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ORIGINAL RESEARCH

# Echocardiographic Reference Ranges of Global Longitudinal Strain for All Cardiac Chambers Using Guideline-Directed Dedicated Views

John Nyberg, MD,[a] Even Olav Jakobsen, CCN,[a,b] Andreas Østvik, MSc, PhD,[a,c] Espen Holte, MD, PhD,[a,b] Stian Stølen, MD,[b] Lasse Lovstakken, MSc, PhD,[a] Bjørnar Grenne, MD, PhD,[a,b,*] Havard Dalen, MD, PhD[a,b,d,*]

## ABSTRACT

**BACKGROUND** Myocardial deformation by echocardiographic strain imaging is a key measurement in cardiology, providing valuable diagnostic and prognostic information. Reference ranges for strain should be established from large healthy populations with minimal methodologic biases and variability.

**OBJECTIVES** The aim of this study was to establish echocardiographic reference ranges, including lower normal limits of global strains for all 4 cardiac chambers, by guideline-directed dedicated views from a large healthy population and to evaluate the influence of subject-specific characteristics on strain.

**METHODS** In total, 1,329 healthy participants from HUNT4Echo, the echocardiographic substudy of the fourth wave of the Trøndelag Health Study, were included. Echocardiographic recordings specific for each chamber were optimized according to current recommendations. Two experienced sonographers recorded all echocardiograms using GE Health-Care Vivid E95 scanners. Analyses were performed by experts using GE HealthCare EchoPAC.

**RESULTS** The reference ranges for left ventricular (LV) global longitudinal strain and right ventricular free-wall strain were −24% to −16% and −35% to −17%, respectively. Correspondingly, left atrial (LA) and right atrial (RA) reservoir strains were 17% to 49% and 17% to 59%. All strains showed lower absolute values with higher age, except for LA and RA contractile strains, which were higher. The feasibility for strain was overall good (LV 96%, right ventricular 83%, LA 94%, and RA 87%). All chamber-specific strains were associated with age, and LV strain was associated with sex.

**CONCLUSIONS** Reference ranges of strain for all cardiac chambers were established based on guideline-directed chamber-specific recordings. Age and sex were the most important factors influencing reference ranges and should be considered when using strain echocardiography. (J Am Coll Cardiol Img 2023;■:■–■) © 2023 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

From the [a]Department of Circulation and Medical Imaging, NTNU-Norwegian University of Science and Technology, Trondheim, Norway; [b]Clinic of Cardiology, St. Olavs Hospital, Trondheim, Norway; [c]Medical Image Analysis, Health Research, SINTEF Digital, Trondheim, Norway; and the [d]Department of Medicine, Levanger Hospital, Nord-Trøndelag Hospital Trust, Levanger, Norway.
*Drs Grenne and Dalen contributed equally to this paper as joint senior authors.



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**ABBREVIATIONS AND ACRONYMS**

**BSA** = body surface area

**ES** = end-systole

**FW** = free-wall

**GLS** = global longitudinal strain

**LA** = left atrial

**LV** = left ventricular

**MAP** = mean arterial pressure

**RA** = right atrial

**ROI** = region of interest

**RV** = right ventricular

Quantification of the size and function of cardiac chambers is essential in clinical echocardiography. Chamber function is commonly measured by myocardial deformation (strain), which offers valuable diagnostic and prognostic insights and is more reliable than traditional measurements such as ejection fraction.[1-5] To accurately identify myocardial dysfunction, it is vital to know the expected reference ranges of strain in healthy populations. For individual patients, the differentiation between normality and pathology may be improved using reference ranges accounting for variables influencing the measurements. Age, sex, anthropometry, and blood pressure have been shown to modulate strain.[6-12]

Reference ranges for strain should be based on individuals without known cardiac disease and without symptoms that could imply yet undiagnosed cardiac disease. It is therefore crucial to base reference ranges on strain measurements from a healthy cohort and not on subjects referred for echocardiography based on clinical indication. Furthermore, acquisition, methodology, and analyses should be standardized to limit sources of systematic and random variability.[13,14] Possible sources of variability include the population examined, image acquisition and interpretations, vendor-specific methodology, and the level of experience of the study personnel.[13,14]

Most reference ranges for strain have been obtained from meta-analyses or multicenter studies.[6,11,12,15-18] Such designs are beneficial to achieve large samples and increase generalizability but may also introduce random variability (noise) influencing the results. Country- and hospital-specific biases, limited participants per hospital, measurement differences between operators, variations in echocardiographic view recordings, and different ultrasound scanners within or between vendors are all factors that increase variability.[2,13,14,19] Moreover, most studies have focused on the left ventricle, whereas very few large studies have reported reference ranges for strain in all 4 cardiac chambers. Thus, there is a need to establish reference ranges in a large study in which variability is minimized.

In HUNT4Echo, the echocardiographic substudy of the fourth wave of the Trøndelag Health Study, guideline-directed dedicated echocardiographic views were acquired from all cardiac chambers by highly experienced sonographers and analyzed by expert imaging cardiologists from an internationally accredited echocardiography laboratory.

The aim of the present study was to establish echocardiographic reference ranges, including lower normal limits of global strains for all 4 cardiac chambers, based on a large population of presumably healthy individuals with guideline-directed chamber-specific recordings, thereby limiting systematic and random variability. Secondary aims were to evaluate the variability of strains and the importance of subject-specific characteristics across cardiac chambers.

## METHODS

**STUDY POPULATION.** The HUNT study is a population-based cohort study ongoing since 1984. HUNT4 is the fourth wave of the study and included the echocardiographic substudy (HUNT4Echo), evaluating a subgroup of 2,462 study participants between 2017 and 2018. Clinical measurements such as height, weight, and blood pressure were collected on the day of echocardiography. Body mass index (BMI) was calculated as height in meters divided by the squared weight in kilograms. Body surface area (BSA) was calculated using the DuBois formula. Blood pressure was measured using a Dinamap Carescape V100 (GE HealthCare) in sitting position with arm rested, as the average of the last 2 of 3 measurements. Information on smoking status and medical history was based on self-reported questionnaires. A detailed description of the HUNT4 study cohort profile has been published previously,[20] and comprehensive reference ranges for cardiac chamber dimensions and volumes, as well as blood flow and tissue Doppler from the HUNT4Echo Study, have recently been published.[21]

This study of normal myocardial strain included all presumably healthy study participants in the HUNT4Echo study. Exclusion criteria were: 1) presence of one of the following diseases by self-report or validation of hospital medical records: diabetes mellitus, atrial fibrillation, any other known cardiac disease, antihypertensive treatment, malignant disease, and pulmonary disease; 2) echocardiographic pathologic findings such as significant left ventricular (LV) hypertrophy or dilatation; segments with hypokinesia, akinesia, or dyskinesia by visual assessment; more than mild valvular regurgitation, or stenosis; and 3) systolic blood pressure >160 mm Hg.

**ECHOCARDIOGRAPHY ACQUISITIONS.** Echocardiographic images were obtained as recommended by the ASE (American Society of Echocardiography) and the EACVI (European Association of Cardiovascular Imaging).[22] Participants were positioned in the left lateral decubital position and imaged using Vivid E95 scanners (GE HealthCare) equipped with 4Vc-D and M5S-D phased-array transducers. Two experienced sonographers (>2,000 recordings and readings each) acquired the echocardiograms at the study center located at Levanger Hospital (Levanger, Norway). The echocardiograms included at least 3 cardiac cycles per specified recording. The echocardiographic acquisitions included guideline-directed dedicated 2-dimensional grayscale recordings for each of the 4 cardiac chambers: 1) 3 guideline-directed LV-focused apical views (the apical long-axis view, the 2-chamber [2CH] view, and the 4-chamber [4CH] view); 2) 2 left atrial (LA)-focused apical views (2CH and 4CH); 3) one right ventricular (RV)-focused 4CH view; and 4) one right atrial (RA)-focused 4CH view. Mean frame rate ranged from 71 to 85 frames per second for all 4CH-specific recordings. Each view was recorded during quiet breathing or breath-hold based on the operators' choice. Data were digitally stored using the DICOM (Digital Imaging and Communications in Medicine) format.

**STRAIN MEASUREMENTS IN ALL CHAMBERS.** All strains were analyzed by using EchoPAC SWO version 204 (GE HealthCare) by experienced personnel at the EACVI-accredited echocardiography laboratory at St. Olavs University Hospital (Trondheim, Norway). From guideline-directed dedicated recordings of the individual chambers and views, the operator chose 1 of the 3 cycles for the specific strain analyses. In general, the regions of interest (ROIs) included the whole myocardial wall excluding trabeculations. Chamber-specific details are provided in the following 4 sections. For ventricular strain analyses, segments were excluded if judged by the operator to influence global longitudinal strain (GLS) values. To better visualize tracking of ROI points, the color overlay was turned off if tracking quality was difficult to evaluate.

The expert cardiologists, both certified by the EACVI in transthoracic echocardiography, supervised training and performance of strain analyses by the less experienced operators. All 4 operators were involved in analyses of LV GLS, whereas RV, LA, and RA strains were measured by the 2 expert cardiologists only. Details of the expertise and workflow of the 4 operators who performed the strain analyses are presented in Supplemental Table 1.

**LEFT VENTRICULAR GLOBAL STRAINS.** LV GLS was analyzed in 3 apical LV-focused views (apical long-axis view, 4CH, and 2CH) using the two-dimensional Strain speckle-tracking application (2DS). LV GLS by 2DS was first analyzed by one cardiology resident (J.N.) or one experienced sonographer (E.O.J.), and then reread and adjusted by 1 of 2 cardiologist experts in echocardiography and strain imaging (B.G. or H.D.). Importantly, the ROIs from the less experienced operators were made available for the experts, who adjusted or replaced the ROIs to achieve the best possible tracking of the myocardial walls, based on their individual expert opinion. The ROIs were positioned to include the whole myocardium from base to apex, excluding papillary muscles, trabeculations, and the pericardium. Adjustments of the semiautomatic segmentation by the 2DS method were deemed necessary in all views and recordings (100% with manual adjustments). Based on the myocardial tracking, segments in which the propagation of the ROI points did not follow the motion of the myocardium were excluded if they were judged by the operators to influence global strain values. Thus, individual segments could be included despite suboptimal tracking of segment borders if the whole wall strain was judged to be acceptable. Only examinations with at least 10 of 18 segments accepted were included in the reference ranges.

End-systole (ES) was defined by aortic valve closure in the apical long-axis view recording, and the same systolic duration was applied for 4CH and 2CH views. If the timing of aortic valve closure was uncertain, the default timing of ES was based on time to peak strain in all segments. End-diastolic timing was defined as the application default and adjusted if needed by changing to the frame of mitral valve closure in the apical long-axis view recording. The application default settings for spatial and temporal smoothing, and drift compensation were used. LV GLS was reported as whole chamber peak systolic GLS in a standard ASE 18-segment model, by averaging all segmental values with approved tracking in each subject.[13,22] To adjust for the relative overweight of the apical segments compared with the actual amount of myocardium in the 18 segments evaluated, global averages were also calculated from the standard ASE 16-segment model with only 4 segments at the apical level by averaging the anterolateral and inferolateral as well as the inferoseptal and anteroseptal segments.[13,22] In addition, LV GLS was presented as the standard processing output from the 2DS (2DS standard) method when at least 17 of 18 segments were accepted, even though these measurements also include the discarded segments.

LV GLS was also analyzed in a subsample of 514 (39%) individuals using the AFI (Automated Function Imaging) application by the experienced sonographer (E.O.J.) for comparison. For these measurements, a separate ROI initialization and tracking evaluation was performed. Thus, no information from the 2DS analyses was included. Beyond these details and the lack of repeated reading or adjustment by the expert cardiologists, the methodology followed the description for 2DS given earlier.

**RV FREE WALL STRAIN.** RV strain was analyzed using the dedicated RV AFI package in EchoPAC by 1 of the 2 expert cardiologists. The ROI was semiautomatically initialized in the free wall (FW) and interventricular septum, and the ROI of the septal wall was kept at the same width as for the RV FW and not adjusted to the whole thickness of the interventricular septum. ES was defined as the application default and adjusted if needed by annotating the end of the pulmonary blood flow Doppler signal using the "Event timing" functionality in EchoPAC. According to the recommendation,[23] only the RV FW strain, representing the average of 3 RV FW segments, was reported. The RV FW strain was calculated by the software when at least 2 of 3 segments were accepted.

**LA STRAIN.** LA strain was analyzed by the 2 expert cardiologists using the dedicated LA AFI package in the software and was based on both LA-focused 4CH and 2CH views.[14] The ROIs were semiautomatically initiated by manually annotating the septal and lateral (or inferior and anterior in 2CH) bases and the roof of the left atrium. The ROI was then manually adjusted to cover the LA wall but extrapolated across the pulmonary veins and the LA appendage. Tracking was visually evaluated, and the ROI width and position was adjusted in case of reduced tracking quality. Timing of cardiac events (end-diastolic, ES, and preatrial contraction) was done automatically by the software. When needed, the pre-atrial contraction timing was manually adjusted, based on identification of the P wave in the electrocardiogram and the sudden fall in the strain curve associated with atrial contraction. In cases in which the tracking was not acceptable by visual inspection, the measurements were rejected. The total (reservoir strain), passive (conduit strain), and active (contractile strain) strains were reported. According to the recommendation, the R wave was used as reference, and thus zero strain was set at the R wave.[14] LA strains were reported as biplane values (mean of 4CH and 2CH views) and also separately for 4CH views.

**RA STRAIN.** A dedicated application for strain measurements in the right atrium had not yet been implemented in the EchoPAC analysis software at the time of this study. Thus, RA strain was analyzed by the 2 expert cardiologists using the LA AFI package in RA-focused 4CH views. The positioning and adjustment of the ROI, the visual control of tracking, timing of cardiac events, acceptance or rejection of the analyses, and presentation of strain values were performed following the details described earlier for LA strain.[14]

**DATA REPRODUCIBILITY.** The reproducibility of all presented strain measurements was evaluated by the expert cardiologists. In a random selection of 60 study participants, the 2 expert cardiologists analyzed strain in all chambers blinded to each other. It was left to the choice of the operators to select which cardiac cycle to analyze. In addition, the reproducibility of LV GLS was further elaborated by including the LV GLS measured by the resident and the experienced sonographer.

**ETHICAL APPROVAL.** The HUNT4Echo study was approved by the Mid-Norway Regional Committee for Medical and Health Research Ethics (REK 13083). The study was conducted in compliance with the ethical principles of the Declaration of Helsinki. Personal data security and data handling were approved by the institutional personal data officer at St. Olavs Hospital, Levanger Hospital, and the Norwegian University of Science and Technology (Trondheim, Norway).

**FEASIBILITY.** The feasibility of strain measurements was calculated for each chamber and method as the proportion of study participants with successful strain measurements. Strain measurements were judged as successful in examinations in which the respective chamber was properly visualized, the underlying myocardium was not obliterated by significant reverberations or other artifacts, and the myocardial tracking was acceptable. For the LV GLS measurements, a minimum of 10 of 18 segments had to be accepted to be judged as feasible. For the right ventricle, 2 of 3 FW segments had to be accepted to be judged as feasible. In case of missing recordings, these data were treated as nonfeasible. Only feasible measurements were included in the analyses.

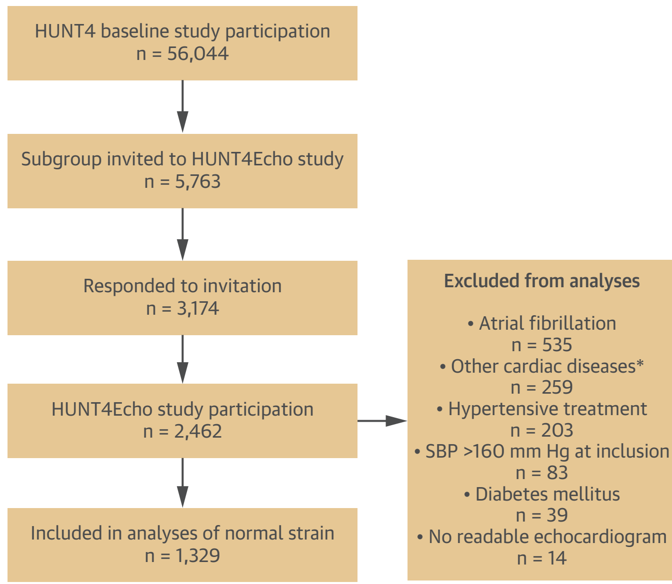
**STATISTICAL ANALYSIS.** Continuous normally distributed data are reported as mean $\pm$ SD, and data with non-normal distributions are reported as median (IQR). However, even though strains were normally or near-normally distributed, both mean $\pm$ SD and median (IQR) were reported for better comparison with previous studies. The normality of data was assessed using histograms and quantile-quantile (Q-Q) plots as well as the Shapiro-Wilk test. Frequencies are reported as number (%). Comparisons between sexes in patient characteristics were done using Pearson's chi-square test or the Wilcoxon rank sum test, as appropriate. The reference ranges for chamber-specific strains were defined as (mean - 1.96 SD, mean + 1.96 SD), as we expect 95% of the population to fall within for normally distributed variables. Sex-specific strains were tabulated categorically by decades. Because few subjects were <30 years or >80 years of age, these categories were not presented as separate groups. In a sensitivity analysis, we compared strains in individuals with BMI >30 kg/m$^2$ vs individuals with BMI ≤30 kg/m$^2$ by Student's *t*-test. For the feasibility of LV GLS and RV FW, LA, and RA strains, the total population was used as the reference.

The associations of chamber-specific strains with subject characteristics (age, male sex, height, weight, BMI, BSA, systolic blood pressure [SBP], diastolic blood pressure [DBP], mean arterial pressure [MAP], and heart rate) were analyzed by simple and multiple linear regressions. Variable selection in multiple linear regressions were done by choosing the model with the lowest Akaike information criterion (AIC) value in all subset regression. Multicollinearity was avoided by checking the variance inflation factor and significance of each predictor variable in each model. The assumptions of constant SDs, linearity, and normality were reasonably met for all multiple linear regression models when assessed by Q-Q plots, Components-Residuals-plots and Absolute Studentized Residuals vs Fitted Values plots (data not shown). The directions of associations were presented by direction of the beta values. This means that a positive association for negatively annotated strains indicates lower absolute strain values with male sex or higher values of the 9 other subject characteristics specified.

The results of multiple linear regression analyses are presented as original models as well as standardized models (in which the variables were standardized before fitting the model) to enable direct comparison of beta coefficients. In addition, sex-specific linear prediction intervals for reference ranges of chamber-specific strain are presented according to age.

LV GLS was compared across methods (2DS and AFI) by using the paired-sample Student's *t*-test. LV GLS by 2DS was compared for the 16-segment model, 18-segment model, and the 2DS standard processing model by linear regression, using categorical dummy-variables for the three models. Interobserver agreement of the experts' strain analyses were presented by Bland-Altman (differences vs means) plots and intraclass correlation coefficients (ICCs). In addition, the ICCs including the analyses by the less experienced readers were presented. The ICCs were calculated by linear mixed models with 95% CIs created by bootstrapping. Data were analyzed using R software version 4.2.2 (packages: car, ggplot2, ggpmisc, gtsummary, leaps, and lme4; R Foundation for Statistical Computing). A value of $P < 0.05$ was considered statistically significant.

**FIGURE 1** **Flowchart of the Study**




*From self-report, validation of medical record files or pathologic echocardiographic findings. HUNT4Echo = echocardiographic substudy of the fourth wave of the Trøndelag Health Study; SBP = systolic blood pressure.

## RESULTS

Figure 1 displays a flowchart of the study participants. Of 56,044 individuals participating in the HUNT4 baseline study, a random subgroup of 5,763 were invited to the HUNT4Echo study. Of the 3,174 individuals who responded, a total of 2,462 study participants were included. To study normal myocardial strains, the following were excluded: 535 individuals with atrial fibrillation, 259 with a history of other cardiac diseases, 203 receiving treatment for hypertension, 83 with SBP > 160 mm Hg at inclusion, and 14 without a readable echocardiogram. Thus, a total of 1,329 study participants were included.

A summary of the baseline characteristics is presented in Table 1. The mean age was 57 years in both sex groups. Male subjects had higher BMI than female subjects (26.3 kg/m$^2$ vs 25.2 kg/m$^2$; $P < 0.001$). The proportion of smokers was low, with only 5% current smokers. The mean left ventricular ejection fraction was 60.3% in female subjects and 59.7% in male subjects, as presented recently.[21]

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**TABLE 1 Baseline Characteristics of the Study Population**

| | Overall (N = 1,329) | Female (n = 741) | Male (n = 588) | *P* Value |
|---|---|---|---|---|
| Age, y | 57 ± 12 | 57 ± 12 | 57 ± 13 | 0.5 |
| Height, cm | 172 ± 9 | 166 ± 6 | 179 ± 7 | <0.001 |
| Weight, kg | 76 ± 14 | 70 ± 12 | 85 ± 11 | <0.001 |
| Body mass index, kg/m$^2$ | 25.7 ± 3.6 | 25.2 ± 3.9 | 26.3 ± 3.1 | <0.001 |
| Body surface area, m$^2$ | 1.89 ± 0.20 | 1.77 ± 0.14 | 2.04 ± 0.15 | <0.001 |
| Systolic blood pressure, mm Hg | 126 ± 14 | 124 ± 15 | 128 ± 13 | <0.001 |
| Diastolic blood pressure, mm Hg | 74 ± 9 | 71 ± 8 | 77 ± 9 | <0.001 |
| Mean arterial pressure, mm Hg | 93 ± 10 | 91 ± 10 | 96 ± 10 | <0.001 |
| Heart rate, beats/min | 68 ± 11 | 70 ± 11 | 66 ± 11 | <0.001 |
| $HbA_{1c}$, mmol/mol | 33.3 ± 3.2 | 32.9 ± 3.1 | 33.8 ± 3.2 | <0.001 |
| Cholesterol, mmol/L | 5.63 ± 1.03 | 5.67 ± 1.08 | 5.58 ± 0.97 | 0.3 |
| Current smoker | 67 (5.0) | 44 (5.9) | 23 (3.9) | 0.094 |
| Medications for hyperlipidemia | 106 (8.0) | 61 (8.2) | 45 (7.7) | 0.7 |
| Medications for asthma or COPD | 29 (2.2) | 17 (2.3) | 12 (2.0) | 0.8 |
| Medications for anxiety or depression | 53 (4.0) | 36 (4.9) | 17 (2.9) | 0.069 |
| Medications for allergy | 131 (9.9) | 86 (12) | 45 (7.7) | 0.016 |
| LAESV, mL | 54 ± 19 | 49 ± 15 | 61 ± 20 | <0.001 |
| LVEDV, mL | 110 ± 31 | 95 ± 22 | 129 ± 30 | <0.001 |
| LVEF, % | 60.1 ± 5.0 | 60.3 ± 4.9 | 59.7 ± 5.1 | 0.016 |

Values are mean ± SD or n (%).

COPD = chronic obstructive pulmonary disease; $HbA_{1c}$ = glycosylated hemoglobin; LAEDV = left atrial end-diastolic volume; LAESV = left atrial end-systolic volume; LVEF = left ventricular ejection fraction.

The reference ranges for the total population and by sex and age categories are presented in **Central Illustration**, **Table 2**, **Table 3**, and Supplemental Tables 2 and 3.

The unadjusted lower normal limits for LV GLS and RV FW strain were -15.7% and -17.4%, respectively. The lower normal limits for LA reservoir, conduit, and contractile strain were 16.7%, -2.8%, and -7.0% and the corresponding values for RA strain were 17.2%, -4.2%, and -6.0%. The absolute values of chamber-specific strains were lower by higher age, except for contractile strains in the left and right atria (**Figures 2 to 5**). Female subjects had higher absolute values of LV strains, whereas sex differences were not consistent for RV FW and atrial strains. Sex-specific linear prediction intervals for reference ranges according to age as a continuous variable for each of the chamber-specific strains are presented in Supplemental Table 4. Some strains had marginally lower absolute values in subjects with BMI >30 kg/m$^2$ compared with those with BMI ≤30 kg/m$^2$, whereas others were similar between groups (Supplemental Table 5).

Supplemental Table 6 presents the subjects' characteristics that provided the lowest AIC in multiple linear regression analyses for the chamber-specific strains and the total explained variability for each model by the coefficient of determination ($R^2$).

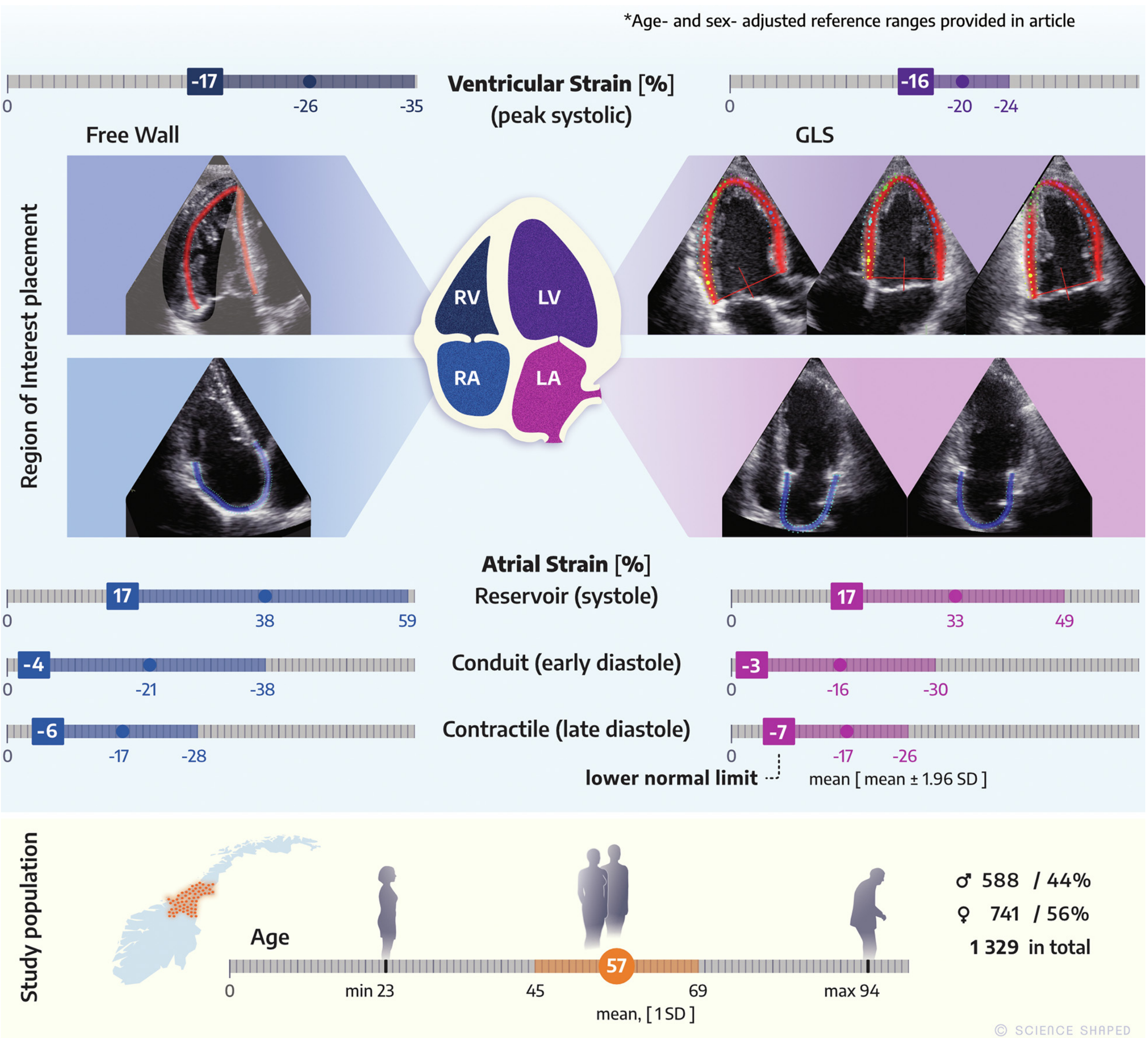
**LV GLS.** There were significant positive associations indicating lower absolute LV GLS by 2DS with all 10 specified subject characteristics in the unadjusted analyses ($R^2$ ranging from 0.8%-10.0%, highest for age; all $P < 0.001$). In the adjusted analyses, the combination of age, male sex, MAP, and heart rate explained 17% of the variability in GLS. Sex and age showed the strongest associations with LV GLS.

Similar results were found for LV GLS by AFI in unadjusted analyses ($R^2$ ranging from 1.3%-6.7% for each of the 10 subject characteristics [highest for sex and age]; all $P \leq 0.02$). The results of the adjusted analyses were in line with findings for LV GLS by 2DS, showing the strongest associations with age and sex.

**RV FW STRAIN.** RV FW strain was not significantly associated with height, sex, or heart rate but with all other specified characteristics ($R^2$ ranging from 0.7%-4.2%, highest for BMI and age; all $P \leq 0.01$) in the unadjusted analyses. The direction of all associations was similar as for LV GLS indicating lower absolute RV FW strain with higher values of the specified subject characteristics. In the adjusted analyses, the combination of BMI and age explained approximately 7% of the variability in FW strain (both with standardized beta values of approximately 0.2).

**LA STRAINS.** There were significant negative associations indicating lower LA reservoir strain with

**CENTRAL ILLUSTRATION** Reference Ranges of Global Longitudinal Strain for All Cardiac Chambers

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Unadjusted global longitudinal strain values based on guideline-directed dedicated views for all 4 cardiac chambers. Images were acquired by experienced sonographers and analyzed by expert cardiologists. For illustrative purposes, reference ranges and lower normal limits for each strain value are given with lower absolute values to the left and higher absolute values to the right of the reference range bar. GLS = global longitudinal strain; LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle.

higher values of age, SBP, DBP, and MAP in the unadjusted analyses ($R^2$ for age 27.4%; $P < 0.001$; others ranging from 0.4% to 4.2%, all $P \leq 0.05$). In the adjusted analysis, the $R^2$ was highest for age and DBP, which explained approximately 28% of the variability in LA reservoir strain.

There were significant positive associations indicating lower absolute LA conduit strain with higher values for age, sex, weight, BMI, SBP, DBP, MAP, and heart rate in the unadjusted analyses ($R^2$ for age 46%; $P < 0.001$; others ranging from 0.5%-9.7%, all $P \leq 0.05$). In the adjusted analysis,

**TABLE 2 Reference Ranges of GLS for Cardiac Chambers According to Methods**

| | Overall (N = 1,329) | Female (n = 741) | Male (n = 588) |
|---|---|---|---|
| LV GLS-2DS (18 segments) | -19.8 (-23.9 to -15.7) | -20.2 (-24.3 to -16.0) | -19.3 (-23.2 to -15.4) |
| LV GLS-2DS (16 segments) | -19.6 (-23.6 to -15.5) | -20.0 (-24.1 to -15.9) | -19.0 (-22.8 to -15.3) |
| LV GLS-2DS (standard) | -20.0 (-24.0 to -16.0) | -20.4 (-24.5 to -16.4) | -19.6 (-23.3 to -15.9) |
| LV GLS-AFI (18 segments) | -20.1 (-24.2 to -16.0) | -20.6 (-24.6 to -16.6) | -19.5 (-23.5 to -15.6) |
| LV GLS-AFI (standard) | -19.5 (-23.6 to -15.4) | -20.0 (-24.0 to -16.0) | -19.0 (-22.9 to -15.0) |
| RV FW strain | -25.9 (-34.5 to -17.4) | -26.1 (-35.1 to -17.1) | -25.7 (-33.7 to -17.7) |
| LA reservoir strain-biplane | 33.0 (16.7-49.3) | 33.2 (17.2-49.2) | 32.7 (16.0-49.3) |
| LA reservoir strain-4CH | 32.6 (15.8-49.4) | 32.8 (16.3-49.2) | 32.4 (15.3-49.6) |
| LA conduit strain-biplane | -16.4 (-30.1 to -2.8) | -17.0 (-30.8 to -3.3) | -15.7 (-29.1 to -2.3) |
| LA conduit strain-4CH | -17.2 (-32.0 to -2.5) | -17.9 (-32.7 to -3.1) | -16.4 (-30.9 to -1.9) |
| LA contractile strain-biplane | -16.5 (-26.1 to -7.0) | -16.2 (-25.4 to -7.0) | -17.0 (-26.9 to -7.0) |
| LA contractile strain-4CH | -15.4 (-25.6 to -5.1) | -14.9 (-24.5 to -5.2) | -16.0 (-26.9 to -5.2) |
| RA reservoir strain | 38.1 (17.2-58.9) | 37.9 (16.7-59.0) | 38.3 (17.8-58.9) |
| RA conduit strain | -21.0 (-37.7 to -4.2) | -20.8 (-38.1 to -3.5) | -21.2 (-37.2 to -5.1) |
| RA contractile strain | -17.1 (-28.2 to -6.0) | -17.1 (-28.1 to -6.1) | -17.2 (-28.4 to -6.0) |

Values are mean (mean - 1.96 SD, mean + 1.96 SD). The unit of all strain measurements is percentage (%).

2DS = 2D strain; 4CH = four-chamber view; AFI = Automated Function Imaging; FW = free-wall; LA = left atrial; LV = left ventricular; RA = right atrial; RV = right ventricular.

age, weight, DBP, and heart rate explained approximately 50% of the variability in strain. Age was by far the single most important predictor of LA conduit strain.

There were significant negative associations indicating higher absolute LA contractile strain, with higher values for all specified subject characteristics except height in the unadjusted analyses ($R^2$ ranging from 0.6%-2.7% [highest for heart rate]; all $P \le 0.01$). In the adjusted analysis, age, BMI, DBP, and heart rate explained only 5% of the variability of LA contractile strain (the highest absolute standardized beta value was for heart rate).

For LA strains measured only in the 4CH view, the corresponding $R^2$ values for reservoir, conduit, and contractile strains were 23%, 46%, and 7%, respectively, reflecting the findings from LA biplane analyses.

**RA STRAINS.** There were significant associations of RA reservoir strain for age, weight, BMI, SBP, DBP, and MAP in the unadjusted analyses. $R^2$ for age was 9.8% ($P < 0.001$); others ranged from 0.4% to 2.1% (all; $P < 0.05$). In the adjusted analysis, age, sex, and BMI explained approximately 12% of the variability in strain. Age showed the strongest association with RA reservoir strain also in the adjusted analysis.

There were significant positive associations indicating lower absolute RA conduit strain for age, BMI, SBP, DBP, MAP, and heart rate, and significant negative association for height, in the unadjusted analyses ($R^2$ for age 22.4%; $P < 0.001$; others ranging from 0.4%-2.7%, all $P < 0.05$). In the adjusted analysis, the model including age, BMI and heart rate explained approximately 23% of the variability in RA conduit strain.

There were significant negative associations indicating higher absolute RA contractile strain for age, SBP, and heart rate, while the direction was opposite (although significant) for anthropometric characteristics ($R^2$ ranging from 0.4-1.6 [highest for age]; all $P <$ 0.05) in the unadjusted analyses. In the adjusted analyses, age, sex, weight, and heart rate explained only 4% of the variability in RA contractile strain.

**COMPARISON OF LV STRAINS BY DIFFERENT METHODS.** There were small but significant differences in the mean values for LV GLS by 2DS between the 16-segment model, 18-segment model, and the 2DS standard processing model with mean values -19.6%, -19.8%, and -20.0%, respectively $P < 0.001$ (Table 2). We also found a small but significant difference of 0.3% strain units between the LV GLS measured by 2DS and AFI in the 18-segment models ($P < 0.001$).

**FEASIBILITY.** Measurements of global strains were feasible in all chambers; it was highest for LV GLS by the 18-segment model and 16-segment model (feasibility 96%) and lowest for the RV FW strain (feasibility 83%). The details for feasibility of all strains across cardiac chambers and methods are shown in Supplemental Table 7. The numbers of accepted segments for the 18-segment model, 16-segment model, and 2DS standard processing model were median

**TABLE 3 Reference Ranges of GLS According to Sex and Age Groups**

| | <40 Years (N = 111) | 40-49 Years (n = 246) | 50-59 Years (n = 370) | 60-69 Years (n = 378) | ≥70 Years (n = 224) |
|---|---|---|---|---|---|
| Female subjects | | | | | |
| LV GLS-2DS | -21.3 (-24.9 to -17.8) | -21.0 (-25.3 to -16.7) | -20.5 (-24.0 to -17.0) | -19.7 (-23.7 to -15.7) | -19.0 (-22.9 to -15.0) |
| LV GLS-AFI | -21.4 (-24.7 to -18.0) | -21.6 (-25.0 to -18.2) | -20.9 (-24.3 to -17.6) | -20.3 (-24.5 to -16.1) | -19.5 (-23.6 to -15.4) |
| RV FW strain | -27.1 (-34.3 to -19.9) | -27.9 (-35.2 to -20.6) | -26.5 (-35.7 to -17.2) | -24.8 (-33.8 to -15.9) | -24.8 (-34.4 to -15.2) |
| LA reservoir strain-biplane | 41.0 (29.1-52.8) | 37.2 (21.8-52.7) | 34.8 (21.2-48.4) | 30.6 (17.2-44.0) | 26.4 (13.5-39.2) |
| LA reservoir strain-4CH | 40.9 (26.6-55.1) | 36.3 (20.4-52.3) | 34.3 (20.4-48.1) | 30.1 (16.6-43.6) | 26.4 (11.3-41.5) |
| LA conduit strain-biplane | -26.0 (-36.7 to -15.4) | -21.9 (-34.2 to -9.6) | -18.5 (-28.2 to -8.7) | -13.6 (-23.0 to -4.2) | -10.1 (-18.7 to -1.6) |
| LA conduit strain-4CH | -27.7 (-40.4 to -15.0) | -22.7 (-35.5 to -10.0) | -19.3 (-30.1 to -8.6) | -14.3 (-24.7 to -3.9) | -10.9 (-21.0 to -0.8) |
| LA contractile strain-biplane | -14.9 (-22.3 to -7.5) | -15.3 (-24.7 to -6.0) | -16.3 (-25.8 to -6.9) | -17.0 (-26.2 to -7.8) | -16.2 (-25.3 to -7.1) |
| LA contractile strain-4CH | -13.1 (-20.3 to -5.9) | -13.6 (-23.5 to -3.7) | -14.9 (-24.3 to -5.5) | -15.8 (-25.3 to -6.3) | -15.5 (-25.6 to -5.4) |
| RA reservoir strain | 44.5 (20.6-68.5) | 41.1 (17.9-64.4) | 38.2 (17.7-58.7) | 34.9 (18.4-51.5) | 34.2 (15.4-52.9) |
| RA conduit strain | -28.4 (-47.7 to -9.1) | -24.9 (-42.5 to -7.4) | -21.6 (-37.2 to -6.0) | -17.4 (-30.1 to -4.7) | -15.5 (-29.4 to -1.7) |
| RA contractile strain | -16.1 (-31.3 to -1.0) | -16.2 (-27.4 to -5.0) | -16.6 (-26.5 to -6.7) | -17.5 (-27.2 to -7.9) | -18.6 (-29.8 to -7.4) |
| Male subjects | | | | | |
| LV GLS-2DS | -19.8 (-23.5 to -16.0) | -20.1 (-23.7 to -16.5) | -19.5 (-23.1 to -15.8) | -18.9 (-22.6 to -15.3) | -18.5 (-22.7 to -14.3) |
| LV GLS-AFI | -20.3 (-24.8 to -15.9) | -19.9 (-23.2 to -16.7) | -19.5 (-23.3 to -15.8) | -19.5 (-23.4 to -15.5) | -19.1 (-23.2 to -15.0) |
| RV FW strain | -25.9 (-34.7 to -17.1) | -26.4 (-34.3 to -18.5) | -26.1 (-33.4 to -18.8) | -25.0 (-33.3 to -16.8) | -25.0 (-33.1 to -16.8) |
| LA reservoir strain-biplane | 38.7 (24.2-53.2) | 37.0 (21.3-52.7) | 34.2 (19.7-48.7) | 30.6 (15.5-45.7) | 26.1 (12.5-39.6) |
| LA reservoir strain-4CH | 38.7 (22.3-55.1) | 36.7 (21.5-52.0) | 33.0 (17.7-48.4) | 30.6 (14.8-46.4) | 26.9 (11.0-42.9) |
| LA conduit strain-biplane | -24.7 (-36.0 to -13.3) | -19.8 (-31.9 to -7.7) | -16.9 (-27.0 to -6.7) | -12.7 (-22.7 to -2.6) | -10.1 (-19.2 to -1.0) |
| LA conduit strain-4CH | -25.9 (-38.9 to -12.9) | -20.6 (-34.0 to -7.1) | -17.3 (-29.0 to -5.7) | -13.3 (-24.7 to -1.8) | -11.0 (-20.8 to -1.1) |
| LA contractile strain-biplane | -14.0 (-22.9 to -5.1) | -17.2 (-27.5 to -7.0) | -17.4 (-26.6 to -8.1) | -17.9 (-28.2 to -7.7) | -16.0 (-25.5 to -6.4) |
| LA contractile strain-4CH | -12.8 (-22.3 to -3.3) | -16.2 (-26.5 to -5.9) | -15.7 (-25.7 to -5.7) | -17.3 (-28.2 to -6.5) | -16.0 (-27.9 to -4.0) |
| RA reservoir strain | 42.3 (21.1-63.4) | 42.8 (20.7-65.0) | 39.5 (19.6-59.3) | 35.4 (18.1-52.8) | 33.7 (15.7-51.7) |
| RA conduit strain | -27.6 (-45.0 to -10.2) | -25.2 (-41.2 to -9.3) | -22.5 (-37.1 to -8.0) | -18.0 (-30.3 to -5.7) | -15.6 (-27.9 to -3.4) |
| RA contractile strain | -14.6 (-23.7 to -5.5) | -17.6 (-29.0 to -6.2) | -16.9 (-28.1 to -5.8) | -17.4 (-27.5 to -7.4) | -18.1 (-31.0 to -5.2) |

Values are mean (mean - 1.96 SD, mean + 1.96 SD). The unit of all strain measurements is percentage (%). LV strains are mean of the 18 segments.
Abbreviations as in Table 2.

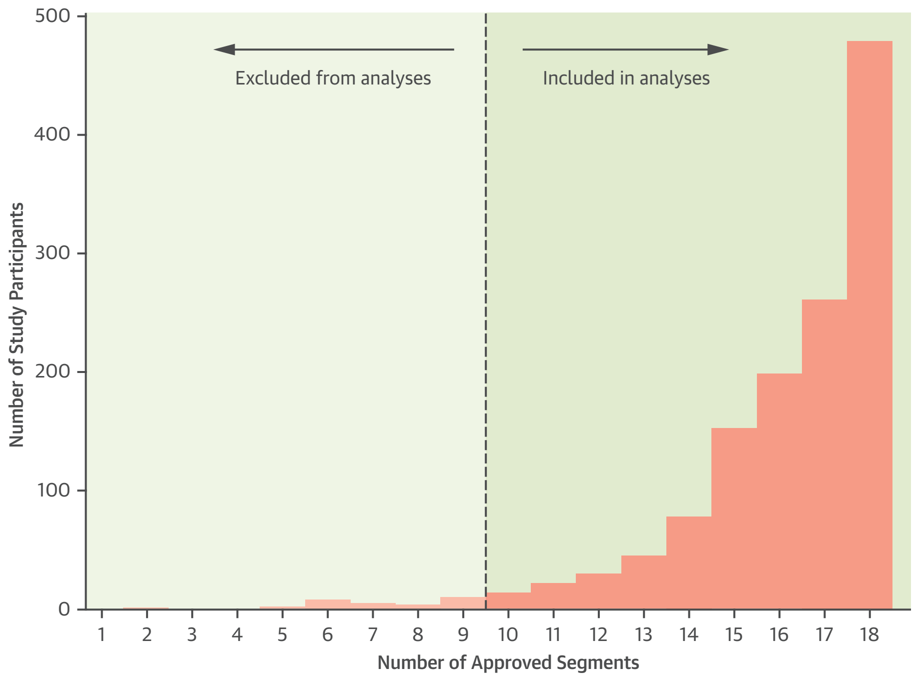
(IQR) 17 (3), 17 (3), and 18 (1), and 1,090 (82%) subjects had ≥15 of 18 segments included in the analyses of LV GLS by 2DS (**Figure 2**).

**REPRODUCIBILITY.** The Bland-Altman plots (Supplemental Figure 1) shows that the limits of agreements for LV GLS, RV FW strain, LA strains, and RA strains were approximately (-3.5, 3.5), (-6, 6), (-10, 10), and (-5 to -10, 5 to 10), respectively. The reference ranges were narrower for LV GLS, and the plots indicate a gradient with respect to reproducibility being best for LV GLS and poorest for atrial strains. LA strain measured only in the 4CH view had marginally narrower limits of agreements for the conduit and contractile phases compared with biplane measurements. The ICCs for the different strains ranged from 0.72 to 0.93, with lowest coefficients for LA contractile strain and highest for RA strains (0.90-0.93). For the LV strains, the ICCs were 0.83 to 0.84 for 2DS and 0.70 to 0.71 for AFI (both with overlapping 95% CIs), and there were no significant differences whether the ICCs were calculated based on 2 or 4 operators for LV GLS (2DS) and 2 or 3 operators for LV GLS (AFI). All ICC values are presented in Supplemental Table 8.

## DISCUSSION

We present echocardiographic reference ranges for chamber-specific global strains based on guideline-directed dedicated views in a large cross-sectional normal population study of >1,300 healthy subjects with a wide age span and balanced sex distribution (**Central Illustration**). All recordings were acquired by highly experienced sonographers and analyzed by EACVI-certified expert cardiologists at an EACVI-accredited echocardiography laboratory. The absolute strain values for all chambers were lower by higher age. Furthermore, the chamber-specific strains were associated with several subject characteristics. Absolute LV GLS was lower with higher age, BSA, MAP, and heart rate, and was approximately 1% lower in male subjects than in female subjects. The difference between the sexes seems

**FIGURE 2** Number of Approved Left Ventricular Segments During 2DS Strain Measurements by Number of Study Participants




The distribution of study participants per number of approved left ventricular segments during strain measurement with the two-dimensional strain (2DS) method. Study participants with ≥10 approved segments were included in data analyses, while those with ≤9 approved segments were not.

mainly to be explained by other subject characteristics. The presented reference ranges can be used to support clinical decision-making when evaluating individual patients.

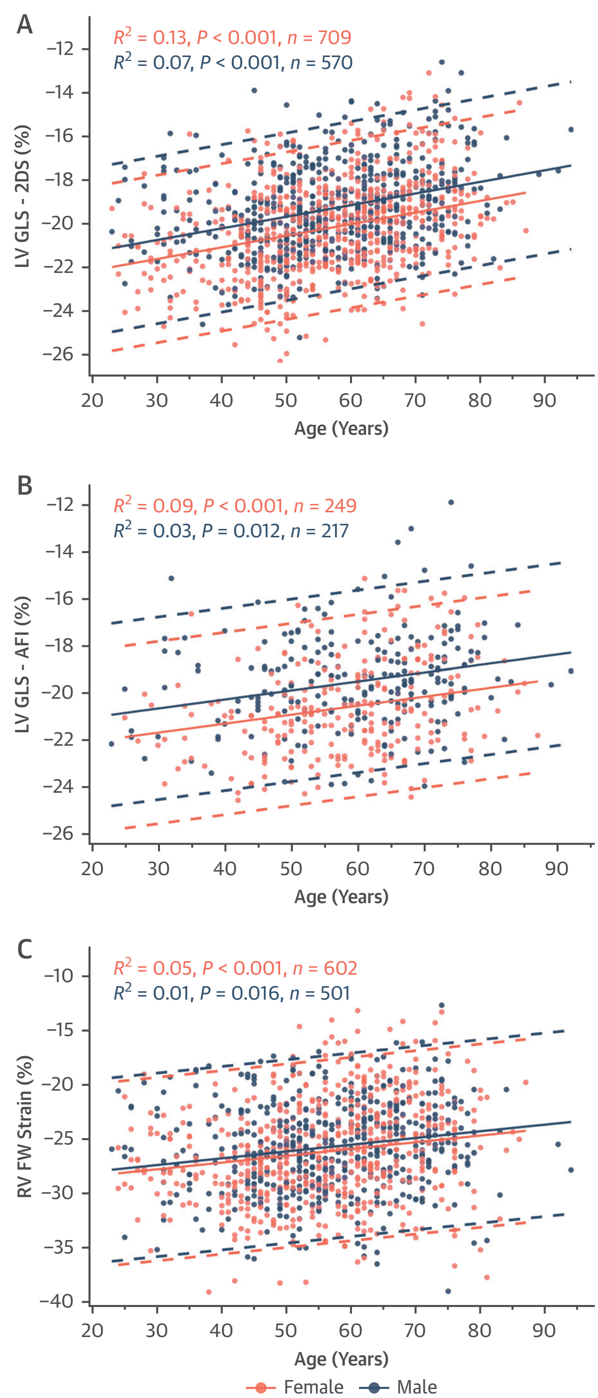
LV GLS is the most widely used strain measurement in clinical practice, providing incremental prognostic information and better reproducibility than LV ejection fraction.[1,2] The robustness of LV GLS is highlighted by the presented finding of LV GLS being the strain measurement with the narrowest reference ranges. The finding of lower absolute LV GLS with higher age and in male subjects compared with female subjects are in line with the findings from a decade ago.[8] However, the associations with sex and age have not been consistent between publications.[11,12,24,25] Differences in age distribution, size of the studied samples, and the method used to analyze strain may partly explain the differences across publications. The stringent methodology and large number of included subjects in the present work strongly suggest that these findings are actual associations with implications for clinical interpretation of strain measurements.

**VENTRICULAR STRAINS.** As shown in the present study, age and sex are the most important predictors for LV GLS, illustrated by the highest standardized beta coefficients. They therefore constitute the most important variables to adjust for when assessing LV GLS to more precisely determine whether measurements are within the reference ranges. However, most of these sex differences can be attributed to differences in body size.[26-28] Female subjects have smaller left ventricles even after indexing for body size.[26] It is therefore mathematically evident that strain will differ between sexes (strain is defined by deformation per length unit), and it is important to highlight that strain is not equal to contractility. Age is a continuous variable, and its relationship with LV GLS is approximately linear. It is therefore beneficial to adjust the reference ranges to continuous age and not to age groups. The same applies to RV, LA, and RA strains. The lower normal limit of LV GLS was -15.7% compared with -17.2% reported in the NORRE (Normal Reference Ranges for Echocardiography) study.[11] The population of the WASE (World Alliance Societies of Echocardiography) and NORRE studies were significantly younger, with a mean age of 45 and 46 years, respectively, [11,12] whereas mean age in the present population was 57 years. This may explain some of the differences in strains between these large studies.

However, data from the CCHS (Copenhagen City Heart Study) showed a lower normal limit of 15.8%, similar to our results, despite a population with a similar age as the WASE and NORRE studies.[29] Also, the recently published SUCCOUR (Strain Surveillance of Chemotherapy for Improving Cardiovascular Outcomes) trial shows baseline LV GLS in line with those presented.[30] A meta-analysis showed that most data of normal LV GLS were from younger patients, supporting our consistent finding of lower absolute LV GLS with higher age.[6,7] Thus, an important contribution of the present study is to extend the use of reference ranges to a more clinically relevant age group. Furthermore, the methods used for LV GLS perform spatial smoothing of the apex and may therefore overestimate apical strain, particularly in narrow ventricles. Overestimation of apical strain is indicated by somewhat lower absolute strain values for the 16-segment model compared with the 18-segment model and the standard processing values. This tendency will be more important in foreshortened images. All images in the present study were recorded by highly experienced sonographers, and great care was taken to obtain optimal views. This might have resulted in less foreshortening and may explain some of the differences between studies. Improved image quality by technological advances and software revisions may also alter the strain measurements caused by differences in ROI initialization, tracking and analyses, but its effect on differences between studies is unknown.

RV FW strain provides incremental prognostic information compared with other measurements of RV systolic function.[3,4] RV FW strain is, as LV GLS, the recommended measurement by the ASE and the EACVI.[22,31] The reference ranges were much wider for RV FW strain than they were for LV GLS, meaning the between-subject variability is larger than for LV GLS. RV FW strain was not significantly associated with sex in multiple linear regression analyses, including BMI. In line with these results, the WASE study showed lower absolute RV FW strain with higher age. The WASE study also reported a difference of 2% in RV FW strain between sexes, compared with a 0.4% absolute difference in the present study. Because BMI was not adjusted for in the WASE study, we do not believe these findings are conflicting.

**FIGURE 3** **Left and Right Ventricular Strains According to Sex and Age**




(A) Left ventricular global longitudinal strain-two-dimensional strain (LV GLS 2DS). (B) LV GLS- Automated Function Imaging (AFI) application. (C) Right ventricular free-wall (RV FW) strain. Data for female subjects are shown in red, and data for male subjects are shown in blue. Lines refer to mean and prediction intervals by age and sex. n = numbers; $R^2$ = coefficient of determination.

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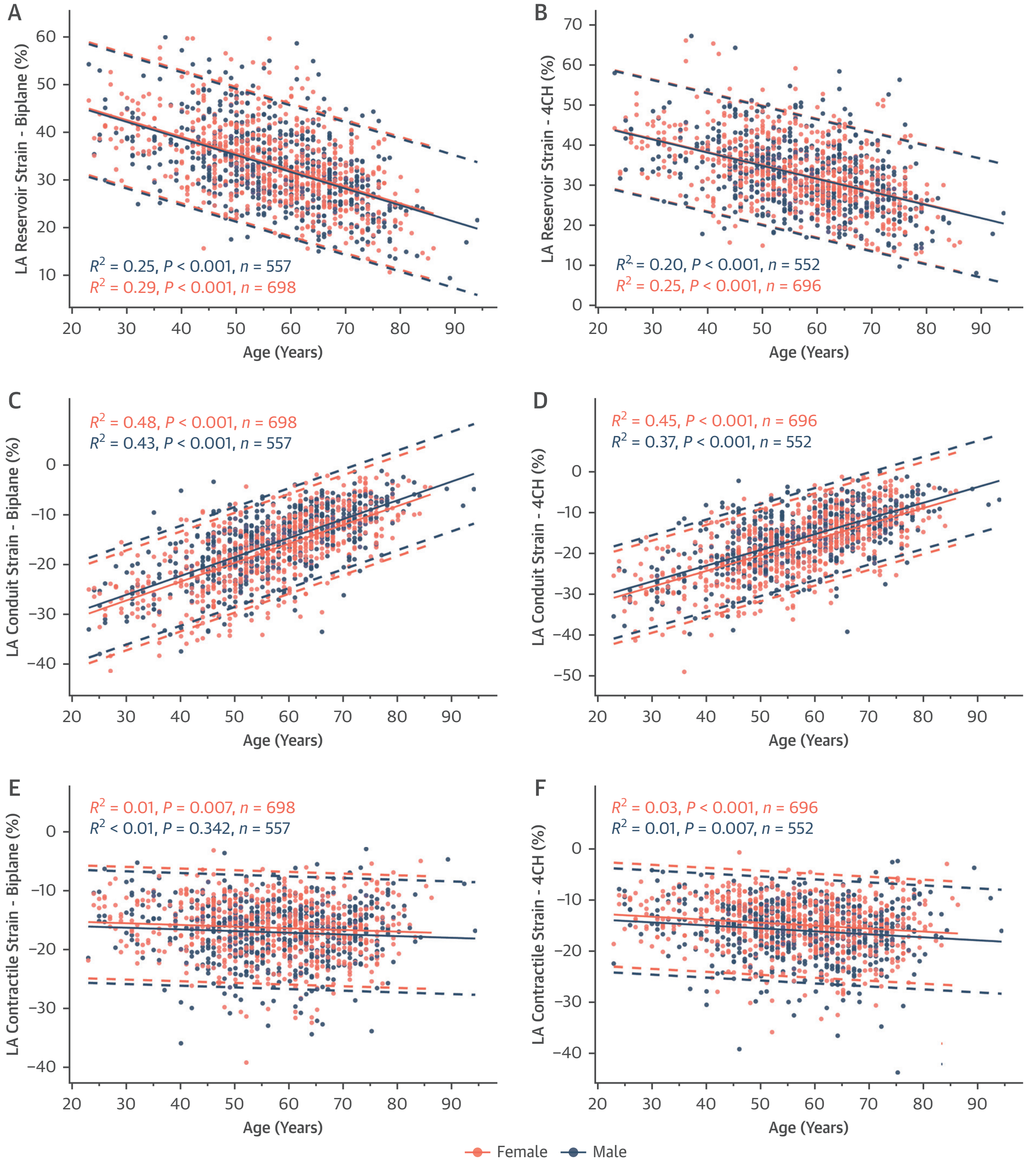
**FIGURE 4 LA Strains According to Sex and Age**



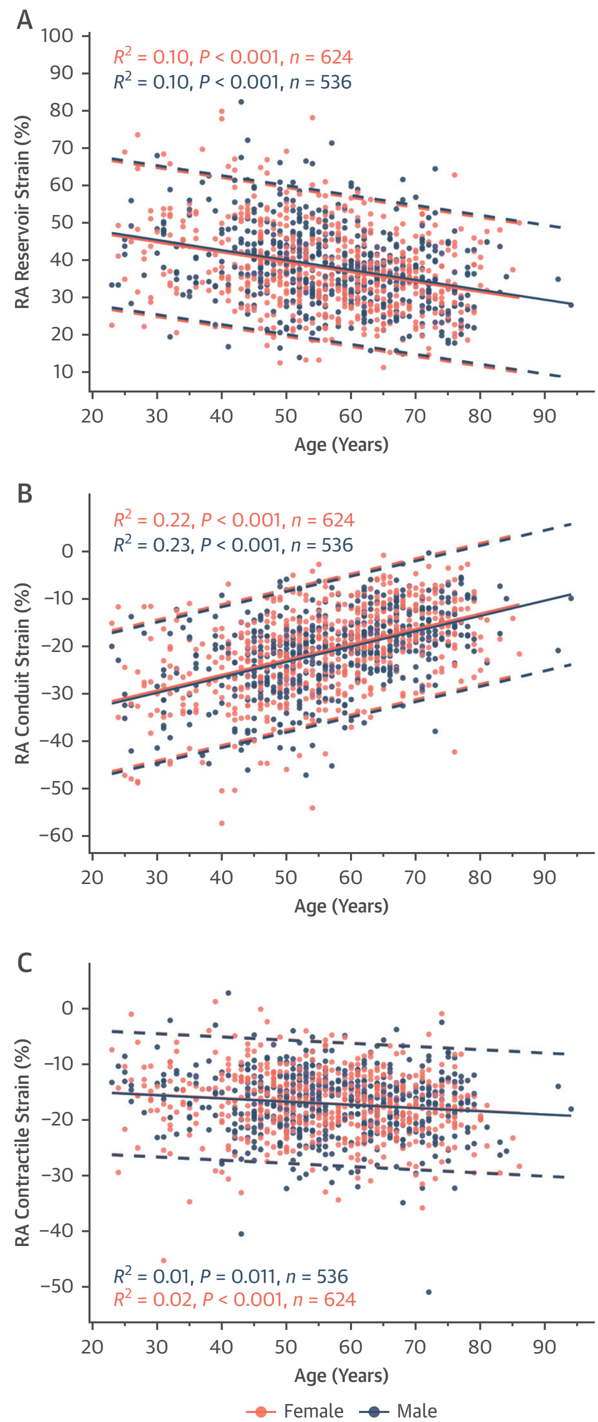

(A) Left atrial (LA) reservoir strain-biplane. (B) LA reservoir strain-four-chamber (4CH). (C) LA conduit strain-biplane. (D) LA conduit strain-4CH. (E) LA contractile strain-biplane. (F) LA contractile strain-4CH. Data for female subjects are shown in red, and data for male subjects are shown in blue. Lines refer to mean and prediction intervals by age and sex. Other abbreviations as in Figure 3.

**ATRIAL STRAINS.** The atrial strains had wide reference ranges compared with the ventricular strains. This was highly evident for LA and RA reservoir and conduit strains, for which the overall lower limit for LA and RA conduit strains was close to zero. This shows that the atrial strains are highly variable between normal subjects even though measurement reproducibility is good. The finding of wide reference ranges for atrial strains has previously been shown.[15,17,32,33] Thus, atrial strains should be used with caution in clinical decision-making. We have no indication that the wide CIs were due to inclusion of individuals with underlying cardiac disease. From a mathematical point of view, atrial strains are even more sensitive to relative out-of-plane motion and foreshortening as the length is shorter than for the ventricles. Both LA reservoir and conduit strains were closely negatively associated with age in this study (both $P <$ 0.001, $R^2 = 0.27$ and 0.46, respectively). The $R^2$ values for LA strain were somewhat lower when measured in 4CH only than in biplane, possibly indicating that less information was gathered in single-plane measurements. Similarly, we found a trend for associations between all RA strains and age, but the $R^2$ was lower and the associations weaker for reservoir and conduit strains compared to LA. The available published reports of normal RA strain shows significant heterogeneity between studies.[32,33] LA strain measurements have, in some studies, been shown to provide prognostic information beyond traditional prognosticators,[34] while they are not yet recommended in routine practice.[22,35] The close correlation of atrial strain with ventricular function is logical and documented,[36] as the ventricular proportion of the myocardium is much larger than the atrial. However, as atrial strains also take the morphology of the atria into account, future studies will determine their clinical role.

**REPRODUCIBILITY.** The limits of agreement in the reproducibility analyses were narrowest for LV GLS and widest for atrial strains. The finding of highest ICCs for RA strains must be interpreted by the large difference in lower and upper normal limits and the fact that all these strains are measured in one single view compared with the narrower reference ranges and 3 different views of LV GLS.

**STUDY STRENGTHS AND LIMITATIONS.** Main strengths of the study are recruitment of participants from the large HUNT population study, the chamber-specific echocardiographic recordings, and the study

**FIGURE 5** Right Atrial Strains According to Sex and Age




(A) Right atrial (RA) reservoir strain. (B) RA conduit strain. (C) RA contractile strain. Data for female subjects are shown in red, and data for male subjects are shown in blue. Lines refer to mean and prediction intervals by age and sex. Other abbreviations as in Figure 3.

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groups' extensive experience in clinical and technological echocardiography and strain imaging. Importantly, all acquisitions were obtained by highly experienced sonographers, and strain analyses for all chambers were assessed by 2 EACVI-certified expert cardiologists with >15 years of experience with strain imaging. The study has some limitations, including that the population was predominantly ethnic Norwegians (Caucasians). The limited numbers of individuals of non-Caucasian origin may limit generalizability to other ethnicities. Importantly, the WASE study did not reveal any associations between ethnicity and LV, LA, or RV strain, indicating that the presented data may be broadly implemented.[12,17,18] Even though we made significant efforts to ensure the normalcy of the population, long-term follow-up and natriuretic peptides were not part of the protocol. The study was conducted in a single center using novel GE HealthCare scanners and vendor-specific software, which limits the applicability to other scanner and software vendors. The importance of vendor specificity varies between studies, but in the EACVI-ASE Strain Standardization Task Force, the variability of LV GLS was significant between vendors, and the authors concluded that these differences should be considered in the everyday clinic.[2,11] Because many hospitals use vendor-specific analysis software, more data on reference ranges are needed because standardization among vendors is not yet fully achieved.[13,35] It is important to emphasize that although the reference ranges may be vendor specific, the associations with anthropometric and clinical variables and the difference between chambers are more general. It would be expected that the variability of strain measurements introduced by age and sex also applies to acquisitions and analyses performed with equipment from other vendors. Assessment of the associations with subject characteristics were limited to parameters easily available in the everyday clinic. The feasibility of global ventricular strains must be interpreted considering that analyses were performed with respect to global values for the 18-segment model and not for assessment of segmental strain or the standard processing output of the software. Similarly, the difference in feasibility between LV strain methods relates to the cutoff of accepted segments defined by the software. LV strains were obtained from the whole wall. Both 2DS and AFI provide options for assessment of layer-specific strains, but such evaluation was not part of this study. No circumferential or radial strains were analyzed by either of the methods. The use of the LA AFI package in the software for RA strain analyses represents off-label use, but because the ROI was manually adjusted and the LA AFI package does not utilize a priori models for strain calculation, we found no signs of interference with the tracking or RA strain analyses.

## CONCLUSIONS

Reference ranges for chamber-specific GLSs in echocardiography were established based on guideline-directed dedicated image views and measurements performed by experts. The reference ranges including lower normal limits vary with clinical characteristics such as age and sex, body size measures, blood pressure measurements, and heart rate. The unadjusted LV GLS and RV FW strain lower normal limits were -16% and -17%, respectively. RV FW strain, LA strains, and RA strains had wider reference ranges than LV GLS, as well as wider limits of agreement, challenging their clinical use. Reference ranges of strains based on age and sex can help to improve the differentiation between normal and pathologic conditions and thereby support clinical decision-making.

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**ADDRESS FOR CORRESPONDENCE:** Professor Havard Dalen, Department of Circulation and Medical Imaging, Norwegian University of Science and Technology, Box 8905, 7491 Trondheim, Norway. E-mail: havard.dalen@ntnu.no.

## PERSPECTIVES

**COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS:** Using the adjusted reference ranges can enhance diagnostic capabilities for any cardiologist or sonographer practicing echocardiography.

**TRANSLATIONAL OUTLOOK:** The updated reference ranges of strain for the cardiac chambers may improve care of individual patients. The reference ranges are associated with age, sex, and measurements of anthropometry and blood pressure and heart rate that should be considered for the best clinical implementation. In the future, this study allows for linear adjustments of the reference ranges based on implementation of the reference ranges adjusted for age and sex (provided in Supplemental Table 4) in echocardiographic scanners and analysis software.

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**KEY WORDS** GLS, left atrium, left ventricle, right atrium, right ventricle

**APPENDIX** For supplemental tables and a figure, please see the online version of this paper.