SUPPLEMENTAL MATERIAL

Data S1.

SUPPLEMENTAL METHODS AND RESULTS

Self-reported questionnaires and clinical measurements

Information on smoking status (current, former, occasional, and never) and previous medical history was gathered from self-reported questionnaires. Trained nurses performed anthropometric measurements. Weight were measured with participants wearing light clothes to the nearest half kilogram, height without shoes to the first decimal, and waist and hip circumference to the nearest centimeter while standing with hands in a relaxed position. Blood pressure and resting heart rate were measured three times using an oscillometry-based Dinamap 845XT (Critikon) with the participants resting in sitting position with cuff on arm. Non-fasting blood samples analyzed for total-cholesterol, high-density lipoprotein (HDL) cholesterol, and glucose were drawn.

Supplemental methods to echocardiographic measurements

For 21 participants left atrial volume index (LAVI) was estimated from one plane only. The endocardial border of the left atrium (LA) was traced in end-systole with start and stop at the mitral annulus, so a straight line closed the mitral annulus. The pulmonary veins and the LA appendage were not included in the trace.

Mitral inflow pulsed-wave Doppler indices were assessed from apical 4-chamber with sample volume at the tip of the mitral leaflets. Peak mitral annular longitudinal velocities were assessed from the septal and lateral wall by pulsed-wave tissue Doppler with sample volume localized to the basal part of the myocardium (near the insertion of the mitral leaflets). The peak velocities were measured at the outer contour of the Doppler spectrum at low gain settings. The average of the septal and lateral early diastolic velocity was used for calculation of the ratio of the early mitral inflow to the early diastolic mitral annular velocity (E/e’). It was up to the discretion of the physician echocardiographer to assess if the image quality was appropriate for analyses of left ventricular diastolic function.

Supplemental methods to cardiorespiratory fitness measurements

Familiarization to treadmill use was given during a ten-minute warm-up while establishing initial treadmill inclination and speed for the test. An individualized protocol was used with increasing inclination (2%), speed (1 km/h), or both (1% and 0.5 km/h) every minute until voluntary exhaustion. Maximal oxygen uptake (VO_{2max}) was achieved when the respiratory exchange ratio was ≥1.05 and oxygen uptake did not increase >2 mL/kg/min despite increasing workload. For simplicity the term VO_{2peak} including those not meeting VO_{2max} criteria is used in the manuscript. Heart rate was measured by a heart rate monitor from Polar (S610i; Polar Electro Oy, Kempele, Finland).

Restricted cubic spline models

A model was fitted using restricted cubic splines for LAVI by percent of predicted peak oxygen consumption from age and sex ($VO_{2\%pred}$) (based on model 2 from main results). Both a linear and a cubic spline model was fitted, but the cubic model had the lowest Akaike information criterion (AIC). Knots were set 80%, 100%, and 120% of $VO_{2\%pred.}$ The AIC for model 2 and the restricted cubic splines model was similar despite the loss of freedom from introducing splines (AIC 1499.7 vs AIC 1502.3, respectively).

Since age is considered both in $VO_{2\%pred}$ and in age itself the observations could potentially be observed by non-additivity of the age-effect on LAVI. In addition to the previously tested models including higher-order interactions for age we therefore fitted models by a restricted cubic splines approach for the age covariate. Different number and cut-offs for knots were explored with knots at 45 and 65 years showing the lowest AIC. These models gave similar results as the chosen models from main results, as shown in Figure S4. Neither the overall or sex-specific models had AIC lower than the models presented in the main results. None of the models for women significantly predicted LAVI, as for the reported main models.

Table S1. **Linear regression analyses with left atrial volume index as the dependent variable and indices of diastolic dysfunction as independent variables.**

		Univariate model			Age and sex-adjusted model		
	n	***β (95% CI)***	**R^2**	**p**	***β (95% CI)***	**R^2**	**p**
E/e' ratio	228	0.17 (-0.28-0.61)	-0.002	0.46	0.14 (-0.36-0.63)	0.04	0.59
Septal e'	228	0.03 (-0.28-0.34)	-0.004	0.84	0.24 (-0.11-0.59)	0.04	0.19
Lateral e'	228	-0.04 (-0.29-0.20)	-0.004	0.72	0.12 (-0.20-0-43)	0.04	0.48
TRV max	35	6.03 (-1.1-13.1)	0.07	0.09	5.48 (-1.57-12.5)	0.06	0.12

95% CI = 95 % confidence interval, E = peak early diastolic mitral inflow velocity, e' = peak early diastolic mitral annular velocity, TRV = tricuspid regurgitant velocity.

Table S2. Linear regression analyses with indices of diastolic dysfunction as dependent variable and VO_{2peak}/$VO_{2\%pred}$ as independent variable.

		Univariate model			Age and sex-adjusted model		
	n	***β (95% CI)***	**R^2**	**p**	***β (95% CI)***	**R^2**	**p**
VO_{2peak} as independent variable							
E/e' ratio	240	-0.04 (-0.07- -0.007)	0.02	0.017	-0.01 (-0.05-0.04)	0.12	0.73
Septal e'	240	0.08 (0.04-0.12)	0.06	<0.0001	0.045 (-0.002-0.092)	0.36	0.06
Lateral e'	240	0.10 (0.04-0.15)	0.05	0.001	0.035 (-0.03-0.10)	0.43	0.27
TRV max	39	0.002 (-0.01-0.02)	-0.023	0.76	0.01 (-0.01-0.03)	-0.01	0.50
$VO_{2\%pred}$ as independent variable							
E/e' ratio	240	0.00 (-0.02-0.02)	-0.004	0.96	-0.003 (-0.02-0.014)	0.12	0.70
Septal e'	240	0.001 (-0.02-0.02)	-0.004	0.91	0.019 (0.00-0.04)	0.36	0.047
Lateral e'	240	-0.01 (-0.04-0.02)	-0.002	0.47	0.013 (-0.01-0.04)	0.43	0.28
TRV max	39	0.003 (-0.003-0.009)	0.006	0.39	0.002 (-0.004-0.009)	-0.01	0.49

95% CI = 95% confidence interval, VO_{2peak} = peak oxygen consumption, $VO_{2\%pred}$ = percent of age and sex predicted VO_{2peak}, E = peak early diastolic mitral inflow velocity, e' = peak early diastolic mitral annular velocity, TRV = tricuspid regurgitant velocity.

Figure S1. Prediction diagrams of left atrial volume index (A-L method) for ages 40 and 70 years for men and women by percent of age and sex predicted VO_{2peak} with confidence (blue dotted line) and prediction (red dotted line) intervals based on main results model 2 (n=229).

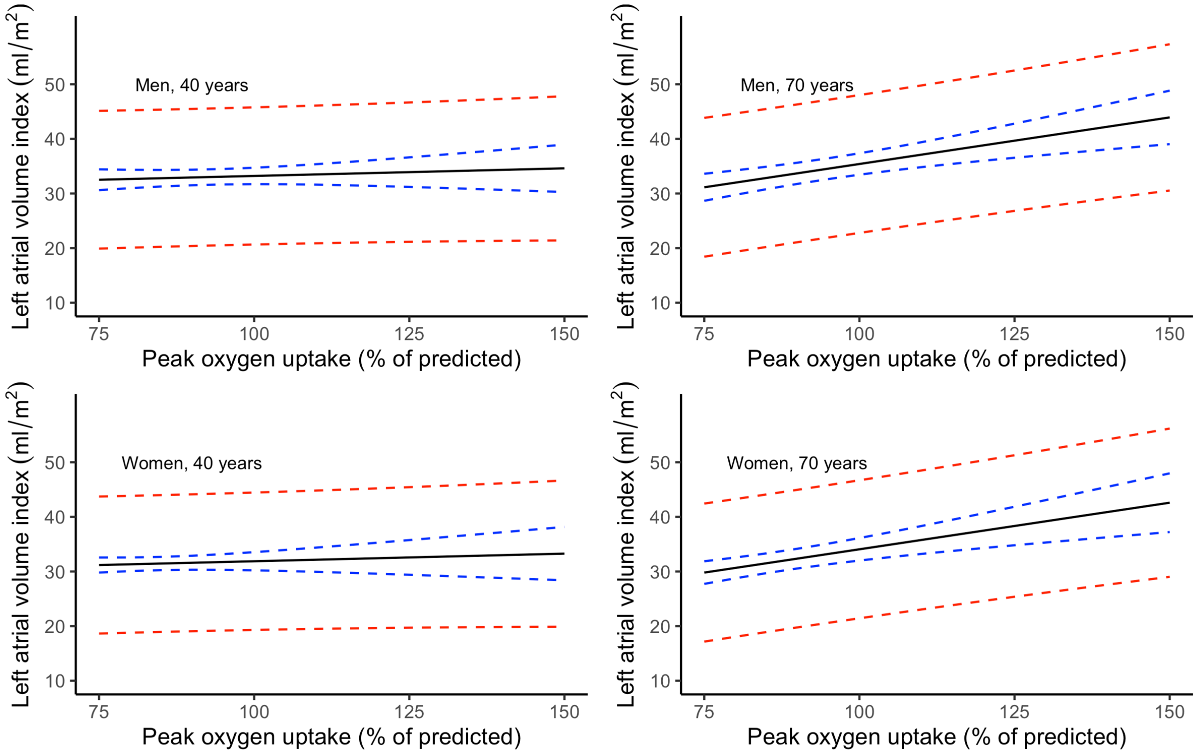


Figure S2. Prediction diagrams of left atrial volume index measured by biplane method of discs for different ages by a) VO_{2peak} (n=209), b) percent of age and sex predicted VO_{2peak} (n=209), and c) percent of age and sex predicted VO_{2peak} in men only (n=96).

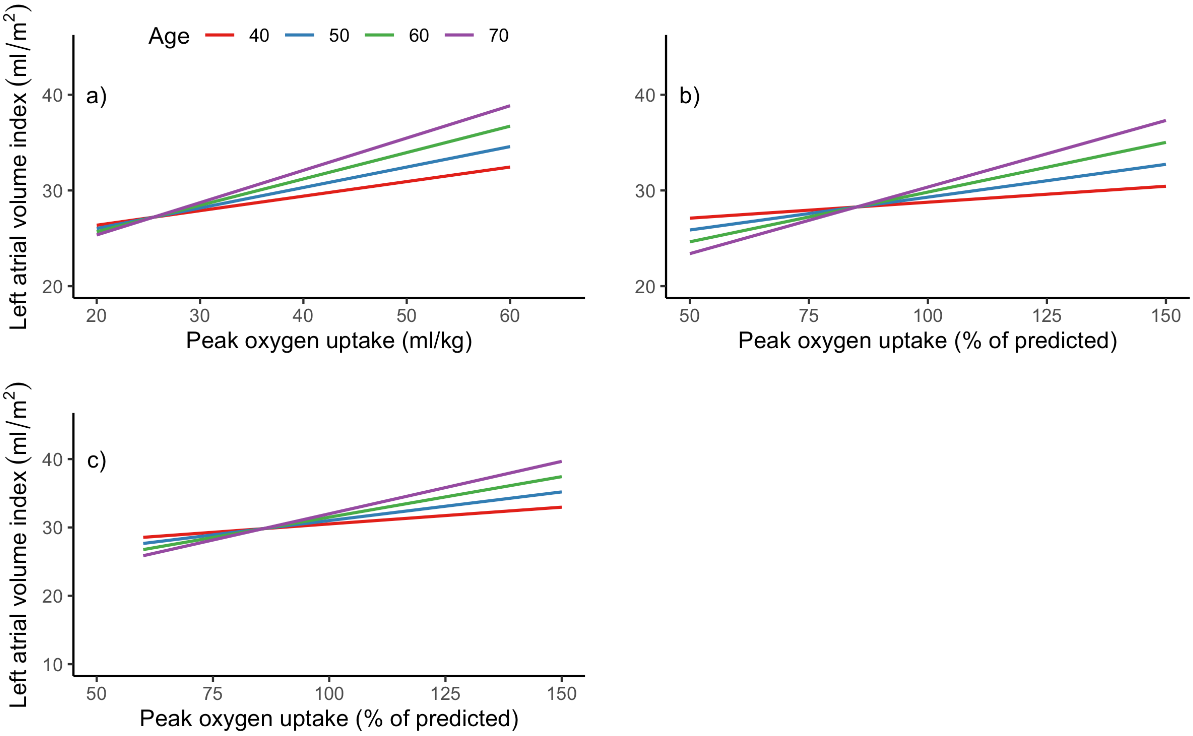


Figure S3. Prediction of left atrial volume index (A-L method) based on a restricted cubic spline model for percent of age and sex predicted VO_{2peak} (n=229).

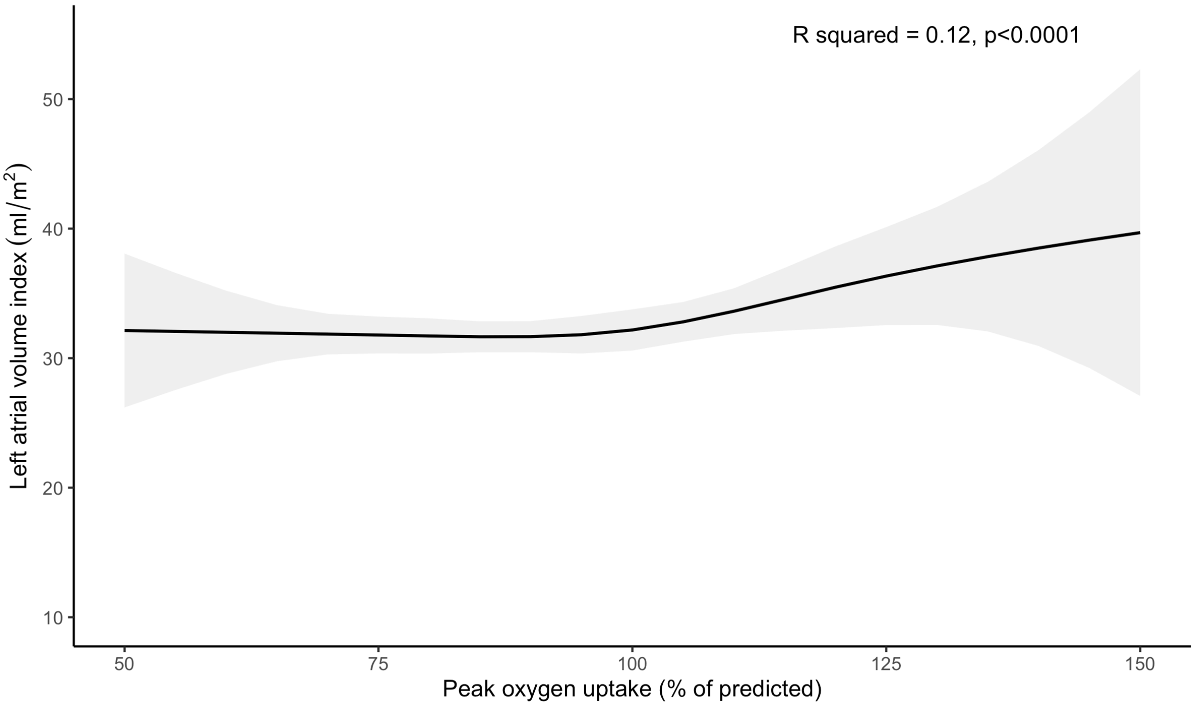
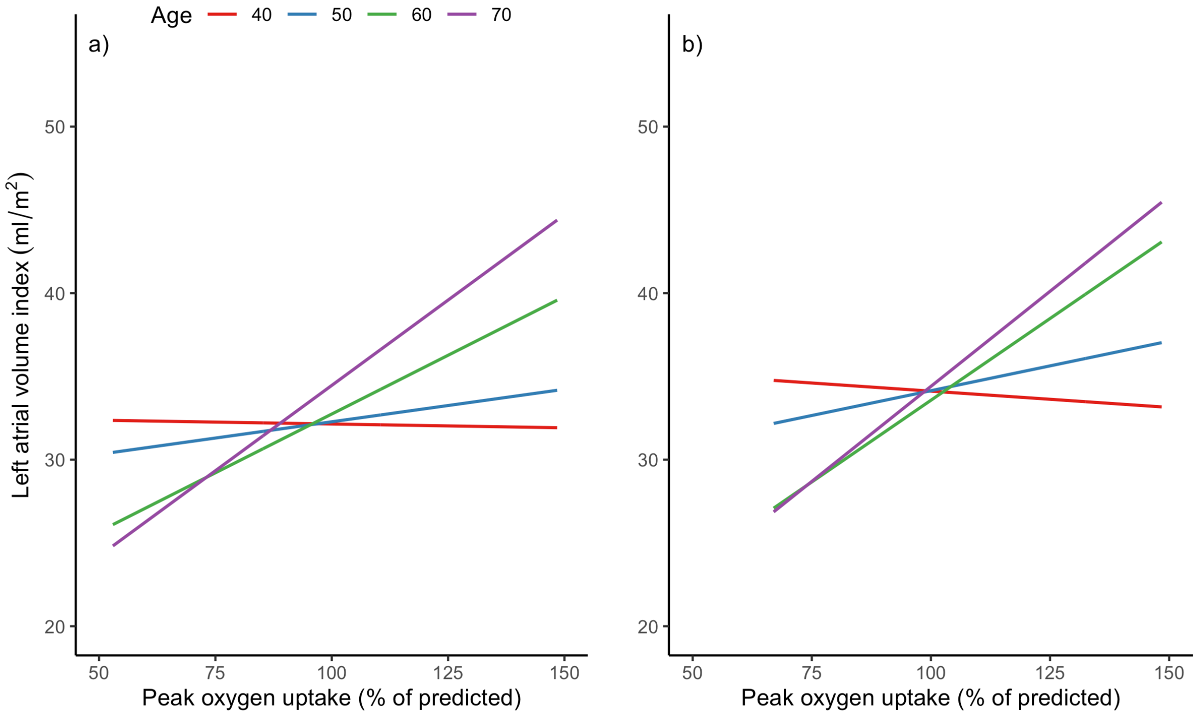


Figure S4. Prediction of left atrial volume index (A-L method) by percent of age and sex-predicted VO2peak based on a restricted cubic spline model for age.



a) Sexes combined (n=229), b) men only (n=103).