Right atrium size in the general population

Karsten Keller1,2,3, Christoph Sinning4,5, Andreas Schulz6, Claus Jünger7, Volker H. Schmitt1,8, Omar Hahad1,8, Tanja Zeller4,5, Manfred Beutel7, Norbert Pfeiffer9, Konstantin Strauch10, Stefan Blankenberg4,5, Karl J. Lackner11,8, Jürgen H. Prochaska1,2,4,8, Eberhard Schulz1,12, Thomas Münzel1,8,13 & Philipp S. Wild1,2,6,8,13

Echocardiography is the most common routine cardiac imaging method. Nevertheless, only few data about sex-specific reference limits for right atrium (RA) dimensions are available. Transthoracic echocardiographic RA measurements were studied in 9511 participants of the Gutenberg-Health-Study. A reference sample of 1942 cardiovascular healthy subjects without chronic obstructive pulmonary disease was defined. We assessed RA dimensions and sex-specific reference limits were defined using the 95th percentile of the reference sample. Results showed sex-specific differences with larger RA dimensions in men that were attenuated by standardization for body-height. RA-volume was 20.2 ml/m in women (5th–95th: 12.7–30.4 ml/m) and 26.1 ml/m in men (5th–95th: 16.0–40.5 ml/m). Multivariable regressions identified body-mass-index (BMI), coronary artery disease (CAD), chronic heart failure (CHF) and atrial fibrillation (AF) as independent key correlates of RA-volume in both sexes. All-cause mortality after median follow-up-period of 10.7 (9.81/11.6) years was higher in individuals who had RA volume/height outside the 95% reference limit (HR 1.70 [95%CI 1.29–2.23], P = 0.00014)). Based on a large community-based sample, we present sex-specific reference-values for RA dimensions normalized for height. RA-volume varies with BMI, CHF, CAD and AF in both sexes. Individuals with RA-volume outside the reference limit had a 1.7-fold higher mortality than those within reference limits.

Abbreviations
AF  Atrial fibrillation
BMI  Body mass index
BSA  Body surface area
CAD  Coronary artery disease
CHF  Chronic heart failure
COPD  Chronic obstructive pulmonary disease
CVD  Cardiovascular diseases
CVRF  Cardiovascular risk factors
FH  Family history
GHS  Gutenberg Health Study

1Department of Cardiology, Cardiology I, University Medical Center, Johannes Gutenberg University Mainz, Langenbeckstrasse 1, 55131 Mainz, Germany. 2Center for Thrombosis and Haemostasis, University Medical Center Mainz, Mainz, Germany. 3Medical Clinic VII, Department of Sports Medicine, University Hospital Heidelberg, Heidelberg, Germany. 4Department of General and Interventional Cardiology, University Heart Center Hamburg, Hamburg, Germany. 5German Center for Cardiovascular Research (DZHK), Partner Site Hamburg/Kiel/Lübeck, Hamburg, Germany. 6Preventive Cardiology and Preventive Medicine – Department of Cardiology, University Medical Center, Johannes Gutenberg University Mainz, Langenbeckstr. 1, 55131 Mainz, Germany. 7Department of Psychosomatic Medicine and Psychotherapy, University Medical Center, Johannes Gutenberg University Mainz, Langenbeckstr. 1, 55131 Mainz, Germany. 8German Center for Cardiovascular Research (DZHK), Partner Site Hamburg/Kiel/Lübeck, Hamburg, Germany. 9Institute for Medical Biometrics, Epidemiology and Informatics (IMBIE), University Medical Center, Johannes Gutenberg University Mainz, Obere Zahlbacher Str. 69, 55131 Mainz, Germany. 10Institute of Clinical Chemistry and Laboratory Medicine, University Medical Center, Johannes Gutenberg University Mainz, Langenbeckstr. 1, 55131 Mainz, Germany. 11Department of Cardiology, Allgemeines Krankenhaus Celle, Celle, Germany. 12These authors contributed equally: Thomas Münzel and Philipp S. Wild. *email: Karsten.Keller@unimedizin-mainz.de
sex-specific reference limits for the RA. A large-scale, epidemiological study conducted with state-of-the-art echocardiography imaging technology in order to define novel cardiovascular risk factors (CVRF) in the population.

Primary aim of the GHS was to characterize a general population-based cohort study in Rhine-Main region of mid-western Germany. Primary aim of the GHS was to characterize novel cardiovascular risk factors (CVRF) in the population.

GHS design as well as inclusion/exclusion criteria have been published previously. Briefly summarized, a 1:1 stratification of the study sample for sex (4794 men, 4717 women), residence (urban and rural) and equal strata for age decades was assigned. Enrolled subjects were between 35 and 74 years of age. A written informed consent from each participant was required to take part in the study. The Ethics Committee of the State Chamber of Physicians of Rhineland-Palatinate, Germany (Reference No.: 837.020.07[5555], date of approval: 22.03.2007), and the local and federal data safety commissioners approved the study protocol and the sample design.

Between April 2007 and April 2012, cross-sectional data from 9511 people were acquired and investigated. Overall, 55.5% of the individuals who were invited consented to participate in the study. Participants were interviewed in a standardized fashion. Measurements of laboratory parameters from venous blood samples, blood pressure, anthropometric data and a transthoracic echocardiography (TTE) were performed. All examinations were carried out according to a standardized protocol by certified medical technical assistants.

Reference sample. In order to obtain cardiac metric values of healthy participants from the GHS study sample, a subset of subjects without CVRF or history of cardiovascular disease (CVD) as well as right heart strain associated diseases such as chronic obstructive pulmonary disease (COPD) was defined as the reference sample. The reference sample comprised 1942 cardiovascular healthy subjects with no apparent or reported history of chronic heart failure (CHF), myocardial infarction (MI), coronary artery disease (CAD), peripheral artery disease, stroke, arterial hypertension, smoking, dyslipidaemia, obesity (defined as Body-Mass-Index [BMI] > 30 kg/m²), diabetes mellitus or family history (FH) of MI/stroke as well as chronic obstructive pulmonary disease (COPD). This group was used to formulate reference values.

Echocardiography. All participants underwent multimodal TTE with an iE33 echocardiography system and a 5S-1 sector array transducer (Royal Philips Electronics, Amsterdam, Netherlands), phased array with 80 elements and a 5- to 1-MHz operating frequency range. Echocardiographic measurements were performed according to current American and European guidelines.

Linear measurements were acquired from 2D images in the apical four-chamber view at ventricular end-systole (maximum RA size). Short and long axis as well as circumference were determined and recorded (Fig. 1), while planimetric area and volume were calculated from these linear measurements. Long axis (apico-basal axis) diameter was measured from RA roof (center of superior RA wall) to the center of tricuspid valve annulus, parallel to interatrial septum. For analysis of the short axis (septal-lateral axis), plane perpendicular to RA long axis was defined that reflects the maximum diameter between the lateral border of the RA and the inter-atrial septum (Fig. 1).

Circumference was drawn from lateral to septal border of the tricuspid annulus, excluding the area between tricuspid leaflets and annulus, along RA endocardium, excluding Vena cava inferior/Vena cava superior and RA appendage (Fig. 1). Circumference value was used to calculate RA area and volume. RA volume was analysed and calculated by the monoplane area-length ellipsoid method. The reproducibility of this method has been previously reported.
Data recording and quality control. All digitally recorded datasets (image-management system Xcelera (Royal Philips Electronics, Amsterdam, Netherlands)) were controlled for quality by an experienced echocardiographer. Moreover, data were checked by a central data management unit. Echocardiographic measurements were available in 98.1%, which were included in the final analysis (only 1.9% were missings due patient factors or technical aspects).

Statistics. Analyses were performed sex-specifically. Data are presented as absolute numbers, percentages, mean with standard deviation or median with 25th and 75th percentiles as appropriate. Distributions of RA measurements were approximately normal. Reference limits, cut-off values for deviation of the reference and percentile values were presented as absolute values and normalized for height and BSA (BSA formula according to Du Bois was used for calculation of the BSA values). Categorization of the reference limits and of the deviation categories of values exceeding the reference limits were defined as followed: the healthy reference comprised all values between the 5th and 95th percentile of the reference sample. Mild deviation contained values between the 95th percentile of the reference sample and the 98th percentile of the entire GHS population sample. Moderate deviation was defined as values between the 98th and 99th percentile of population sample of GHS; and severe deviation included values > 99th percentile of the population sample. A similar strategy has been used by other investigators.

Sex-specific nomograms were generated to correlate RA volume normalized for height and age with defined categories of pathological conditions. Nomograms were generated by quantile regression. We used a multivariable linear regression model to investigate the association between CVRF, co-morbidities and RA dimensions. The model was adjusted for age (10 years), BMI (5 kg/m²), diabetes mellitus, dyslipidaemia, arterial hypertension, smoking, and FH of MI.

In addition, Kaplan–Meier plots for cumulative survival were computed to investigate the effect of RA volume (standardized for body height) enlargement on the survival of this large cohort during the median follow-up period of 10.7 (9.81/11.6) years. We calculated a Cox-regression model for all-cause mortality to evaluate the effect of being outside of the 95th percentile of the reference sample in regard to RA volume standardized for height. The multivariate Cox regression model was adjusted for (1) age, sex and CVRF and (2) age (10 years), sex, CVRF, CAD, MI, CHF, atrial fibrillation (AF), stroke, COPD and peripheral artery disease.

Figure 1. Long axis (apico-basal axis) diameter was measured from RA roof (center of superior RA wall) to the center of tricuspid valve annulus, parallel to interatrial septum (blue arrow), whereas short axis (septal-lateral axis), plane perpendicular to RA long axis was defined that reflects the maximum diameter between the lateral border of the RA and the inter-atrial septum (yellow arrow). Circumference was drawn from lateral to septal border of the tricuspid annulus, excluding the area between tricuspid leaflets and annulus, along RA endocardium, excluding Vena cava inferior/Vena cava superior and RA appendage (yellow line).
Results were not adjusted for multiple testing and might in part be deemed exploratory and warrant replication. As such, $P$ values $< 0.05$ were indicative of statistical significance. All analyses were performed with the software R version 2.15 (http://www.R-project.org).

Ethical standards and informed consent statement. The Gutenberg Health Study (GHS) has been approved by the local ethics committee (Reference No. 837.020.07[5555]) and the data protection officer. The GHS therefore has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments as well as the recommendations for Good Clinical and Epidemiological Practice. All study participants gave their written informed consent prior to their inclusion in the study.

Results
Overall, 9,511 participants (age range 35–74 years; 4,794 men, 4,717 women) were enrolled in the GHS study sample to investigate RA metrics. Age of men and women of the study sample was similar (54.8 ± 11.2 vs. 54.6 ± 11.1 years). Prevalence of CVRF except for FH of MI/stroke was higher in men than in women. Accordingly, co-morbidities including MI, CAD, stroke and atrial fibrillation (AF) were encountered more frequently in male than in female participants (Table S1 of supplemental data).

Overall, 20.4% of the 9,511 subjects had no CVD, COPD or CVRF and were included in the healthy reference sample (n = 1,942). Women prevailed among this group (61.1% women, 38.9% men). Characteristics of the cardiovascular healthy reference sample are shown in Table S1 of supplemental data.

Absolute RA measurements revealed sex-specific differences with larger values in men. After standardization for body height, these differences were attenuated in the reference sample. Absolute septal-lateral (short axis) and apico-basal (long axis) diameters were 11.2% and 7.6% larger in men than in women. After normalization for height, these differences decreased to 3.7% and 1.8%, respectively. Absolute mean values of RA circumference, area and volume were 10.3%, 19.6% and 28.4% larger in men compared to women. Normalization for height reduced these sex-specific differences to 2.9%, 12.8% and 22.6%, respectively. Values and sex-specific cut-off values for the reference limits of RA diameter, circumference, area and volume are presented in Tables 1 and 2 (values of the overall cohort are shown in Tables S2 and S3 of the supplement and values normalized for body surface area (BSA) are shown in Tables S4 and S5 of the supplement).

In the reference sample, median short axis was 2.1 cm/m in men (5th–95th percentiles: 1.7–2.6) and 2.1 cm/m in women (5th–95th: 1.7–2.5). Median long axis was 2.7 cm/m in both sexes (5th–95th women: 2.2–3.1; men: 2.3–3.2).

|                  | Mean   | 2SD-interval | Median | 5th–95th percentile |
|------------------|--------|--------------|--------|---------------------|
| **Right atrium—absolute values** |        |              |        |                     |
| **Men**          |        |              |        |                     |
| Circumference (cm) | 15.4   | 12.7–18.2    | 15.3   | 13.3–17.8           |
| Area (cm²)       | 16.8   | 10.7–22.8    | 16.4   | 12.4–22.5           |
| Volume (ml)      | 46.9   | 19.7–74.1    | 45.0   | 28.6–73.3           |
| Septal-lateral diameter (cm) | 3.84   | 2.92–4.76    | 3.80   | 3.10–4.70           |
| Apico-basal diameter (cm) | 4.86   | 3.85–5.86    | 4.90   | 4.10–5.80           |
| **Women**        |        |              |        |                     |
| Circumference (cm) | 13.8   | 11.4–16.3    | 13.8   | 12.0–15.9           |
| Area (cm²)       | 13.5   | 8.7–18.4     | 13.3   | 10.0–17.8           |
| Volume (ml)      | 33.6   | 14.6–52.5    | 32.2   | 20.7–51.0           |
| Septal-lateral diameter (cm) | 3.41   | 2.65–4.18    | 3.40   | 2.80–4.10           |
| Apico-basal diameter (cm) | 4.49   | 3.49–5.49    | 4.50   | 3.70–5.30           |
| **Right atrium—values normalized for height** |        |              |        |                     |
| **Men**          |        |              |        |                     |
| Circumference/height (cm/m) | 8.60   | 7.09–10.1    | 8.55   | 7.39–9.88           |
| Area/height (cm²/m) | 9.34   | 6.09–12.8    | 9.17   | 6.93–12.4           |
| Volume/height (ml/m) | 26.1   | 11.4–40.8    | 25.0   | 16.0–40.5           |
| Septal-lateral diameter/height (cm/m) | 2.14   | 1.64–2.64    | 2.11   | 1.74–2.64           |
| Apico-basal diameter/height (cm/m) | 2.71   | 2.14–3.28    | 2.69   | 2.27–3.21           |
| **Women**        |        |              |        |                     |
| Circumference/height (cm/m) | 8.35   | 6.86–9.84    | 8.30   | 7.18–9.69           |
| Area/height (cm²/m) | 8.14   | 5.28–11.0    | 8.01   | 6.08–10.6           |
| Volume/height (ml/m) | 20.2   | 8.99–31.4    | 19.4   | 12.7–30.4           |
| Septal-lateral diameter/height (cm/m) | 2.06   | 1.60–2.51    | 2.04   | 1.73–2.47           |
| Apico-basal diameter/height (cm/m) | 2.66   | 2.09–3.23    | 2.65   | 2.21–3.14           |

Table 1. Distribution of right atrial measurements according to sex in a reference sample of subjects without CVRF and CVD (n = 1942): absolute values and values normalized for height.
Calculated RA volume was 20.2 ml/m in women (5th–95th: 12.7–30.4 ml/m) and 26.1 ml/m in men (5th–95th: 16.0–40.5 ml/m). The 95th percentiles of the reference sample were defined as reference limit.

Figure 2 shows a nomogram for correlation of RA volume/height to age in order to define age-dependent and sex-specific reference values and deviation from the cardiovascular healthy subgroup. Nomograms for the other RA measurements could be seen in Figs. S1–S4 of the supplement.

Changes in echocardiographic RA dimensions according to age were small and are shown in Table S6 of the supplement.

Multivariable regression analysis determined age, arterial hypertension, dyslipidaemia and BMI as independently associated with RA volume in men; in women, diabetes mellitus, BMI and dyslipidaemia remained independently associated (Table 3). CHF, CAD and AF were associated with larger RA volumes in both sexes, while history of MI was associated with larger RA volume in men only and COPD with smaller volume in women only (Table 3). After additional adjustment for the use of antihypertensive medication, arterial hypertension remained associated with a smaller RA volume (normalized for height) in men (β − 1.83 [95%CI − 2.41 to − 1.25]; \(P < 0.0001\)).

The subjects included in the study were continuously observed for a median period of 10.7 (9.81/11.6) years. In this follow-up period 658 (6.9%) of the individuals died (men: 423 [4.4%], women: 235 [2.5%]).

Kaplan–Meier plots for cumulative survival showed a better survival for subjects with RA volume (normalized for height) within the 95th percentile of the reference sample (Fig. 3a) as well as within quartiles with lower RA volumes (normalized for height) (Fig. 3b). In the Cox regression models, an individual’s condition of being outside of the 95th percentile of the reference sample in regard to RA volume (indexed for height) at baseline

| Table 2. Reference limits and categorization of values exceeding the reference limits for variables of the right atrium in the GHS population sample: absolute values and values normalized for height. v stands for the atrial value measured, Pctl for percentile, 95th Ref for 95th percentile of reference sample. |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                | Reference       | Mild 95th Ref–98thPctl | Moderate 98th–99thPctl | Severe 99th–99.9thPctl | Very severe > 99.9thPctl |
| **Right atrium—absolute values** |                |                    |                    |                    |                     |
| **Men**         |                |                    |                    |                    |                     |
| Circumference (cm) | ≤ 17.8         | 17.9 < v ≤ 18.7    | 18.7 < v ≤ 19.2    | 19.2 < v ≤ 21.0    | > 21.0             |
| Area (cm²) | ≤ 22.5         | 22.4 < v ≤ 23.3    | 23.4 < v ≤ 25.5    | 25.5 < v ≤ 30.4    | > 30.4              |
| Volume (ml) | ≤ 73.3         | 72.0 < v ≤ 81.9    | 81.9 < v ≤ 88.5    | 88.5 < v ≤ 111     | > 111              |
| Septal-lateral diameter (cm) | ≤ 4.70         | 4.60 < v ≤ 4.80    | 4.80 < v ≤ 5.00    | 5.00 < v ≤ 5.40    | > 5.40             |
| Apico-basal diameter (cm) | ≤ 5.80         | 5.80 < v ≤ 6.10    | 6.10 < v ≤ 6.30    | 6.30 < v ≤ 7.00    | > 7.00             |
| **Women**       |                |                    |                    |                    |                     |
| Circumference (cm) | ≤ 15.9         | 16.4 < v ≤ 17.0    | 17.0 < v ≤ 17.5    | 17.5 < v ≤ 18.0    | > 18.0             |
| Area (cm²) | ≤ 17.8         | 18.7 < v ≤ 20.1    | 20.1 < v ≤ 21.0    | 21.0 < v ≤ 25.1    | > 25.1              |
| Volume (ml) | ≤ 51.0         | 54.2 < v ≤ 61.4    | 61.4 < v ≤ 66.1    | 66.1 < v ≤ 84.5    | > 84.5             |
| Septal-lateral diameter (cm) | ≤ 4.10         | 4.10 < v ≤ 4.40    | 4.40 < v ≤ 5.00    | 4.50 < v ≤ 5.01    | > 5.01             |
| Apico-basal diameter (cm) | ≤ 5.20         | 5.30 < v ≤ 5.60    | 5.60 < v ≤ 5.80    | 5.80 < v ≤ 6.40    | > 6.40             |
| **Right atrium—values normalized for height** |                |                    |                    |                    |                     |
| **Men**         |                |                    |                    |                    |                     |
| Circumference/height (cm/m) | ≤ 9.88         | 10.1 < v ≤ 10.6    | 10.6 < v ≤ 10.9    | 10.9 < v ≤ 12.4    | > 12.4             |
| Area/height (cm²/m) | ≤ 12.4         | 12.5 < v ≤ 13.6    | 13.6 < v ≤ 14.4    | 14.4 < v ≤ 17.1    | > 17.1             |
| Volume/height (ml/m) | ≤ 40.5         | 40.1 < v ≤ 46.0    | 46.0 < v ≤ 49.4    | 49.4 < v ≤ 62.5    | > 62.5             |
| Septal-lateral diameter/height (cm/m) | ≤ 2.64         | 2.58 < v ≤ 2.72    | 2.72 < v ≤ 2.81    | 2.81 < v ≤ 3.06    | > 3.06             |
| Apico-basal diameter/height (cm/m) | ≤ 3.21         | 3.30 < v ≤ 3.46    | 3.46 < v ≤ 3.58    | 3.58 < v ≤ 3.93    | > 3.93             |
| **Women**       |                |                    |                    |                    |                     |
| Circumference/height (cm/m) | ≤ 9.69         | 10.0 < v ≤ 10.5    | 10.5 < v ≤ 10.8    | 10.8 < v ≤ 11.9    | > 11.9             |
| Area/height (cm²/m) | ≤ 10.6         | 11.3 < v ≤ 12.2    | 12.2 < v ≤ 13.0    | 13.0 < v ≤ 15.6    | > 15.6             |
| Volume/height (ml/m) | ≤ 30.4         | 32.9 < v ≤ 36.9    | 36.9 < v ≤ 40.0    | 40.0 < v ≤ 52.1    | > 52.1             |
| Septal-lateral diameter/height (cm/m) | ≤ 2.47         | 2.52 < v ≤ 2.65    | 2.65 < v ≤ 2.74    | 2.74 < v ≤ 3.10    | > 3.10             |
| Apico-basal diameter/height (cm/m) | ≤ 3.14         | 3.29 < v ≤ 3.46    | 3.46 < v ≤ 3.55    | 3.55 < v ≤ 4.11    | > 4.11             |
was significantly and independently associated with higher all-cause mortality during the follow-up-period of 10.7 (9.81/11.6) years (adjusted for age, sex and CVRF: HR 1.82 [95%CI 1.40–2.37], \( P < 0.0001 \); adjusted for age, sex, CVRF, CAD, history of MI, CHF, history of stroke, COPD, AF and PAD: HR 1.70 [95%CI 1.29–2.23], \( P = 0.00014 \)).

**Discussion**
The present epidemiological studies established echocardiographic parameters in more than 9,500 participants together with information concerning anthropometric data, laboratory results, disease history and CVRF. The definition of RA reference values was based on a healthy reference group of nearly 2,000 participants without CVRF, right heart strain due COPD or known CVD. Absolute RA measurements revealed sex-specific differences
with larger values in men compared to women. After standardization for body height, these sex-specific differences were significantly reduced but remained significant.

To our knowledge, the present investigation is the largest systematic assessment to define reliable sex-specific reference limits of RA long and minor axis, area, circumference and volume that enables us to classify categories of deviation from the healthy reference accurately.\(^1\)\(^{-}\)\(^3\)\(^,\)\(^6\)\(^,\)\(^8\)\(^,\)\(^9\)\(^,\)\(^1\)\(^1\). Additionally, normalization for height was used for all measured parameters. Indexation of echocardiographic measurements is a particular area of interest in cardiovascular imaging methologies, since anthropometric differences influence cardiac measurements.\(^1\)\(^2\)\(^,\)\(^1\)\(^3\)\(^,\)\(^1\)\(^4\). Absolute measured parameters. Indexation of echocardiographic measurements is a particular area of interest in cardiovascular imaging methologies, since anthropometric differences influence cardiac measurements.\(^1\)\(^2\)\(^,\)\(^1\)\(^3\)\(^,\)\(^1\)\(^4\).

| RA-volume/height (ml/m) | Crude \(\beta\) (95%CI) | \(p\) value (crude) | Adj. \(\beta^*\) (95%CI) | \(p\) value* |
|-------------------------|------------------------|-------------------|------------------------|--------------|
| Men                     |                        |                   |                        |              |
| Age (10 years)          | 0.41 (0.21–0.60)       | \(<\) 0.0001      | 0.48 (0.27–0.69)       | \(<\) 0.0001 |
| BMI (5 kg/m\(^2\))      | 1.48 (1.23–1.72)       | \(<\) 0.0001      | 1.66 (1.40–1.93)       | \(<\) 0.0001 |
| Diabetes mellitus       | 1.10 (0.40–1.80)       | 0.0021            | 0.19 (0.54 to 0.92)    | 0.62         |
| Dyslipidemia            | 0.04 (0.40 to 0.49)    | 0.85              | \(-0.56 (1.01–0.10\)   | 0.016        |
| Family history of MI or stroke | \(-0.09 (0.64–0.47\) | 0.76              | \(-0.10 (0.65 to 0.46\) | 0.74        |
| Arterial hypertension   | \(-0.08 (0.52 to 0.36\) | 0.71              | \(-1.30 (1.78 to 0.82\) | \(<\) 0.0001 |
| Smoking                 | \(-0.24 (0.18–0.10\)  | 0.021             | \(-0.41 (0.95 to 0.46\) | 0.74        |
| Coronary artery disease | 2.62 (1.71–3.53)       | \(<\) 0.0001      | 2.36 (1.42–3.30)       | \(<\) 0.0001 |
| History of MI           | 2.14 (1.08–3.20)       | \(<\) 0.0001      | 1.51 (0.43–2.59)       | 0.0060       |
| Chronic heart failure   | 4.46 (2.44–6.48)       | \(<\) 0.0001      | 3.85 (1.84–5.85)       | 0.00017      |
| History of Stroke       | 1.19 (0.23 to 2.61)    | 0.10              | 1.04 (0.37 to 2.45)    | 0.15         |
| COPD                    | \(-0.50 (0.59 to 0.59\) | 0.37              | \(-0.72 (1.80 to 0.36\) | 0.19        |
| Atrial fibrillation     | 7.27 (6.10–8.43)       | \(<\) 0.0001      | 6.88 (5.72–8.04)       | \(<\) 0.0001 |
| Peripheral artery disease| 0.74 (0.47 to 1.95)   | 0.23              | \(-0.07 (1.28 to 1.13\) | 0.91        |

| Women                   |                        |                   |                        |              |
| Age (10 years)          | 0.42 (0.26–0.58)       | \(<\) 0.0001      | 0.16 (0.01 to 0.34)    | 0.071        |
| BMI (5 kg/m\(^2\))      | 1.63 (1.49–1.78)       | \(<\) 0.0001      | 1.71 (1.55–1.87)       | \(<\) 0.0001 |
| Diabetes mellitus       | 0.91 (0.21–1.61)       | 0.011             | \(-1.02 (1.73 to 0.31\) | 0.0048       |
| Dyslipidemia            | 0.41 (0.003–0.82)      | 0.048             | \(-0.45 (0.87 to 0.03\) | 0.036        |
| Family history of MI or stroke | 0.10 (0.32 to 0.51) | 0.66              | \(-0.29 (0.69 to 0.12\) | 0.16        |
| Arterial hypertension   | 1.33 (0.98–1.69)       | \(<\) 0.0001      | 0.008 (0.40 to 0.41)   | 0.97         |
| Smoking                 | 1.95 (1.56–2.34)       | \(<\) 0.0001      | 0.07 (0.37 to 0.51)    | 0.76         |
| Coronary artery disease | 2.37 (1.10–3.63)       | 0.00024           | 1.55 (0.31–2.79)       | 0.015        |
| History of MI           | 1.76 (0.19–3.33)       | 0.028             | 0.78 (0.73 to 2.29)    | 0.31         |
| Chronic heart failure   | 3.09 (1.44–4.74)       | 0.00025           | 2.09 (0.51–3.67)       | 0.0097       |
| History of stroke       | 0.25 (1.38 to 1.87)    | 0.77              | \(-0.20 (1.78 to 1.38\) | 0.80        |
| COPD                    | \(-0.58 (1.32 to 0.16\) | 0.12              | \(-1.23 (1.95 to 0.52\) | 0.00075     |
| Atrial fibrillation     | 6.41 (5.12–7.71)       | \(<\) 0.0001      | 5.57 (4.31–6.82)       | \(<\) 0.0001 |
| Peripheral artery disease| 0.86 (0.25 to 1.97)   | 0.13              | \(-0.11 (1.18 to 0.96\) | 0.84        |

Table 3. Sex-specific association in GHS study sample between right atrial measurements and classical CVRF and cardiovascular diseases in uni- and multivariable linear regression models. \(\beta\) stands for \(\beta\)-estimate. *In the multivariable linear regression models all classical risk factors except sex listed in this table were included. \(p\) values < 0.05 were indicative of statistical significance.
study sex-specific cut-off values of RA short axis from healthy to pathologic were 4.7 cm in men and 4.1 cm in women. Lang et al. described sex-specific reference values indexed for BSA close to the results of our study. For RA long axis, less data is available. Absolute RA long axis mean values in the present study of 4.9 cm in males and 4.5 cm in females are both larger than the values reported in literature. Rudzki et al. defined a RA long axis diameter of > 5.3 cm as pathological. Upper cut-off values in our study were 5.8 cm in men and 5.2 cm in women. Kou et al. reported absolute sex-specific values and Lang et al. sex-specific reference values indexed for BSA both close to our results.

Up to now, there are only limited published data available regarding RA circumference and RA area. Results of our study showed slightly larger RA area values than the NORRE study. However, the NORRE study is not a population-based study and presented only absolute values and results normalized for BSA, with the well-known problems described above.

In contrast to available literature, our study found higher absolute sex-specific RA mean volume values of 46.9 ml in men and 33.6 ml in women. Lang et al. reported RA volumes normalized for BSA of 21 ml/m² in women and 25 ml/m² in men, which were similar to our results after indexing for BSA (Table S5 of supplemental data). In a study of 159 healthy participants, reference values of 18–50 ml/m² for males and of 17–41 ml/m² for females were reported, which showed higher upper reference limits than our study (≤ 36.1 ml/m² in men and ≤ 28.7 ml/m² in women). In contrast to our study, only a smaller number of participants were enrolled and their healthy reference group also included obese subjects up to a BMI of 35 kg/m² as well as participants with a screening blood pressure up to 160/90 mmHg. Our exclusion criteria were more strict with BMI > 30 kg/m² and blood pressure > 139/89 mmHg considering pathological. Therefore, these differences in the exclusion criteria for the cardiovascular reference group may explain the differences regarding cut-off values.

The presented nomogram is analyzed for simple and quick relation between measured RA volume/linear dimensions and age as well as sex.

However, height as indexation also has problems, particularly as it violates geometric assumptions with the theory of similarity (e.g. indexing a 3-dimensional measurement such as volume against a one-dimension parameter such as height).

Identified causes of abnormal RA dimensions in our reference sample are in accordance with some, but not all studies. In the present study a higher BMI, CAD, CHF and AF were independently associated with an increase of RA volume. Arterial hypertension was associated with a smaller RA volume in males, whereas COPD in females.

RA enlargement was described for several diseases such as chronic pulmonary hypertension, pulmonary embolism (PE), COPD, dilated cardiomyopathy, right atrial myocardial infarction and AF. With respect to CHF as well as AF, the results of our study are in accordance with the available literature showing RA dilation, while arterial hypertension and COPD did not (as expected) induce RA enlargement in our cohort. Relevance of RA enlargement for survival was emphasized in a Cox regression model. RA enlargement outside the reference limit was associated with approximately 1.7-fold increase of all-cause mortality during median follow-up period of more than 10.5 years. Several pathomechanisms might contribute to this higher mortality rate: the right heart plays a central role for morbidity and mortality of patients with cardiopulmonary diseases. RV dysfunction predicts a reduced exercise capacity, autonomic dysbalance and poorer prognosis. After acute...
cardiovascular events such as MI and PE, RV dysfunction is associated with higher mortality and development of heart failure. RA dilation could be observed a few months after successful cardioversion. Overall, there is evidence that incorporated in echocardiographic standard examination and well defined RA reference limits are an indispensable basis for future investigations.

Limitations. There are some limitations on this study. RA volume is calculated by using 2D parameters (diameters, RA area) and difficult anatomy of the RA may disturb these calculations. Therefore, additional methods to assess RA volumes in such people should be investigated. Further, only 35–75 years aged individuals of German nationality were included. Thus, these data may not be extrapolated to other populations with different ethnic/racial background or other age groups.

Conclusions

Based on a large population-based study sample, our data present sex-specific reference values for cardiac dimensions of the RA. RA volume varies with BMI and pathological conditions that affect RA size in both sexes include CAD, CHF and AF. Individuals with RA volume outside the reference limit at baseline had an approximately 1.7-fold higher long-term mortality than those subjects within the reference limits.

Received: 7 August 2021; Accepted: 28 October 2021
Published online: 18 November 2021

References

1. Kou, S. et al. Echocardiographic reference ranges for normal cardiac chamber size: Results from the NORRE study. Eur. Heart J. Cardiovasc. Imaging 15, 680–690 (2014).
2. Lang, R. M. et al. Recommendations for cardiac chamber quantification by echocardiography in adults: An update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J. Am. Soc. Echocardiogr. 28, 1–39 (2015).
3. Lang, R. M. et al. Recommendations for cardiac chamber quantification by echocardiography in adults: An update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur. Heart J. Cardiovasc. Imaging 16, 233–270 (2015).
4. Steeds, R. P. et al. EACVI appropriateness criteria for the use of transthoracic echocardiography in adults: A report of literature and current practice review. Eur. Heart J. Cardiovasc. Imaging 18, 1191–1204 (2017).
5. Wild, P. S. et al. Distribution and categorization of left ventricular measurements in the general population: Results from the population-based Gutenberg heart study. Circ. Cardiovasc. Imaging 3, 604–613 (2010).
6. Ajmone Marsan, N. et al. EACVI survey on standardization of cardiac chambers quantification by transthoracic echocardiography. Eur. J. Cardiovasc. Imaging 21, 119–123 (2020).
7. Do, D. H. et al. Right atrial size relates to right ventricular end-diastolic pressure in an adult population with congenital heart disease. Echocardiography 28, 109–116 (2011).
8. Aune, E., Baekkevar, M., Rodevand, O. & Otterstad, J. E. Normal reference ranges for left and right atrial volume indexes and ejection fractions obtained with real-time three-dimensional echocardiography. Eur. J. Echocardiogr. J. Work. Group Echocardiogr. Eur. Soc. Cardiol. 10, 738–744 (2009).
9. Rudski, L. G. et al. Guidelines for the echocardiographic assessment of the right heart in adults: A report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. J. Am. Soc. Echocardiogr. Off. Publ. Am. Soc. Echocardiogr. 23, 685–713 (2010).
10. Wild, P. S. et al. The Gutenberg health study. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz 55, 824–829 (2012).
11. Innelli, P., Esposito, R., Nistri, S. & Galderisi, M. The impact of ageing on right ventricular longitudinal function in healthy subjects: A pulsed tissue Doppler study. Eur. J. Echocardiogr. J. Work. Group Echocardiogr. Eur. Soc. Cardiol. 10, 491–498 (2009).
12. Cuspidi, C. et al. Indexation of left ventricular mass to body surface area and height to allometric power of 2.7: Is the difference limited to obese hypertensives? J. Hum. Hypertens. 23, 728–734 (2009).
13. Jeyaprakash, P. et al. A systematic review of scaling left atrial size: Are alternative indexation methods required for an increasingly obese population? J. Am. Soc. Echocardiogr. 34, 1067–1076 (2021).
14. Park, J. H., Hwang, I. C., Park, J. J., Park, J. B. & Cho, G. Y. Left atrial strain to predict stroke in patients with acute heart failure and sinus rhythm. J. Am. Heart Assoc. 10, e020414 (2021).
15. Kuch, B. et al. Distribution, determinants and reference values of left ventricular parameters in the general population: Results of the MONICA/KORA echocardiography studies. Gesundheitswesen 67(Suppl 1), S68–73 (2005).
16. Kuch, B. et al. Body composition and prevalence of left ventricular hypertrophy. Circulation 102, 405–410 (2000).
17. Cui, Q. et al. Left and right atrial size and the occurrence predictors in patients with paroxysmal atrial fibrillation. Int. J. Cardiol. 130, 69–71 (2008).
18. Lang, R. M. et al. Recommendations for chamber quantification. Eur. J. Echocardiogr. J. Work. Group Echocardiogr. Eur. Soc. Cardiol. 7, 79–108 (2006).
19. Van de Veire, N. R. et al. Echocardiographically estimated left ventricular end-diastolic and right ventricular systolic pressure in normotensive healthy individuals. *Int. J. Cardiovasc. Imaging* **22**, 633–641 (2006).

20. Caglar, I. M. et al. Evaluation of atrial conduction features with tissue Doppler imaging in patients with chronic obstructive pulmonary disease. *Clin. Res. Cardiol. Off. J. Germ. Card. Soc.* **101**, 599–606 (2012).

21. D’Andrea, A. et al. Right atrial size and deformation in patients with dilated cardiomyopathy undergoing cardiac resynchronization therapy. *Eur. J. Heart Fail.* **11**, 1169–1177 (2009).

22. Cioffi, G., de Simone, G., Mureddu, G., Tarantini, L. & Stefenni, C. Right atrial size and function in patients with pulmonary hypertension associated with disorders of respiratory system or hypoxemia. *Eur. J. Echocardiogr. J. Work. Group Echocardio. Eur. Soc. Cardiol.* **8**, 322–331 (2007).

23. Gosselink, A. T., Crijns, H. J., Hamer, H. P., Hillege, H. & Lie, K. I. Changes in left and right atrial size after cardioversion of atrial fibrillation: Role of mitral valve disease. *J. Am. Coll. Cardiol.* **22**, 1666–1672 (1993).

24. Houlz, B. et al. Left ventricular diastolic function and right atrial size are important rhythm outcome predictors after intraoperative ablation for atrial fibrillation. *Echocardiography* **27**, 961–968 (2010).

25. Lindqvist, P., Calcutteea, A. & Henein, M. Echocardiography in the assessment of right heart function. *Eur. J. Echocardiogr. J. Work. Group Echocardio. Eur. Soc. Cardiol.* **9**, 225–234 (2008).

26. Sanfillippo, A. J. et al. Atrial enlargement as a consequence of atrial fibrillation. A prospective echocardiographic study. *Circulation* **82**, 792–797 (1990).

27. Zornoff, L. A. et al. Right ventricular dysfunction and risk of heart failure and mortality after myocardial infarction. *J. Am. Coll. Cardiol.* **39**, 1450–1455 (2002).

28. Konstantinides, S. V. et al. 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism. *Eur. Heart J.* **35**, 3033–3069 (2014).

29. Bustamante-Labarta, M. et al. Right atrial size and tricuspid regurgitation severity predict mortality or transplantation in primary pulmonary hypertension. *J. Am. Soc. Echocardiogr. Off. Publ. Am. Soc Echocardiogr.* **15**, 1160–1164 (2002).

30. Padelli, M. et al. Right atrial speckle tracking analysis as a novel noninvasive method for pulmonary hemodynamics assessment in patients with chronic systolic heart failure. *Echocardiography* **28**, 658–664 (2011).

31. Ogren, M., Bergqvist, D., Eriksson, H., Lindblad, B. & Sternyb, N. H. Prevalence and risk of pulmonary embolism in patients with intracardiac thrombosis: A population-based study of 23,796 consecutive autopsies. *Eur. Heart J.* **26**, 1108–1114 (2005).

32. de Divitiis, M. et al. Right atrial appendage thrombus in atrial fibrillation: Its frequency and its clinical predictors. *Am. J. Cardiol.* **84**, 1023–1028 (1999).

33. Keller, K. et al. Right ventricular dysfunction in hemodynamically stable patients with acute pulmonary embolism. *Thromb. Res.* **133**, 555–559 (2014).

34. Sievers, B., Addo, M., Breuckmann, F., Barkhausen, J. & Erbel, R. Reference right atrial function determined by steady-state free precession cardiovascular magnetic resonance. *J. Cardiovasc. Magn Reson Off J Soc Cardiovasc Magn Reson* **9**, 807–814 (2007).

35. Keller, A. M., Gopal, A. S. & King, D. L. Left and right atrial volume by freehand three-dimensional echocardiography: In vivo validation using magnetic resonance imaging. *Eur. J. Echocardiogr.* **1**, 55–65 (2000).

36. Pelsso, D. et al. Right atrial size and function assessed with three-dimensional and speckle-tracking echocardiography in 200 healthy volunteers. *Eur. Heart J. Cardiovasc. Imaging* **14**, 1106–1114 (2013).

37. Muller, H., Reverdin, S., Burri, H., Shah, D. & Lerch, R. Measurement of left and right atrial volume in patients undergoing ablation for atrial arrhythmias: Comparison of a manual versus semiautomatic algorithm of real time 3D echocardiography. *Echocardiography* **31**, 499–507 (2014).

Acknowledgements

We are indebted to all study participants and all members of the GHS, who were involved in planning and conduction of the study.

Author contributions

K.K. wrote the manuscript, A.S. did the statistical analyses, T.M. and P.S.W. supervised the project. All authors reviewed and revised the manuscript.

Funding

Open Access funding enabled and organized by Projekt DEAL. The Gutenberg Health Study is supported by the government of Rheinland-Pfalz (‘Stiftung Rheinland-Pfalz für Innovation’), the research programs ‘Wissen schafft Zukunft’ and the Center for Translational Vascular Biology (CTVB) of the Johannes Gutenberg-University of Mainz, Germany, and its contract with Boehringer Ingelheim and Philips Medical Systems including an unrestricted grant for the Gutenberg Health Study. P.S.W. and J.H.P. are funded by the Federal Ministry of Education and Research (BMBF 01EO1503). P.S.W. and T.M. are principal investigators of the German Center for Cardiovascular Research (DZHK). P.S.W. is principal investigator of the DIASyM research core (BMBF 161L0217A).

Competing interests

J.H.P. received funding for lecturing by Bayer AG and Boehringer Ingelheim outside the topic of this work. P.S.W. reports the submitted work grants from Bayer AG, non-financial grants from Philips Medical Systems, grants and consulting fees from Boehringer Ingelheim, grants and consulting fees from Novartis Pharma, grants and consulting fees from Sanofi-Aventis, grants, consulting and lecturing fees from Bayer Health Care, grants from Daiichi Sankyo Europe, consulting fees from Astra Zeneca, consulting fees and non-financial support from Diasorin and non-financial support from I.E.M., outside the submitted work. All other authors declare no disclosures that could be perceived as conflict of interest in the context of the present work.

Additional information

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1038/s41598-021-01968-y.

Correspondence and requests for materials should be addressed to K.K.

Reprints and permissions information is available at www.nature.com/reprints.
Publisher’s note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article’s Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article’s Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/.

© The Author(s) 2021