigators* (see *Table 1*).

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Conflict of interest: Dr Badano is on the speakers' bureau of GE VingMed; Dr Muraru has received speakers' honoraria from GE VingMed; Dr Simova has received support from Sopharma Trading (distributor of GE Healthcare, Bulgaria) and speakers and consultancy honoraria from Infomed (distributor of Aloka, Bulgaria). Dr Dalen and Dr Støylen hold positions in MI Lab, a collaboration of the Norwegian University of Science and Technology with industrial partners, where GE VingMed contributes ~6% of the total budget.

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