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ORIGINAL RESEARCH

Lower Cardiorespiratory Fitness Is Associated With Right Ventricular Geometry and Function – The Sedentary's Heart: SHIP

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BACKGROUND: Lower cardiorespiratory fitness (CRF) is associated with an increased risk for cardiovascular disease. However, very little information is available about the association between lower CRF and right ventricular (RV) remodeling. We investigated the relationship between CRF and RV structure and function in a large, aging, and largely sedentary adult population–based cohort.

METHODS AND RESULTS: We used cross-sectional data of 2844 subjects (1486 women; median age, 51 years; interquartile range, 40–62 years) from the population-based cohort SHIP (Study of Health in Pomerania) with echocardiography, of which 941 also had cardiac magnetic resonance imaging. We analyzed the associations of peak oxygen uptake with RV parameters determined by both imaging techniques using multivariable-adjusted linear regression models. In echocardiography, a 1 L/min lower peak oxygen uptake was associated with a 1.18 mm (95% CI, 0.66–1.71; $P<0.001$) smaller RV end-diastolic diameter and a 1.41 mm (95% CI, 0.90–1.92; $P<0.001$) narrower RV end-diastolic outflow tract diameter. Similarly, using cardiac magnetic resonance imaging measurements, a 1 L/min lower peak oxygen uptake was associated with a 23.5 mL (95% CI, 18.7–28.4; $P<0.001$) smaller RV end-diastolic volume, a 13.0 mL (95% CI, 9.81–16.2; $P<0.001$) lower RV end-systolic volume, and a 10.7 mL/beat (95% CI, 8.10–13.3; $P<0.001$) lower RV stroke volume.

CONCLUSIONS: Our results indicate a significant association between CRF and RV remodeling. Lower CRF was associated with smaller RV chamber and lower RV systolic function, stroke volume, and cardiac output.

Key Words: cardiorespiratory fitness ■ peak oxygen uptake ■ physical inactivity ■ right ventricular geometry and function ■ right ventricular volumes

Cardiorespiratory fitness (CRF) is inversely associated with cardiovascular diseases,[1] which remain the most common cause of death worldwide.[2] Interestingly, in the middle of the worldwide COVID-19 pandemic, a recent study was also able to show that maximal exercise capacity was inversely associated with the probability of hospitalization because of COVID-19.[3,4]

CRF refers to the ability of the circulatory and respiratory systems to supply oxygen to skeletal muscles during sustained physical activity (PA).[5–7] The gold standard to determine CRF is the measurement of the peak oxygen uptake (VO_{2peak}) assessed during cardiopulmonary exercise testing (CPET).[8] Higher levels of CRF are associated with a lower risk for cardiovascular disease

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CLINICAL PERSPECTIVE

What Is New?

- Our study demonstrates that lower cardiorespiratory fitness is associated with smaller chambers size and lower systolic function, stroke volume, and cardiac output of the right heart.
- We believe that this relation might explain the previously described aging-related decrease in size of the heart wherein the sedentary lifestyle of most individuals throughout life might be the most important contributor.

What Are the Clinical Implications?

- Further studies are needed to identify the mechanisms of these changes in detail for a possible therapeutic use and to develop more information about the clinical relevance of the right ventricle, possibly also in different populations.

Nonstandard Abbreviations and Acronyms

CRF	cardiorespiratory fitness
PA	physical activity
RVEDD	right ventricular end-diastolic diameter
RVEDV	right ventricular end-diastolic volume
SHIP	Study of Health in Pomerania
VO_{2peak}	peak oxygen uptake

and morbidity.[9] Higher CRF is related with a higher cardiac output through augmented stroke volume or heart rate,[10,11] lower systolic blood pressure,[12] pulmonary arterial pressure, and vascular resistance.[11,13] Moreover, greater CRF is associated with increased left ventricular (LV) mass, volume, end-diastolic diameter and wall thickness as well as with lower resting heart rate—"the athlete's heart."[11,14–17] On the other side, in a previous study of our group,[18] we found that lower CRF was associated with a smaller heart size, lower LV stroke volume, cardiac output, LV mass, and higher LV diastolic stiffness.

However, very little information is available about the association between CRF and right ventricular (RV) remodeling. Previous studies mostly included young male endurance athletes.[19–23] To the best of our knowledge, only 1 study reported that intentional PA was associated with a higher RV mass in the general population.[11]

The aim of our study was to assess the relationship between CRF and RV structure and function in a large, aging, and largely physically inactive adult population–based cohort. We used data from the SHIP (Study of Health in Pomerania) with available cardiac measurements based on echocardiography and cardiac magnetic resonance imaging (cMRI).

METHODS

SHIP data are publicly available for scientific and quality control purpose. Data usage can be applied for via www.community-medicine.de.[24]

Study Population

The Study of Health in Pomerania

The presented data were derived from the population-based prospective cohort SHIP.[25] Recruitment strategy and study design have been reported elsewhere.[24] Briefly, between 1997 and 2001 a random cluster sample of 6265 subjects (aged 20–79) was drawn from the population of West Pomerania, a region in the northeast of Germany. A total of 4308 (2193 women) subjects participated in the baseline (SHIP-0) study (response=68.8%). In the first examination follow-up (SHIP-1), which was realized between 2002 and 2006, of 3949 eligible persons, 3300 subjects were reexamined (follow-up response=83.6%). In the second examination follow-up (SHIP-2), which took place between 2008 and 2012, of 3708 eligible persons, 2333 subjects were reexamined (follow-up response=62.9%).[24] Between 2008 and 2012, while SHIP-2 was being conducted, a second independent cohort was established, called Study of Health in Pomerania (SHIP) - Trend, covering a population from the same region as SHIP. A stratified random sample of 8826 adults (aged 20–79) was selected. Subjects who participated in the initial SHIP cohort were excluded from SHIP-TREND. Thus, 4420 individuals were examined in SHIP-TREND (response=50.1%).[24]

For the present study, we pooled data from SHIP-2 and SHIP-TREND (n=6753; 3510 women [52.0%]) and performed cross-sectional analyses. We excluded, sequentially, participants with previous myocardial infarction or stroke (n=367), pacemakers (n=60), left bundle block (n=51), and LV ejection fraction (determined by echocardiography) <40% (n=38). We also excluded individuals with missing values for either CRF (n=1869) or RV end-diastolic diameter (RVEDD; n=769) as well as both CRF and RVEDD (n=716) or any of the covariates (n=39) (Figure 1). The final sample comprised 2844 subjects with echocardiographic data (1486 women; 52.3%) aged 20 to 88 years. A subsample of 966 individuals also underwent cMRI, and data of 941 subjects with good-quality images for the RV were available for further analyses (Figure 1).

All study participants gave written informed consent. The study was approved by the ethics committee of the University of Greifswald and complies with the Declaration of Helsinki.

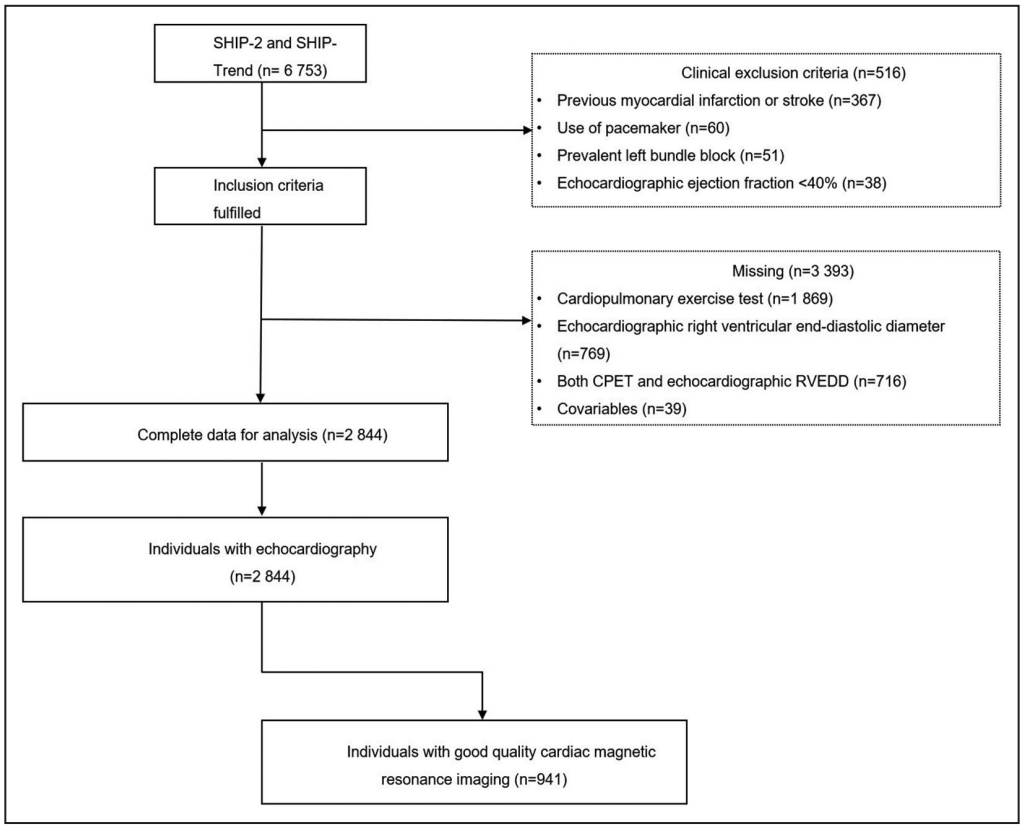

Figure 1. Participants flowchart.
CPET indicates cardiopulmonary exercise test; RVEDD, right ventricular end-diastolic diameter; SHIP, Study of Health in Pomerania; and Study of Health in Pomerania (SHIP) - Trend.

Exercise Testing and Gas Exchange Variables

A symptom-limited CPET using a calibrated electromagnetically braked cycle ergometer (Ergoselect 100, Ergoline, Germany) was performed with a physician in attendance according to a modified Jones protocol (3 minutes of rest, 1 minute of unloaded cycling at 60 rpm, 1-minute increases in workload of 16 W/min until symptom-limited [volitional exertion, dyspnea, or fatigue] or terminated by the physician because of chest pain or ECG abnormalities, and 5 minutes of recovery).[26,27] All tests were performed at room air according to current guidelines for exercise testing, with continuous monitoring of ECG, blood pressure, and pulse oximetry. Gas exchange and ventilatory variables VO_{2peak} was analyzed breath by breath averaged over 10-second intervals using a computer-based system called VIASYS HEALTHCARE system (Oxycon Pro, Rudolph`s mask, JAEGER/VIASYS Healthcare system; Hoechberg, Germany).[26] Exercise duration was defined from the start of exercise (without resting period) up to its termination. VO_{2peak} in L/min was defined as the highest 10-second average of absolute oxygen uptake during late exercise or early recovery.[26] The median time interval between the core examination and the cardiopulmonary exercise testing was 28 days (interquartile range, 9; 48 days).

Echocardiographic Examination

Two-dimensional, M-mode and Doppler echocardiography were performed by physicians (vivid-i, GE Medical Systems, Waukesha, Wisconsin, WI) as described in detail elsewhere.[28] Measurements of RVEDD, RV outflow tract diameter, pulmonary velocity acceleration time and tricuspid annular plane systolic excursion were performed according to the guidelines of the American Society of Echocardiography.[29,30] Mean pulmonary arterial pressure was calculated in mm Hg using the following equation: mean pulmonary arterial pressure=10^ (−0.0068 * pulmonary valve acceleration time + 2.1). Certification examinations for interobserver variations revealed an agreement of >90%.

cMRI and Analysis

cMRI was performed on a 1.5-T MR system (Magnetom Avanto; Siemens Medical Systems, Erlangen, Germany) as previously described.[31] Quantitative image analysis was performed by 2 observers with 3 and 5 years of MRI experience using semiautomatic tools in QMass MR 7.2 (MEDIS, Leiden, Netherlands). Interobserver

variability was computed in a random subsample of 5%. Certification examinations for interobserver variations revealed an agreement of >90%.[28] Postcontrast images were interpreted of the 2 readers mentioned above and supervised in a consensus reading by a radiologist with 12 years of experience. All observers were unaware of the participants' medical history.

For the RV measurements, RV end-diastolic volume (RVEDV) and RV end-systolic volume were manually traced in end diastole and end systole in transverse axis view. Volumes below the pulmonary valve were included. At the inflow tract, thin-walled structures without trabeculations were not included as part of the RV. RVEDV was determined during the first image of the acquisition. RV end-systolic volume was measured by determining the phase in which the RV intracavity blood pool was at its smallest by visual assessment at the midventricular level. RV stroke volume, RV cardiac output and RV ejection fraction were calculated following the equations below:

$$\mathrm{RVSV(ml)} = \mathrm{RVEDV} - \mathrm{RVESV}$$

$$\mathrm{RVCO(l/}min\mathrm{)} = \mathrm{RVSV} \times \mathrm{heart\,rate} \times 0.001$$

$$\mathrm{RVEF}(\%) = (\mathrm{RVEDV} - \mathrm{RVESV})/\mathrm{RVEDV}$$

Statistical Analyses

To characterize the study sample, data are reported as the median (25th and 75th percentile) for continuous variables and as percentages for categorical variables stratified by quartiles and sex. The *P* for trend was calculated by univariate linear regression models with the continuous VO_{2peak} variable as outcome and each of the listed variables as explanatory variables. The association of VO_{2peak} with RV parameters was investigated by multivariable linear regression models adjusted for age, sex (not when stratified by sex), body fat mass, height$^{2.7}$, systolic blood pressure, use of antihypertensive medication, glycated hemoglobin, use of hypoglycemic medication, smoking status, and estimated glomerular filtration rate. To evaluate the robustness of our findings in light of dropout from baseline to follow-up examination (SHIP-0 to SHIP-2) and individuals that did not take part in the echocardiographic and magnetic resonance imaging examinations, we performed inverse probability weighting,[32] assuming a missing at random mechanism,[33] based on sociodemographic and health-related variables in our analyses. We used fractional polynomials to test potentially nonlinear relationships between exposure and outcomes.[34] A 2-sided $P<0.05$ was considered as statistically significant. Statistical analyses were performed using Stata 14.1 (Stata Corporation, College Station, TX).

Please see Data S1 for a more detailed description.

RESULTS

Characteristics of the Study Population

The clinical and laboratory characteristics of all study participants stratified by quartiles of VO_{2peak} and sex are summarized in Table 1. The median age of the sample was 51 (interquartile range, 40–62) years and 52.3% were women. Compared to women, men had a higher total body weight ($P<0.001$), body mass index ($P=0.198$) and fat-free mass ($P<0.001$), while women were less likely to have hypertension ($P<0.001$), type 2 diabetes mellitus ($P=0.001$) and hypercholesterolemia ($P<0.001$). The prevalence of hypertension was 53.1% (men) and 38.3% (women), and of type 2 diabetes mellitus (8.9%, men; and 6.8%, women). Further, 48.1% of the men and 39.4% of the women had hypercholesterolemia. In higher quartiles of VO_{2peak}, men and women had lower levels of physical inactivity (both $P<0.001$).

Table S1 shows the characteristics of the study sample stratified by the whole sample and the analyses sample.

Although the associations of VO_{2peak} with echocardiographically and cMRI-determined parameters were not modified by age or sex (all *P* values for interaction >0.3), we decided to evaluate all the associations of VO_{2peak} with parameters of cardiac geometry and function not only in pooled sex analyses (the total sample) but also stratified by sex. In sensitivity analyses, we also stratified by age (Table S2 shows our results stratified by age).

Association Between VO_{2peak} and RV Structural and Functional Parameters

Table 2 shows the adjusted β-coefficients (95% CI) of the associations between VO_{2peak} and different RV structural and functional parameters based on echocardiography and cMRI, respectively.

Echocardiography

Since CRF (independent variable in our analysis) decreases with age[35] and we aimed to assess the relationship between CRF and RV parameters (dependent variable) in our aging and mostly physically inactive study population, we inverted the *x* axis. A more detailed explanation can be found in the discussion. Figure 2A illustrates the associations of VO_{2peak} with different echocardiographic parameters. Specifically, a 1 L/min lower VO_{2peak} was associated with a 1.18 mm (95% CI; 0.66–1.71; $P<0.001$) smaller RVEDD and 1.41 mm (95% CI, 0.90–1.92; $P<0.001$) narrower RV outflow tract. In addition, a 1 L/min lower VO_{2peak} was related with 0.97 mm Hg (95% CI, –1.71 to –0.22; $P=0.011$) greater mean pulmonary arterial pressure

Table 1. Characteristics of the Study Sample Stratified by Quartiles of VO_{2peak} and Sex (n=2853)

Parameter		First quartile	Second quartile	Third quartile	Fourth quartile	Total	*P* for trend*
N (%)	Men	341	338	340	339	1358 (47.75)	
	Women	372	372	371	371	1486 (52.25)	
Age, y	Men	65 (54–72)	55 (45–64)	47 (39–56)	43 (35–49)	51 (41–62)	<0.001*
	Women	62 (51–69)	55 (43–62)	49 (41–58)	41 (35–50)	51 (40–61)	<0.001*
Fat-free mass, kg	Men	62.9 (57.9–69.0)	65.3 (60.6–71.1)	66.8 (61.7–72.0)	69.4 (64.1–74.4)	66.1 (60.9–72.0)	<0.001*
	Women	44.3 (41.8–47.6)	46.0 (43.5–49.2)	47.3 (44.3–50.4)	49.9 (46.8–53.4)	46.9 (43.8–50.5)	<0.001*
Fat mass, kg	Men	19.9 (16.0–24.3)	20.0 (16.6–24.7)	20.6 (16.3–25.0)	20.6 (16.3–25.0)	19.4 (15.2–24.5)	0.715
	Women	21.3 (16.4–28.0)	23.4 (18.1–28.8)	23.8 (18.3–29.0)	25.1 (19.0–32.0)	23.3 (18.0–29.6)	<0.001*
Body mass index, kg/m^2	Men	27.7 (25.4–30.3)	27.7 (25.6–30.3)	27.7 (25.3–30.1)	26.9 (24.9–29.8)	27.5 (25.3–30.1)	0.198
	Women	25.7 (22.7–28.8)	26.3 (23.1–29.4)	25.8 (23.3–29.1)	26.2 (23.6–30.2)	26.0 (23.1–29.4)	0.001*
Systolic blood pressure, mm Hg	Men	135 (125–148)	133 (125–145)	133 (123–143)	130 (122–140)	133 (123–144)	<0.001*
	Women	126 (111–138)	119 (109–130)	119 (109–130)	116 (109–126)	119 (109–132)	<0.001*
Diastolic blood pressure, mm Hg	Men	79 (73–86)	81 (74–87)	82 (76–89)	79 (74–86)	80 (74–87)	0.550
	Women	75 (68–81)	75 (69–80)	75 (70–81)	75 (69–81)	75 (69–81)	0.771
Hypertension, %	Men	70.7	56.8	49.7	35.1	53.1	<0.001*
	Women	56.2	41.1	31.3	24.5	38.3	<0.001*
Glycated hemoglobin, n (%)	Men	5.5 (5.2–5.9)	5.4 (5.0–5.7)	5.3 (5.0–5.6)	5.2 (4.9–5.4)	5.3 (5.0–5.7)	<0.001*
	Women	5.3 (4.9–5.6)	5.2 (4.9–5.6)	5.2 (4.8–5.5)	5.1 (4.7–5.4)	5.2 (4.8–5.5)	<0.001*
Diabetes mellitus type 2, %	Men	15.8	11.2	5.59	2.95	8.91	<0.001*
	Women	8.87	9.41	5.12	3.77	6.80	0.001*
Total cholesterol, mmol/L	Men	5.30 (4.60–6.10)	5.50 (4.70–6.10)	5.50 (4.80–6.30)	5.20 (4.50–6.00)	5.40 (4.70–6.10)	0.053*
	Women	5.70 (5.00–6.50)	5.70 (5.00–6.50)	5.40 (4.80–6.10)	5.20 (4.60–5.90)	5.50 (4.80–6.20)	<0.001*
LDL-cholesterol, mmol/L	Men	3.30 (2.76–3.87)	3.46 (2.90–4.05)	3.56 (3.00–4.12)	3.28 (2.69–3.85)	3.42 (2.83–3.97)	0.153
	Women	3.42 (2.82–4.08)	3.42 (2.81–4.12)	3.27 (2.68–3.91)	3.13 (2.44–3.70)	3.31 (2.69–3.97)	<0.001*
HDL-cholesterol (mmol/L)	Men	1.22 (1.03–1.47)	1.26 (1.08–1.48)	1.30 (1.11–1.49)	1.31 (1.12–1.54)	1.28 (1.09–1.50)	<0.001*
	Women	1.58 (1.36–1.83)	1.60 (1.36–1.87)	1.55 (1.36–1.77)	1.58 (1.35–1.81)	1.58 (1.36–1.81)	0.733
Cholesterol-HDL ratio	Men	4.30 (3.49–5.19)	4.34 (3.54–5.20)	4.32 (3.48–5.15)	3.89 (3.32–4.70)	4.21 (3.46–5.08)	<0.001*
	Women	3.52 (3.00–4.18)	3.46 (2.91–4.28)	3.42 (2.93–4.04)	3.31 (2.73–3.99)	3.43 (2.89–4.11)	<0.001*
Estimated glomerular filtration rate, (mL/min per 1.73 m^2)	Men	82.0 (69.4–93.0)	90.9 (78.7–100)	94.3 (83.1–105)	99.5 (88.7–109)	91.9 (79.5–103)	<0.001*
	Women	85.4 (71.9–96.1)	90.4 (77.5–101)	93.8 (80.6–106)	96.0 (85.4–108)	91.7 (78.8–103)	<0.001*
Smoking, %	Men						
Never		21.7	26.9	30.9	38.6	29.5	
Current		28.5	24.9	23.8	18.0	23.8	<0.001*
Former		49.9	48.2	45.3	43.4	46.7	<0.001*
	Women						
Never		58.3	46.2	42.6	41.5	47.2	
Current		14.5	21.0	21.3	22.6	19.9	<0.001*
Former		27.2	32.8	36.1	35.9	33.0	0.002*
Physical inactivity, %	Men	36.1	30.2	28.2	19.5	28.5	<0.001*
	Women	33.3	26.6	24.3	15.4	24.9	<0.001*

Data are medians (25th–75th percentile) or percentage.

**P* for trend was calculated by univariate linear regression models with the continuous VO_{2peak} variable as outcome and each of the listed variables as explanatory variables. HDL indicates high-density lipoprotein; LDL, low-density lipoprotein; and VO_{2peak}, maximal oxygen uptake.

and 0.84 mm (95% CI, 0.46–1.22; *P*<0.001) lower tricuspid annular plane systolic excursion. There was no association between VO_{2peak} and lateral early and late tricuspid annular peak diastolic velocity ratio.

Cardiac Magnetic Resonance Imaging

Figure 2B shows the associations of VO_{2peak} with cMRI parameters. A 1 L/min lower VO_{2peak} was associated with a 23.5 mL (95% CI, 18.7–28.4; *P*<0.001) smaller

Table 2. Adjusted* β-Coefficient (95% CI) of the Associations of Peak Oxygen Uptake (VO_{2peak}) with Echocardiographic and Cardiac Magnetic Resonance Imaging Derived Parameters in Pooled Sex Analyses and Stratified by Sex

	Overall			Men			Women		
Parameter	β coefficient (95% CI)	*P* value	R^2	β coefficient (95% CI)	*P* value	R^2	β coefficient (95% CI)	*P* value	R^2
Right ventricular structural parameters based on echocardiography									
RVEDD, mm	1.18 (0.66 to 1.71)	<0.001	0.16	1.08 (0.42 to 1.74)	0.001	0.06	1.34 (0.40 to 2.27)	0.005	0.11
RVOT, mm	1.41 (0.90 to 1.92)	<0.001	0.25	1.35 (0.70 to 2.00)	<0.001	0.13	1.59 (0.83 to 2.34)	<0.001	0.19
Functional right ventricular parameters based on echocardiography									
MPAP, mm Hg	−0.97 (−1.71 to −0.22)	0.011	0.17	−1.25 (−2.20 to −0.31)	0.009	0.17	−0.28 (−1.52 to 0.95)	0.650	0.17
TAPSE, mm	0.84 (0.46 to 1.22)	<0.001	0.05	0.82 (0.34 to 1.30)	0.001	0.04	1.15 (0.48 to 1.81)	0.001	0.06
e′/a′ ratio	−0.016 (−0.062 to 0.030)	0.499	0.10	0.034 (−0.021 to 0.089)	0.222	0.18	−0.111 (−0.239 to 0.017)	0.090	0.18
Functional and structural right ventricular parameters based on cMRI									
RVEDV, mL	23.5 (18.7 to 28.4)	<0.001	0.53	19.6 (13.2 to 25.9)	<0.001	0.32	27.4 (19.2 to 35.6)	<0.001	0.35
RVESV, mL	13.0 (9.81 to 16.2)	<0.001	0.49	11.1 (6.97 to 15.1)	<0.001	0.24	14.0 (8.93 to 19.1)	<0.001	0.32
RVSV, mL/beat	10.7 (8.10 to 13.3)	<0.001	0.40	8.50 (4.91 to 12.1)	<0.001	0.25	13.5 (9.05 to 17.9)	<0.001	0.29
RVCO, L/min	0.58 (0.36 to 0.79)	<0.001	0.40	0.45 (0.18 to 0.72)	0.001	0.30	0.76 (0.38 to 1.14)	<0.001	0.29
RVEF, %	−0.91 (−1.96 to 0.15)	0.092	0.17	−0.78 (−1.99 to 0.43)	0.206	0.03	−0.97 (−2.80 to 0.86)	0.297	0.14

*Linear regression adjusted for age, sex (not when stratified by sex), body fat mass, $height^{2.7}$, systolic blood pressure, use of antihypertensive medication, glycated hemoglobin, use of hypoglycemic medication, smoking status, and estimated glomerular filtration rate (Chronic Kidney Disease Epidemiology Collaboration formula). Data were weighted according to dropout from baseline to follow-up examination (SHIP-0 to SHIP-2) and individuals who did not take part in the echocardiographic and magnetic resonance imaging examinations (SHIP-2 and SHIP-Trend).

cMRI indicates cardiac magnetic resonance imaging; e′/a′ ratio, lateral early and late tricuspid annular peak diastolic velocity ratio; MPAP, mean pulmonary arterial pressure; RVCO, right ventricular cardiac output; RVEDD, right ventricular end-diastolic diameter; RVEDV, right ventricular end-diastolic volume; RVEF, right ventricular ejection fraction.; RVESV, right ventricular end-systolic volume; RVOT, right ventricular end-diastolic outflow tract diameter; RVSV, right ventricular stroke volume; SHIP, Study of Health in Pomerania; and TAPSE, tricuspid annular plane systolic excursion.

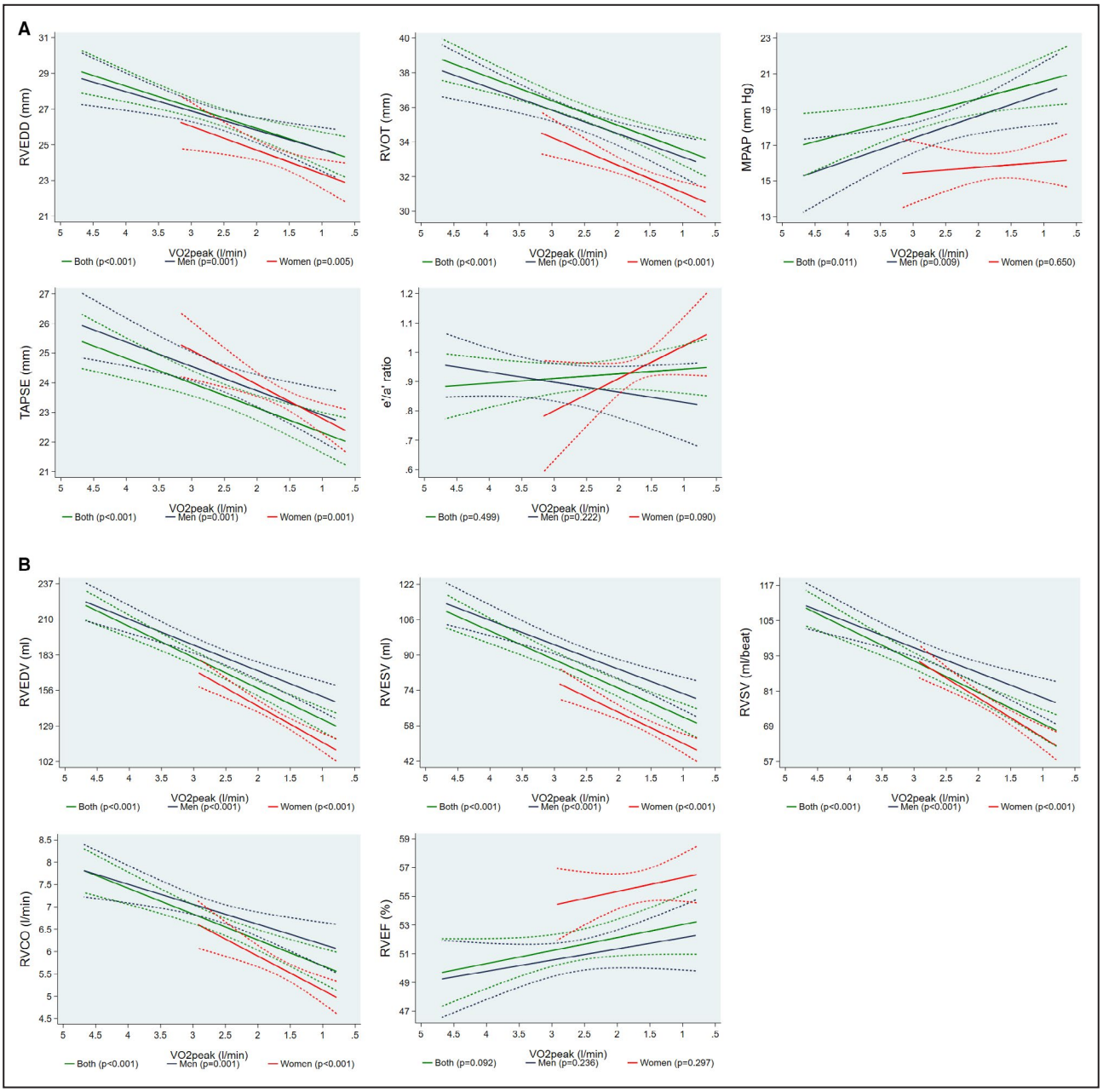

Figure 2. Associations of VO_{2peak} values with echocardiographic and cardiac magnetic resonance imaging determined right ventricular parameters.

(**A**) Adjusted* line (95% CI) showing the associations of peak oxygen uptake (VO_{2peak}) values with echocardiographic determined right ventricular end-diastolic diameter (RVEDD), right ventricular end-diastolic outflow tract diameter (RVOT), mean pulmonary arterial pressure (MPAP), tricuspid annular plane systolic excursion (TAPSE) and lateral early and late tricuspid annular peak diastolic velocity ratio (e′/a′ ratio) for both sexes together (n=2844) and stratified by sex (men=1358; women=1486). **(B)** Adjusted* line (95% CI) showing the associations of peak oxygen uptake (VO_{2peak}) values with magnetic resonance imaging determined right ventricular end-diastolic volume (RVEDV), right ventricular end-systolic volume (RVESV), right ventricular stroke volume (RVSV), right ventricular cardiac output (RVCO) and right ventricular ejection fraction (RVEF) for both sexes together (n=941) and stratified by sex (men=499; women=442). *Linear regression adjusted for age, sex (not when stratified by sex), body fat mass, height$^{2.7}$, systolic blood pressure, use of antihypertensive medication, glycated hemoglobin, use of hypoglycemic medication, smoking status, and estimated glomerular filtration rate (Chronic Kidney Disease Epidemiology Collaboration formula). Data were weighted according to dropout from baseline to follow-up examination (SHIP-0 to SHIP-2) and individuals that did not take part in the echocardiographic and magnetic resonance imaging examinations (SHIP-2 and SHIP-Trend).

RVEDV and a 13.0 mL (95% CI, 9.81–16.2; $P<0.001$) lower RV end-systolic volume. Furthermore, lower levels of VO_{2peak} were associated with a 10.7 mL/beat (95% CI, 8.10–13.3; $P<0.001$) and 0.58 L/min (95% CI, 0.36–0.79; $P<0.001$) smaller RV stroke volume and RV cardiac output, respectively. There was no statistically significant association between VO_{2peak} and RV ejection fraction. Table S2 shows our results stratified by age.

To investigate which of the echocardiographic variables were independently of each other associated with the VO_2peak, we conducted a linear regression analysis with VO_2peak as outcome and all five echocardiographic variables as exposures adjusting for the same confounder than in the main analyses. In this model RVEDD ($P=0.003$), RV outflow tract ($P<0.001$) and tricuspid annular plane systolic excursion ($P<0.001$) were significantly associated with the VO_2peak. For the MRI variables, such an analysis was not possible because these variables were highly correlated among each other.

DISCUSSION

In this study, we evaluated associations of CRF with RV structure and function in a large sample of the general population that were mostly free of clinically relevant cardiometabolic diseases. Our main result is a positive association between VO_{2peak} values and RV structural (eg, RVEDD and RVEDV) as well as functional parameters (eg, tricuspid annular plane systolic excursion).

In the Context of the Published Literature

To the best of our knowledge, only one previous population-based study, the MESA (Multi-Ethnic Study of Atherosclerosis), reported positive associations between PA and RV remodeling.[11] Higher levels of moderate and vigorous physical activity were linearly associated with greater RV mass and RV volumes. Further, intentional exercise was nonlinearly associated with RV mass (independent of LV mass) and with RVEDV. Study participants who spent more time doing intentional exercise also had greater RV stroke volume. However, there was no significant association between moderate and vigorous PA and RV ejection fraction as well as between intentional exercise and RV ejection fraction. A potential limitation of this analysis was that PA was assessed using self-reported questionnaires, which may induce social desirability bias and overestimate the true levels of PA.[36,37] To exclude the mentioned bias of PA, we used CRF measured with the gold standard CPET. Further, PA and CRF are inversely and independently associated with all-cause and cardiovascular mortality.[38,39] Physical inactivity or sedentary lifestyle is causally associated with deleterious cardiovascular risk profiles and outcomes. Importantly, the pathophysiological mechanisms involved with sedentary lifestyle are not fundamentally the opposite of those related with physical activity and exercise training. Previous studies, like the MESA, have predominantly investigated the effects of exercise training on cardiac parameters—"the athlete's heart," while only a few publications have evaluated the shrinkage of the heart following a sedentary lifestyle. The problem of this view is that, unfortunately, physical activity or exercise training is not a major characteristic of the lifestyle of the normal population. Western society tends to be more and more described as a prevalent sedentary society with all the deleterious effects that accompany this choice. Therefore, we believe that there is a lack of research that analyzes the associations of lower cardiorespiratory fitness with health parameters. Moreover, our study obtained a high agreement using our 2 methods (echo and cMRI) and we have a larger number of participants with a wider age range than MESA.

While higher levels of PA may increase CRF,[38,40] our population-based cohort consists of an aging and largely physically inactive population. Hence, at least 2 interpretations of our findings are possible. One may discuss the positive association between higher levels of VO_{2peak} and RV structural and functional parameters. Alternatively, because of our study population, one may conclude that aging and physical inactivity may also induce RV remodeling. Older individuals have lower levels of CRF and are more sedentary than young individuals. To facilitate the interpretation of our data we changed the directionality of the *x* axis in our figures to clarify this interpretation.

Potential Mechanisms for the Observed Associations

The decline in VO_{2peak} caused by aging is a multifactorial process. The central physiological mechanism that might explicate the finding of our study is the volume unloading of the heart caused by a decline in total blood and plasma volume. Physical inactivity reduces circulating plasma proteins and thirst resulting in reduced oncotic pressure and less fluid intake. In addition, physical inactivity seems to lead to an inhibition of the renin-aldosterone system that results in less renal sodium and water retention, which causes more urine output. All these effects, following physical inactivity, lead to a volume unload of the heart,[35] which decreases venous return and, moreover, reduces cardiac filling and stroke volume, which in turn further lowers VO_{2peak}.[41] In a previous analysis,[18] we found similar results regarding the LV structure and function. In addition, physical inactivity induces endothelial dysfunction as well as vasoconstriction. During aging, the skeletal

muscles also atrophy, which leads to the activation of muscle proteolytic pathways via mitochondrial fission.[42] The cardiac stiffness results from a fibrous conversion of the amorphous intercellular substance, resulting in an impairment of oxygen delivery.[43,44] Hence, our results may be explained by an inactive aging population with less plasma volume and subsequently altered RV structure. This results in a smaller and stiffer heart, particularly in an aging and inactive population.[18,35,45,46]

In modern societies, the prevalence of physical inactivity have reached pandemic levels.[9] Low levels of CRF, partially driven by inactivity, are associated with a higher risk of cardiovascular disease and all-cause mortality.[9,47–49] Physical inactivity has adverse effects on the cardiovascular system (eg, a higher risk for hypertension and myocardial infarction), on the musculoskeletal system (eg, atrophy and sarcopenia) and the metabolism (eg, reduced fatty acid oxidation and glucose uptake).[48]

Maintaining high levels of PA throughout life may help to reduce the age-related RV alterations. The estimated rate of decline in VO_{2peak} between the ages of 25 and 65 was about 40% slower in physically active compared with inactive men.[50] Physically inactive men also have a threefold greater decline in VO_{2peak} than individuals who were recreationally active.[51] The age-related decline in VO_{2peak} is not only a result of lower levels of PA because there is also a 5% decline per decade in highly active individuals.[35] Sarcopenia describes the age-related decline of muscle mass with decreased strength and aerobic and functional capacity.[9,52,53] The prevalence of sarcopenia is 5% to 13% in 60- to 70-year-old subjects and even 11% to 50% in subjects over the age of 80 years.[52] Reduced muscle mass leads to lower VO_{2peak}.[53] VO_{2peak} is also lower in older individuals because of reduced mitochondrial oxidative capacity in skeletal muscles.[35,45] The interaction between aging, age-associated physical inactivity and decreased muscle mass leads to a reduction of VO_{2peak}.[35,54]

In summary and in line with our results, the decline in VO_{2peak} is related primarily to a lower maximal cardiac output. Apart from this, a smaller stroke volume, a slower maximal heart rate, a decreased arteriovenous oxygen difference, and muscle blood flow are other important mechanisms.[35,45,50]

Study Limitations and Strengths

There are at least 2 potential limitations of our study that merit discussion. The first limitation is the cross-sectional design because causal inferences cannot be concluded. Further, our study included only White individuals of European ancestry. In spite of these limitations, our study has some significant strengths. First, our well-characterized population-based cohort with a large number of individuals, including men and women, all socioeconomic strata, and a wide age range. Second, the standardized assessment of VO_{2peak} measured by CPET. One of the most relevant strengths are the 2 different imaging techniques we used. The cMRI data are especially important for the RV parameters because it is difficult to examine them in the echo, and cMRI images are much more meaningful. Finally, the availability of data on several metabolic risk factors, which were used as confounders.

ARTICLE INFORMATION

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Supplementary Material

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Supplemental Material

Data S1.

Supplemental Methods

Study population

The Study of Health in Pomerania (SHIP)

Briefly, between 1997 and 2001 a random cluster sample of 6,265 subjects (aged 20 to 79) was drawn from the population of West Pomerania, a region in the North east of Germany. A total of 4,308 (2,193 women) of them participated in the baseline (SHIP-0) study (response = 68.8%). In the first examination follow-up (SHIP-1), which was realized from 2002 to 2006, of 3,949 eligible persons, 3,300 subjects were reexamined (follow-up response = 83.6%). In the second examination follow-up (SHIP-2), which took place between 2008 and 2012, of 3,708 eligible persons, 2,333 subjects were reexamined (follow-up response = 62.9%) [24]. Between 2008 and 2012, while SHIP-2 was being conducted, a second independent cohort was established, called SHIP-TREND, covering a population from the same region as SHIP. A stratified random sample of 8,826 adults (aged 20 to 79) was selected. Subjects, who participated in the initial SHIP cohort, were excluded from SHIP-TREND. Thus, 4,420 individuals were examined in SHIP-TREND (response = 50,1%) [24].

Interview, medical and laboratory examination

Trained and certified medical staff used standardized computer-assisted interviews to ask the participants about their age, sex, smoking habits (current smoker, nonsmoker or former smoker), physical activity behavior and alcohol consumption. Physical inactivity was defined as less than one hour per week of leisure time exercise, during summer or winter. Assessment of alcohol consumption

(in grams of ethanol per day) was based on data regarding consumption of beer, wine, and spirits during the last 30 days [24]. History of myocardial infarction or stroke was self-reported.

All participants underwent an extensive standardized medical examination. Anthropometric measurements included height and weight based on recommendations of the World Health Organization (WHO) [55]. Weight was measured to the nearest 0.1 kg in light clothing and without shoes using standard digital scales. BMI was calculated as weight (kg) / height² (m^2). Waist circumference (WC) was assessed to the nearest 0.1 cm using an inelastic tape midway between the lower rib margin and the iliac crest in the horizontal plane. The subjects were standing comfortably with body weight evenly distributed between both feet. Waist-to-hip ratio was calculated as WC divided by height. FFM and fat mass (FM) were measured by bioelectrical impedance analysis (BIA) using a multifrequency Nutriguard-M device (Data Input, Pöcking, Germany) and the NUTRI4 software (Data Input, Pöcking, Germany) in participants without pacemakers. BP was assessed after a five-minute resting period in sitting position. Systolic and diastolic BP as well as heart rate were measured three times, with three minutes rest in between, on the right arm using a digital BP monitor (HEM-705CP, Omron Corporation, Tokyo, Japan). The mean of the second and third reading was used for the present analyses. Mean arterial pressure was calculated as (2/3) X diastolic BP + (1/3) X systolic BP. Antihypertensive medication was defined as use of agents with the anatomic, therapeutic, and chemical (ATC) code C02, C03, C07, C08 and C09. Hypertensive patients were identified by either self-reported antihypertensive medication or a systolic BP above 140 mmHg and/or a diastolic value more than 90 mmHg. Fasting (defined as at least 8 hours since the last meal) and non-fasting venous blood samples were obtained from all study participants in supine position between 7 am

and 4 pm. Diabetes mellitus was defined as self-reported and/or glycated hemoglobin ≥ 6.5% and/or non-fasting glucose ≥ 11.1 mmol/l and/or current self-reported use of any hypoglycemic medication defined by the ATC code A10.

Serum levels of total cholesterol, low-density lipoprotein cholesterol (LDLC), high-density lipoprotein cholesterol (HDLC), and triglycerides were assessed photometrically (Hitachi 704, Roche, Mannheim, Germany). Hypercholesterolemia was defined as serum cholesterol ≥ 6.2 mmol/l and/or LDLC ≥ 4.1 mmol/l and/or total cholesterol/HDLC ratio ≥ 5.0 and /or self-reported use of any lipid-lowering medication defined by the ATC code C10. The eGFR was determined according to the Chronic Kidney Disease – Epidemiology Collaboration (CKD-EPI) equation [56] and expressed in ml/min/1.73 m^2:

$eGFR = 141 \times \min(\text{serum creatinine}/\kappa)^{\alpha} \times \max(\text{serum creatinine}/\kappa) - 1.209 \times 0.993^{age} \times 1.018$ (if female),where K is 0.7 for female and 0.9 for male, α is -0.329 for female and -0.411 for male, min indicates the minimum of serum creatinine/κ or 1, and max indicates the maximum of serum creatinine / κ or 1.

Exercise testing and gas exchange variables

A symptom-limited CPET using a calibrated electromagnetically braked cycle ergometer (Ergoselect 100, Ergoline, Germany) was performed with a physician in attendance according to a modified Jones protocol (3 min of rest, 1 min of unloaded cycling at 60 rpm, 1 min increases in work load of 16 W/min until symptom-limited (volitional exertion, dyspnea or fatigue) or terminated by the physician because of chest pain or ECG abnormalities, and 5 min of recovery) [26,27]. All tests were performed at room air according to current guidelines for exercise testing, with continuous monitoring of electrocardiogram, blood pressure and pulse oximetry. Gas exchange and ventilatory variables VO_{2peak} was analyzed breath by breath averaged

over 10-second intervals using a computer-based system called VIASYS HEALTHCARE system (Oxycon Pro, Rudolph`s mask, JAEGER/VIASYS Healthcare system; Hoechberg, Germany) [26]. Exercise duration was defined from the start of exercise (without resting period) up to its termination. VO_{2peak} in l/min was defined as the highest 10-second average of absolute oxygen uptake during late exercise or early recovery [26].

Echocardiographic examination

Two-dimensional, M-Mode and Doppler echocardiography were performed by physicians (vivid-i, GE Medical Systems, Waukesha, Wisconsin, WI, USA) as described in detail elsewhere [28]. Measurements of RVEDD, RVOT, PVAT and TAPSE were performed according to the guidelines of the American Society of Echocardiography [29,30]. MPAP was calculated in mmHg using the following equation: MPAP=10^ (-0.0068 * pulmonary valve acceleration time [PVAT] + 2.1).

Cardiac MR Imaging and Analysis

Cardiac MR imaging was performed on a 1.5-T MR system (Magnetom Avanto; Siemens Medical Systems, Erlangen, Germany) as previously described [31]. Quantitative image analysis was performed by two observers with 3 and 5 years of cardiac MR imaging experience using semiautomatic tools in QMass MR 7.2 (MEDIS, Leiden, Netherlands). Interobserver variability was computed in a random subsample of 5%. Certification examinations for interobserver variations revealed an agreement of >90% [28]. Postcontrast images were interpreted of the two readers mentioned above and supervised in a consensus reading by a radiologist with 12 years of experience. All observers were unaware of the participants' medical history.

For the RV measurements, RVEDV and RVESV were manually traced in end-diastole and end-systole in transverse axis view. Volumes below the pulmonary valve were included. At the inflow tract, thin-walled structures without trabeculations were not included as part of the RV. RVEDV was determined during the first image of the acquisition. RVESV was measured by determining the phase in which the RV intra-cavity blood pool was at its smallest by visual assessment at the midventricular level. RVSV, RVCO and RVEF were calculated following the equations below:

RVSV (ml) = RVEDV – RVESV

RVCO (l/min) = RVSV x heart rate x 0.001

RVEF (%) = (RVEDV - RVESV) / RVEDV

Statistical Analyses

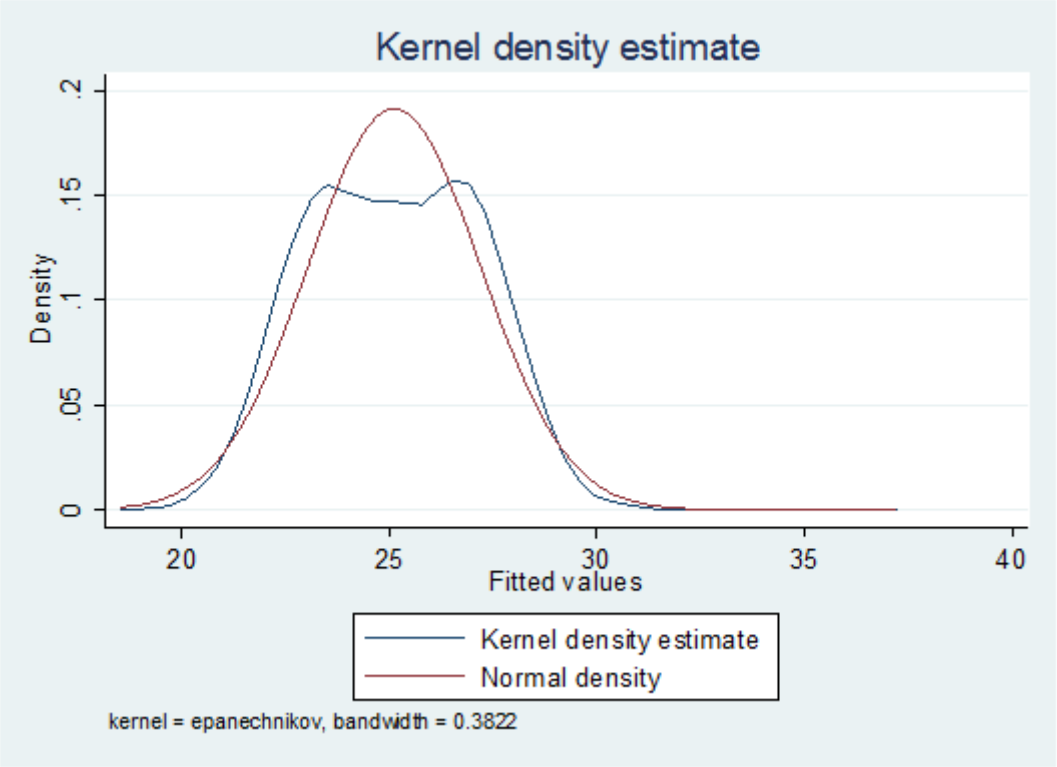
To characterize the study sample, data is reported as the median (25^{th} and 75^{th} percentile) for continuous variables and as percentages for categorical variables stratified by quartiles and sex. The p for trend was calculated by univariate linear regression models with the continuous VO_{2peak} variable as outcome and each of the listed variables as explanatory variables. The association of VO_{2peak} with RV parameters was investigated by linear regression models adjusted for age, sex (not when stratified by sex), body fat mass, $height^{2.7}$, systolic BP, use of antihypertensive medication, glycated hemoglobin, use of hypoglycemic medication, smoking status and eGFR. In order to evaluate the robustness of our findings in light of dropout from baseline to follow-up examination (SHIP-0 to SHIP-2) and individuals that did not take part in the echocardiographic and MRI examinations, we performed inverse probability weighting [32], assuming a missing at random mechanism [33], based on sociodemographic and health-related variables in our analyses. Inverse-probability weights were applied to consider drop-outs of individuals between SHIP-0 and SHIP-

2 and between the basic and the CPET examinations. The intention behind these weights is to weight up the impact of individuals from groups, who are more likely to drop out of the study, and to weight down the impact of individuals from groups, who are less likely to drop out, in the regression analyses. To calculate these weights we used logistic regression models with participation at the CPET-examination as outcome and sociodemographic, behavioral, and cardiovascular risk factors from the core examinations as explanatory variables. For SHIP-2 participants, we additionally computed weights for the drop-out from SHIP-0 to SHIP-2 and multiplicatively combined these weights with the CPET-weights. With this approach, we aimed to improve the representativeness of our analyses.

We used fractional polynomials to test potentially non-linear relationships between exposure and outcomes [34]. A two-sided p-value $p<0.05$ was considered as statistically significant. Statistical analyses were performed using Stata 14.1 (Stata Corporation, College Station, TX, USA).

The choice of the covariates was based on the published literature considering variables available in our dataset that might potentially confound the association between VO_{2peak} and cardiac structure and function. We choose covariates for confounder control that are 1. causes of the outcome, 2. causes of the exposure, but 3. not covariates that are instrumental variables (i.e. instrumental variables affect the outcome only though the exposure and have no direct effect on the outcome)[57].

The model assumptions were verified and confirmed.



We tested for multicollinearity. There was collinearity between age and eGFR (-0.65), but we decided to keep our original adjustment because of the effects of kidney function on CRF and heart geometry and function as suggested by previous cardiovascular studies. On the other hand, the exclusion of eGFR did not lead to a major change in our results (please see below).

Parameter	**With eGFR** **ß-coefficient (95% CI), p-value**	**Without eGFR** **ß-coefficient (95% CI), p-value**
RVEDD (mm)	1.18 (0.66 to 1.71), **p<0.001**	1.16 (0.63 to 1.69), **p<0.001**
RVEDV (ml)	23.5 (18.7 to 28.4), **p<0.001**	23.5 (0.18.7 to 28.4), **p<0.001**

Table S1. Characteristics of the study sample stratified by whole sample and analyses sample.

Parameter	Whole sample	Analyses sample
N (%)	6,753	2,844
Age (years)	54 (42, 66)	51 (41, 62)
Women (%)	52.0	52.3
VO_2peak (l/min)	1.84 (1.48, 2.36)	1.90 (1.51, 2.42)
Fat-free mass (kg)	54.9 (46.8, 65.9)	54.6 (46.7, 65.7)
Fat mass (kg)	22.5 (17.5, 29.0)	21.4 (17.0, 27.1)
Body mass index (kg/m^2)	27.6 (24.6, 31.1)	26.8 (24.2, 29.8)
Systolic blood pressure (mmHg)	129 (116, 142)	127 (115,138)
Diastolic blood pressure (mmHg)	77.5 (70.5, 84.5)	77.0 (71.0, 84.0)
Hypertension (%)	55.0	45.4
Glycated hemoglobin (%)	5.30 (4.90, 5.70)	5.30 (4.90, 5.60)
Diabetes mellitus type 2 (%)	13.4	7.81
Total cholesterol (mmol/l)	5.40 (4.60, 6.20)	5.40 (4.70, 6.20)
LDL-cholesterol (mmol/l)	3.30 (2.66, 3.95)	3.36 (2.75, 3.97)
HDL-cholesterol (mmol/l)	1.39 (1.15, 1.66)	1.43 (1.20, 1.70)
Cholesterol-hdl ratio	3.83 (3.13, 4.73)	3.77 (3.09, 4.63)
Estimated glomerular filtration rate (ml/min/1.73 m²)	88.8 (74.8, 101)	91.7 (79.1, 103)
Smoking (%)		
Never	37.2	38.8
Current	24.8	21.7
Former	38.0	39.5
Physical inactivity (%)	31.3	26.6

Data are medians (25th, 75th percentile) or percentage.

VO_{2peak} - maximal oxygen uptake, LDL-cholesterol – low-density lipoprotein cholesterol, HDL-cholesterol – high density lipoprotein cholesterol.

Table S2. Adjusted* ß-coefficient (95% CI) of the associations of peak oxygen uptake (VO_{2peak}) with echocardiographic and cardiac magnetic resonance imaging derived parameters in pooled age analyses and stratified by age.

Parameter	Overall			≤ 50 years			> 50 years		
	β coefficient (95% CI)	**p-value**	**R^2**	**β coefficient (95% CI)**	**p-value**	**R^2**	**β coefficient (95% CI)**	**p-value**	**R^2**
Right ventricular structural parameters based on echocardiography									
RVEDD (mm)	1.18 (0.66 to 1.71)	**<0.001**	0.16	1.09 (0.47 to 1.71)	**0.001**	0.19	1.17 (0.30 to 2.05)	**0.009**	0.13
RVOT (mm)	1.41 (0.90 to 1.92)	**<0.001**	0.25	0.83 (0.28 to 1.39)	**0.003**	0.30	1.92 (1.04 to 2.80)	**<0.001**	0.21
Functional right ventricular parameters based on echocardiography									
MPAP (mmHg)	-0.97 (-1.71 to -0.22)	**0.011**	0.17	-0.83 (-1.59 to -0.07)	**0.033**	0.16	-1.09 (-2.45 to 0.27)	0.115	0.08
TAPSE (mm)	0.84 (0.46 to 1.22)	**<0.001**	0.05	1.05 (0.55 to 1.55)	**<0.001**	0.07	0.71 (0.12 to 1.29)	**0.019**	0.05
e´/a´ ratio	-0.016 (-0.062 to 0.030)	0.499	0.10	0.002 (-0.042 to 0.045)	0.942	0.14	-0.001 (-0.096 to 0.095)	0.991	0.02
Functional and structural right ventricular parameters based on cMRI									
RVEDV (ml)	23.5 (18.7 to 28.4)	**<0.001**	0.53	20.9 (15.6 to 26.2)	**<0.001**	0.52	29.6 (21.2 to 38.0)	**<0.001**	0.52
RVESV (ml)	13.0 (9.81 to 16.2)	**<0.001**	0.49	11.6 (8.10 to 15.1)	**<0.001**	0.47	16.4 (11.0 to 21.8)	**<0.001**	0.49
RVSV (ml/beat)	10.7 (8.10 to 13.3)	**<0.001**	0.40	9.26 (6.19 to 12.3)	**<0.001**	0.39	13.2 (8.52 to 17.9)	**<0.001**	0.37
RVCO (l/min)	0.58 (0.36 to 0.79)	**<0.001**	0.40	0.44 (0.21 to 0.68)	**<0.001**	0.35	0.80 (0.39 to 1.20)	**<0.001**	0.36
RVEF (%)	-0.91 (-1.96 to 0.15)	0.092	0.17	-0.66 (-1.78 to 0.47)	0.253	0.14	-1.78 (-3.62 to 0.06)	0.058	0.21

Adjusted for age, sex, body fat mass, systolic blood pressure, use of antihypertensive medication, glycated hemoglobin, use of hypoglycemic medication, smoking status and estimated glomerular filtration rate (CKD-EPI formula). Data was weighted according to dropout from baseline to follow-up examination (SHIP-0 to SHIP-2) and individuals that did not take part in the echocardiographic and MRI examinations (SHIP-2 and SHIP-Trend).
RVEDD – right ventricular end-diastolic diameter, RVOT – right ventricular end-diastolic outflow tract diameter, MPAP – mean pulmonary arterial pressure, TAPSE – tricuspid annular plane systolic excursion, e´/a´ ratio – lateral early and late tricuspid annular peak diastolic velocity ratio, RVEDV – right ventricular end-diastolic volume, RVESV – right ventricular end-systolic volume, RVSV – right ventricular stroke volume, RVCO –right ventricular cardiac output, RVEF – right ventricular ejection fraction