Left Atrial Volume, Cardiorespiratory Fitness, and Diastolic Function in Healthy Individuals: The HUNT Study, Norway

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Background—Left atrial (LA) size and cardiorespiratory fitness (CRF) are predictors of future cardiovascular events in high-risk populations. LA dilatation is a diagnostic criterion for left ventricular diastolic dysfunction. However, LA is dilated in endurance athletes with high CRF, but little is known about the association between CRF and LA size in healthy, free-living individuals. We hypothesized that in a healthy population, LA size was associated with CRF and leisure-time physical activity, but not with echocardiographic indexes of left ventricular diastolic dysfunction.

Methods and Results—In this cross-sectional study from HUNT (Nord-Trøndelag Health Study), 107 men and 138 women, aged 20 to 82 years, without hypertension, cardiovascular, pulmonary, or malignant disease participated. LA volume was assessed by echocardiography and indexed to body surface area LAVI (left atrial volume index). CRF was measured as peak oxygen uptake (VO_{2peak}) using ergospirometry, and percent of age- and sex-predicted VO_{2peak} was calculated. Indexes of left ventricular diastolic dysfunction were assessed in accordance with latest recommendations. LAVI was >34 mL/m^2 in 39% of participants, and LAVI was positively associated with VO_{2peak} and percentage of age- and sex-predicted VO_{2peak} (β [95% CI], 0.11 [0.06–0.16] and 0.18 [0.09–0.28], respectively) and weighted minutes of physical activity per week (β [95% CI], 0.01 [0.003–0.015]). LAVI was not associated with other indexes of left ventricular diastolic dysfunction. There was an effect modification between age and VO_{2peak}/percentage of age- and sex-predicted VO_{2peak} showing higher LAVI with advanced age and higher VO_{2peak}/percentage of age-and-sex-predicted VO_{2peak} as presented in prediction diagrams.

Conclusions—Interpretation of LAVI as a marker of diastolic dysfunction should be done in relation to age-relative CRF. Studies on the prognostic value of LAVI in fit subpopulations are needed. (*J Am Heart Assoc*. 2020;9:e014682. DOI: 10.1161/JAHA.119.014682.)

Key Words: echocardiography • endurance training • exercise • heart • physical activity

L eft atrial (LA) volume is established as a strong prognostic marker of future cardiovascular events in high-risk populations.[1–3] The strong association between LA volume and left ventricular (LV) diastolic dysfunction[4,5] has resulted in LA volume becoming one of the diagnostic criteria for LV diastolic dysfunction, with a cutoff of 34 mL/m^2 defining pathological enlargement.[6]

Contrary to this, LA enlargement is often observed among endurance athletes,[7] in whom it is regarded a physiological adaptation.[8] Similarly, LA enlargement has been observed in recreational runners,[9] and higher lifetime training hours in nonelite athletes are linked to LA enlargement.[10] LV diastolic dysfunction, however, is associated with low cardiorespiratory fitness (CRF)[11]; and low CRF has a well-established link to mortality.[12] Thus, enlarged LA in both patients with cardiac disease and endurance athletes represents a paradox as these are populations with different prognoses.

Clinical Perspective

What Is New?

- In previously healthy men and women participating in the HUNT (Nord-Trøndelag Health Study), left atrial size was positively associated with higher cardiorespiratory fitness, but not with indexes of left ventricular diastolic dysfunction.
- The association between cardiorespiratory fitness and left atrial enlargement was stronger with higher age.

What Are the Clinical Implications?

- Cardiorespiratory fitness should be considered when left atrial size is included in clinical decision making.

Although LA size has been studied thoroughly in athletes and patients with cardiac diseases, studies from healthy populations, and particularly studies on the associations between CRF and LA size in general free-living populations, are scarce. Furthermore, as many patients examined by echocardiography do not have a well-defined medical and cardiac history, a universal threshold of 34 mL/m^2 defining LA enlargement may be unfavorable. Still, the current recommendations for assessment of LA volume and diastolic function only include a short precaution about the interpretation of LA volume in athletes.[6,13] However, it is likely that one should be cautious also when assessing LAVI and diastolic function in nonathlete subjects with high CRF and/or a long exercise training history. To avoid misinterpretation of normal LA as pathologically enlarged with following misdiagnosis, overtreatment, and unnecessary worry for patients, knowledge on the association between LA size, CRF, and diastolic function in healthy, free-living, nonathletic subjects is needed.

Therefore, we aimed to investigate the association of LA volume with CRF and LV diastolic function in a healthy, free-living population. Second, to better allow for generalization of the results to populations in whom measurements of CRF are not available, we aimed to assess the association of LA volume with leisure-time physical activity (PA). We hypothesized that in a healthy, free-living population, LA volume is associated with CRF and leisure-time PA, but not with echocardiographic indexes of LV diastolic dysfunction.

Methods

The data from HUNT (Nord-Trøndelag Health Study) used in this study are available on application to the HUNT Data Access Committee in accordance with the policy on data availability (further information and contact information: https://www.ntnu.edu/hunt/data).

Study Population

The subjects of this cross-sectional study participated in the third wave of HUNT (HUNT3). HUNT3 was performed between October 2006 and June 2008, and all inhabitants of the county, aged ≥20 years, were invited, with 50 821 individuals (54%) participating. HUNT has been comprehensively described elsewhere.[14] Subjects free from hypertension or use of hypertensive medications, pulmonary or cardiovascular disease, cancer, and sarcoidosis were invited to cardiopulmonary exercise testing as a part of the HUNT3 Fitness study, a substudy of HUNT3. The HUNT3 Echocardiography study[15] was another substudy with similar inclusion criteria as the HUNT3 Fitness study, and 242 participants contributing in both the HUNT3 Echocardiography study and the HUNT3 Fitness study compose the population in this study. Data collection took place from June 9 to 19, 2008, in the town of Namsos, Norway.

Previously unknown minor pathological features were revealed in 6 study participants, including possible history of angina pectoris (n=2), aortic regurgitation (n=1), LV hypertrophy (n=2), and other (n=1). These individuals were not excluded from the analyses.

The study was approved by the Regional Committee for Medical Research Ethics (2018/929) and conducted according to the second Declaration of Helsinki. Informed consent was obtained from all participants. The study participants could withdraw from the study at any time.

Self-Reported Questionnaires and Clinical Measurements

Questionnaires on medical history, clinical examinations, and blood sampling for biochemical analyses were performed in the HUNT3 baseline examination, and detailed information on the sampling of these data has been reported earlier.[14] Information on PA (frequency, duration, and intensity of leisure-time PA) was gathered from validated questionnaires.[16] PA was then calculated as volume of moderate-to-vigorous PA per week (PA volume), where relative vigorous intensity PA was weighted double in accordance with current recommendations.[17] Information on PA intensity was given on the scale of rated perceived exertion, ranging from 6 (no exertion at all) to 20 (maximal exertion). Rated perceived exertion 12 and 13 were graded as moderate intensity, and rated perceived exertion >13 was graded as vigorous intensity. PA was also classified as adherence or nonadherence to PA guidelines[17] on the basis of these calculations of minutes of PA per week.

Echocardiography

Transthoracic echocardiograms were recorded by one physician (H.D.) highly experienced in echocardiography. Participants were examined in the left-lateral decubitus position

using a Vivid 7 scanner with a phased-array transducer (M3S and M4S) (version BT06; GE Ultrasound, Horten, Norway). All measurements were averaged over 3 cardiac cycles. Echocardiographic data were stored digitally and analyzed subsequently by the same physician echocardiographer.

For quantification of LA volume–specific views, the LA was recorded from apical 4- and 2-chamber views in end systole with tracing of the endocardial border (Figure 1).[13] Mean difference between 4- and 2-chamber length was 0.36 cm (SD, 0.28 cm). LA volume was calculated by the area-length (A-L) method and by the summation of disc method, and subsequently indexed per square meter body surface area LAVI (left atrial volume index). Mitral inflow peak early (E) and late velocity and early filling mitral deceleration time were assessed from apical 4-chamber view by pulsed-wave Doppler. Peak velocity tricuspid regurgitation was measured by continuous Doppler. Mitral annular peak systolic and peak early diastolic (e') longitudinal velocities were assessed by pulsed-wave tissue Doppler. The ratio of the early mitral inflow/the early diastolic mitral annular velocity (E/e') was calculated.

Assessment of diastolic function was based on latest recommendations.[6] The following parameters and corresponding cutoffs were used; mitral annular e' (septal e' <7 cm/s, lateral e' <10 cm/s), E/e' ratio >14, LAVI >34 mL/m^2, and peak tricuspid regurgitation velocity >2.8 m/s. LV diastolic dysfunction was present if more than half of the available parameters met these cutoff criteria.

Data on the reliability of most of the measurements have been comprehensively described previously.[15] Reproducibility for LAVI was calculated in a random subset of 145 study participants by separate analyses performed by 2 physicians experienced in echocardiography (H.D. and H.E.M-H.). Shortly, coefficient of variation for LAVI was 12.1%, and the test-retest coefficients of variation for separate echocardiographic data sets for E, e' (average of septal and lateral), and E/e' were 6.0%, 10.5%, and 7.9%, respectively.[15]

Cardiorespiratory Fitness

Peak oxygen uptake (VO$_{2peak}$) was measured by ergospirometry during walking or running on a treadmill using an individualized protocol to voluntary exhaustion while wearing a tight face mask (Hans Rudolph, Germany) connected to a portable mixing chamber gas-analysis system (MetaMax II; Cortex, Leipzig, Germany). Reliability of the cardiopulmonary exercise testing measurements has been published
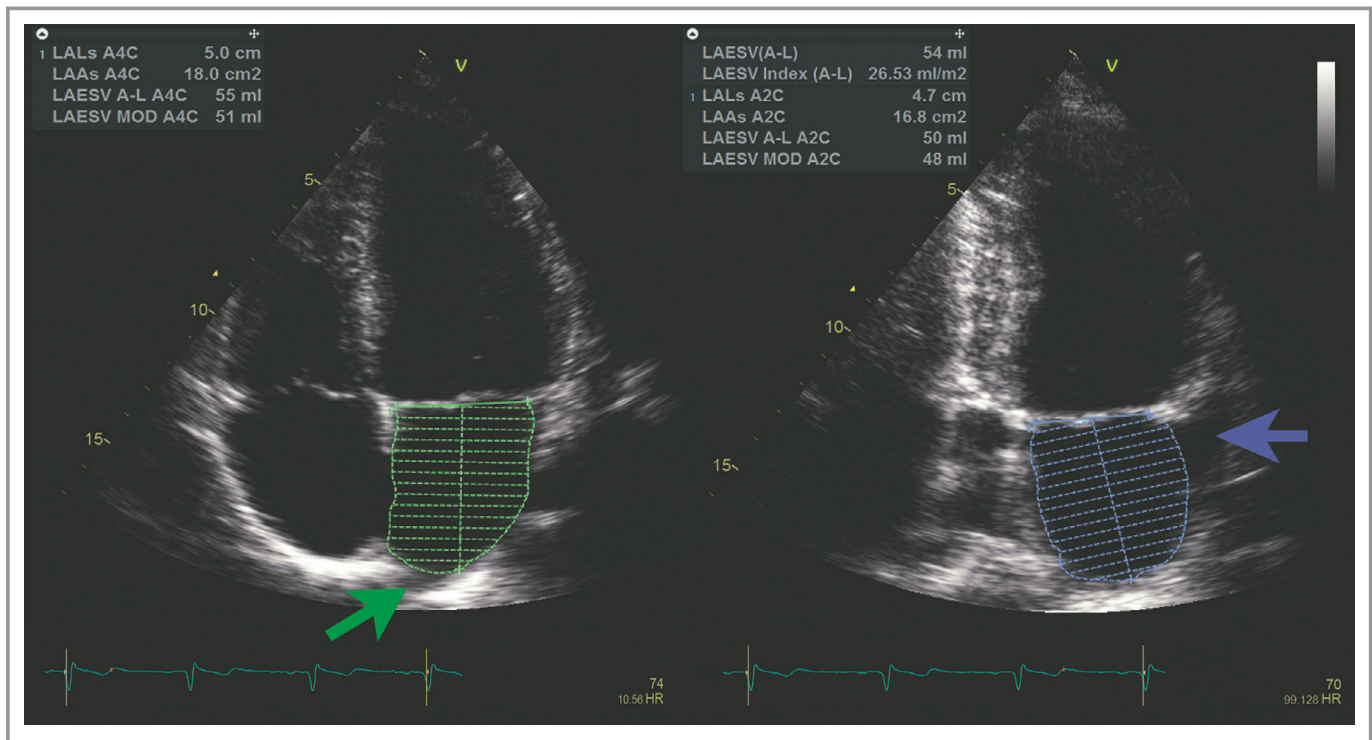
Figure 1. Left atrial (LA) assessment. LA volume was measured from B-mode recordings in apical 4-chamber view (**left**) and 2-chamber view (**right**). Tracing was done from one side at the mitral annular level following the endocardial border around the atrium and to the opposite site at the mitral annular level. The contour was closed at the mitral annulus with a straight line. The area of the atria in the specific view is annotated LAAs in the figure. Pulmonary veins (green arrow) and LA appendage (blue arrow) were excluded from the tracings. LA length was measured in both views, illustrated by the central line in the 2 tracings (annotated as LALs in the figure). LA volume was measured by the area-length method (annotated as LAESV A-L in the figure) and the summation of disks method (annotated as LAESV MOD in the figure).[13]

previously.[18] Test-retest correlation of oxygen uptake was 0.99 ($P<0.001$), and the coefficient of variation was 1.8%.

Statistical Analyses

VO_{2peak} is expressed in milliliters of oxygen consumed per kg body weight per minute and as percentage of predicted from age and sex ($VO_{2\%pred}$). Age- and sex-predicted VO_{2peak} was calculated by previously published sex-specific regression equations of age (men: $VO_{2peak}=63.6-0.393\times age$; women: $VO_{2peak}=55.6-0.328\times age$)[19] based on a larger sample of the

HUNT Fitness study.[18] $VO_{2\%pred}$ was calculated by dividing measured VO_{2peak} by predicted VO_{2peak} and multiplying by 100. We included VO_{2peak} and $VO_{2\%pred}$ in a multiple regression model in addition to other echocardiographic variables shown to be independent predictors of LAVI[10,20] to assess if CRF improved prediction. Furthermore, linear regression was used to assess associations between LAVI and VO_{2peak}, $VO_{2\%pred}$, PA volume, and age. We tested between-group differences of LAVI for sexes and for adherence or nonadherence to PA guidelines using an ANCOVA. We used multiple regression to predict LAVI on the basis of

Table 1. Baseline Characteristics of the 242 Participants by Sex

Characteristics	Men		Women	
	Mean	SD	Mean	SD
Clinical characteristics				
n	107	. . .	135	. . .
Age, y	49	13	48	14
Waist circumference, cm	93	8	87	10
Waist/hip ratio	0.91	0.05	0.86	0.07
Weight, kg	85	11	71	12
BMI, kg/m^2	26.4	3.1	25.6	3.9
Body surface area, m^2	2.05	0.14	1.79	0.14
Systolic BP, mm Hg	129	13	122	15
Diastolic BP, mm Hg	76	9	70	10
Resting HR, bpm	66	10	69	10
Current smoker, %	21.7	. . .	19.2	. . .
Physical activity adherence, %	43.7	. . .	40.3	. . .
Total cholesterol, mmol/L	5.5	0.9	5.4	1.1
HDL cholesterol, mmol/L	1.3	0.3	1.5	0.3
Glucose, mmol/L	5.6	1.1	5.2	0.8
Cardiopulmonary exercise testing variables				
Peak oxygen uptake, mL/kg per min	43.8	7. 7	33.3	7.0
$VO_{2\%pred}$	99	18	83	14
Peak RER	1.14	0.07	1.13	0.07
Peak HR, bpm	181	13	181	14
General echocardiographic indexes				
LV end-diastolic volume, mL	110	22	85	18
LV end-diastolic diameter, mm	52	5	49	5
LV ejection fraction, %	57	6	58	6
Mitral annular S', cm/s	8.6	1.4	8.2	1.4
TAPSE, cm	2.9	0.5	2.8	0.4
Tricuspid annular S', cm/s	13.1	2.2	12.8	2.1
Global longitudinal LV end-systolic strain, %	−17.1	2.1	−18.5	2.1

BMI indicates body mass index; BP, blood pressure; bpm, beats per minute; HDL, high-density lipoprotein; HR, heart rate; LV, left ventricular; RER, respiratory exchange ratio; S', peak mitral annular systolic velocity (by pulsed-wave tissue Doppler); TAPSE, tricuspid annular plane systolic excursion; $VO_{2\%pred}$, percentage of age- and sex-predicted peak oxygen uptake.

VO_{2peak} and $VO_{2\%pred}$, age, and sex, and explored for statistical interaction. The Akaike information criterion was used to assess model performance. The resulting regression models were used to predict LAVI on the basis of the mentioned variables. Linear regression was also performed to assess associations between LAVI and other echocardiographic indexes of diastolic function, as well as between $VO_{2peak}/VO_{2\%pred}$ and diastolic function indexes. Sensitivity analyses were performed with exclusion of measurements from those with 1-plane LAVI measurements only and for those with difference between 4- and 2-chamber atrial length of >0.5 cm. $P<0.05$ was considered statistically significant, and P values and CIs are based on robust SEs. Analyses were conducted using R Studio Version 1.2.1335 (R Foundation for Statistical Computing, Vienna, Austria) and STATA 15.1 (StataCorp, TX).

Results

General characteristics of participants are presented in Table 1 and demonstrate the low cardiovascular risk profile of the population, as well as the normal profile of echocardiographic parameters of LV structure and systolic function. VO_{2peak} was 10% lower than predicted by age and sex, and adherence to PA guidelines was high (40.3%). Echocardiographic LV diastolic function indexes are shown in Table 2. By

Table 2. Echocardiographic Indexes of LV Diastolic Function by Sex

Variables	Men		Women	
	Mean	SD	Mean	SD
LAESV index (A-L), mL/m^2	34.2	7.1	31.3	6.1
LAESV index (MOD), mL/m^2	31.2	6.5	28.2	5.6
Mitral E-wave, cm/s	67	16	72	16
Mitral A-wave, cm/s	50	16	56	18
Mitral E/A	1.5	0.5	1.4	0.6
Mitral E/e'	6.4	2.2	6.5	2.0
Lateral e', cm/s	12.5	3.5	13.2	3.6
Septal e', cm/s	9.6	2.6	10.1	2.9
Mitral deceleration time, ms	214	69	208	68
Pulmonary vein S, cm/s	55	12	61	12
Pulmonary vein D, cm/s	50	12	49	12
Pulmonary vein S/D ratio	1.2	0.4	1.3	0.3
TRV maximum, m/s	2.3	0.3	2.3	0.4

A indicates late diastolic (atrial) mitral inflow; A-L, area-length; D, peak diastolic velocity; E, early diastolic mitral inflow; e', peak early diastolic mitral annular velocity; LAESV, left atrial end-systolic volume; LV, left ventricular; MOD, summation of disc method; S, peak systolic velocity; TRV, tricuspid regurgitant velocity.

the A-L method, LAVI was a mean of 32.6 mL/m^2 (SD, 6.7 mL/m^2), and 39% of participants had LAVI above the cutoff of 34 mL/m^2. Three participants (1.2%) met criteria of diastolic dysfunction. Men had significantly higher LAVI compared with women (mean difference, 2.9 [95% CI, 1.1–4.6] mL/m^2; $P=0.001$), but not after adjusting for VO_{2peak} (mean difference, 1.4 [95% CI, −0.6 to 3.4] mL/m^2; $P=0.17$). VO_{2peak} independently predicted LAVI in a multiple regression model including LV mass index, LV end-diastolic volume, E/e', sex, and age (model: $R^2=0.16$, $P<0.0001$; VO_{2peak} $\beta=0.16$ [95% CI, 0.04–0.28], $P=0.02$).

CRF and LA Volume

Figure 2 shows the positive correlation of LAVI with $VO_{2\%pred}$, and Table 3 shows the positive association with VO_{2peak} and PA volume as well. Participants adhering to PA guidelines had borderline significantly higher LAVI (age- and sex-adjusted mean difference, 1.7 [95% CI, −0.1 to 3.5]; $P=0.06$). In multiple regression analyses, introducing an interaction term between age and $VO_{2peak}/VO_{2\%pred}$ improved the predictions, but other or higher-order interaction terms did not. VO_{2peak}, age, and the interaction of age and VO_{2peak} predicted LAVI (model 1: LAVI~VO_{2peak}+Age+$VO_{2peak}\times$Age, $P<0.0001$, $R^2=0.09$). The linear regression with $VO_{2\%pred}$, age, sex, and the interaction of age and $VO_{2\%pred}$ (model 2: LAVI~$VO_{2\%pred}$+Age+$VO_{2\%pred}\times$Age+Sex, $P<0.0001$, $R^2=0.10$) performed similarly. Sex did not contribute significantly in the prediction equation with VO_{2peak}. The resulting regression equations were used to predict LAVI on the basis of age and $VO_{2peak}/VO_{2\%pred}$. In sex-specific models, the same model 2 (omitting the sex term) had the lowest Akaike information criterion for men ($P<0.002$; $R^2=0.11$), whereas none of the tested models for women significantly predicted LAVI (a model with splines for VO_{2peak} at 25, 35, and 45 mL/kg had the lowest Akaike information criterion; $R^2=0.06$; $P=0.06$). The higher predicted LAVI with advanced age and higher $VO_{2peak}/VO_{2\%pred}$ is presented in Figure 3A and 3B, as well as the male-only $VO_{2\%pred}$ model in Figure 3C. Predicted LAVI by $VO_{2\%pred}$ with associated 95% CIs and 95% prediction intervals by sex for age 40 and 70 years is shown in Figure S1.

Diastolic Function

There were no statistically significant associations between LAVI and e', E/e', and tricuspid regurgitation (Table S1) as well as other indexes of diastolic dysfunction (pulmonary vein systolic and diastolic velocities and their ratio, transmitral flow early and late velocities and their ratio, and mitral deceleration time; data not shown). Septal e' showed a positive association to $VO_{2\%pred}$, but no other association was found in age- and sex-adjusted multiple regression analyses
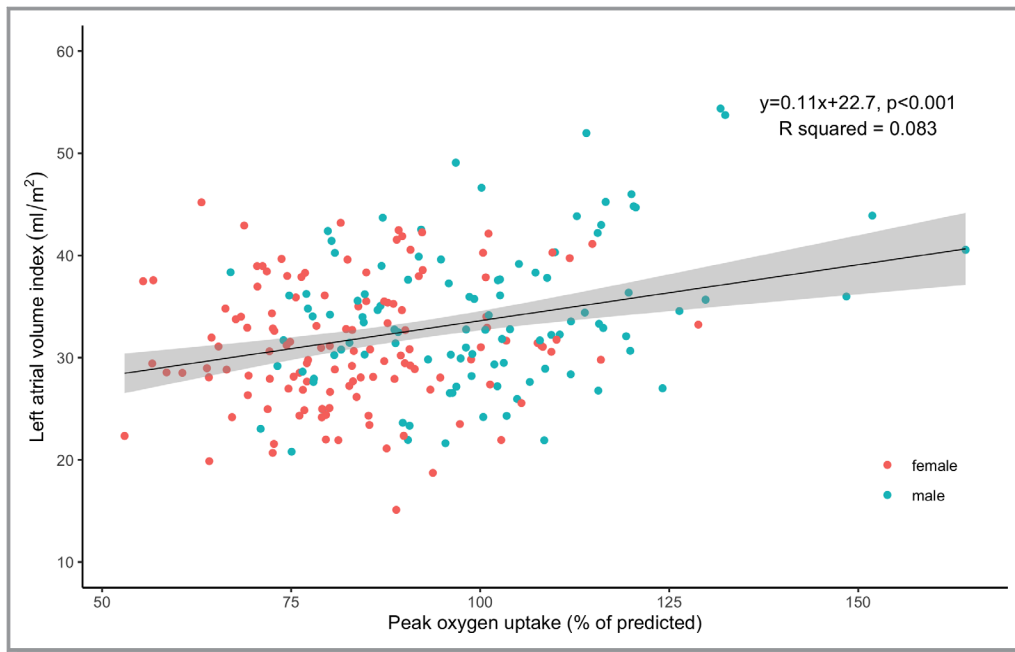
Figure 2. Scatterplot of the relationship between left atrial volume index (mL/m^2) and percentage of age- and sex-predicted peak oxygen uptake (n=229).

with echocardiographic indexes of diastolic function as dependent variable and VO_{2peak} and $VO_{2\%pred}$ as independent variables (Table S2).

Sensitivity Analyses

Excluding those with only single-plane measurement of LAVI, those with >0.5-cm difference between 2- and 4-chamber measurements, and those with diastolic dysfunction (n=3), did not make notable changes to the main results. LAVI was systematically lower when measured by the biplane method of discs compared with the A-L method (LAVI [summation of disc method] mean, 29.5 mL/m^2; mean difference, 3.3 [95% CI, 3.1–3.5] mL/m^2; *P*<0.0001; n=209), and 22% had LAVI >34 mL/m^2 when measured by the summation of disc method. Predicted LAVI based on model 1 and model 2 was therefore also lower, and higher $VO_{2peak}/VO_{2\%pred}$ was

needed to reach thresholds for enlarged LAVI (Figure S2). The same effect modification between $VO_{2peak}/VO_{2\%pred}$ and age was seen when using LAVI measured by the biplane method of discs.

Using a different approach fitting a restricted cubic spline model for the prediction of LAVI by $VO_{2\%pred}$ showed similar results as model 2 (Data S1, Figure S3). Allowing for different β coefficients at different levels of $VO_{2\%pred}$, this model showed an effect on LAVI when $VO_{2\%pred}$ was >100%.

We also fitted spline models allowing different β coefficients at different ages, with similar findings as in the main models (Data S1, Figure S4).

Discussion

Our main finding is that higher CRF is associated with higher LAVI in a healthy, free-living general population sample, and

Table 3. Linear Regression Analyses With LA Volume Index (A-L Method) as Dependent Variable

Variable	n	Univariate Model			Age- and Sex-Adjusted Model		
		β (95% CI)	R^2	P Value	β (95% CI)	R^2	P Value
VO_{2peak}	229	0.18 (0.09–0.28)	0.06	<0.001	0.20 (0.08–0.33)	0.07	0.002
$VO_{2\%pred}$	229	0.11 (0.06–0.16)	0.08	<0.001	0.09 (0.04–0.14)	0.08	0.001
PA volume	225	0.01 (0.003–0.015)	0.04	0.006	0.009 (0.003–0.015)	0.08	0.005
Age	229	0.03 (−0.03 to 0.01)	0.004	0.34	N/A	N/A	N/A

A-L indicates area-length; LA, left atrial; PA volume, minutes of physical activity per week with high-intensity activity weighted 2:1; $VO_{2\%pred}$, percentage of age- and sex-predicted VO_{2peak}; VO_{2peak}, peak oxygen consumption; N/A, not applicable.
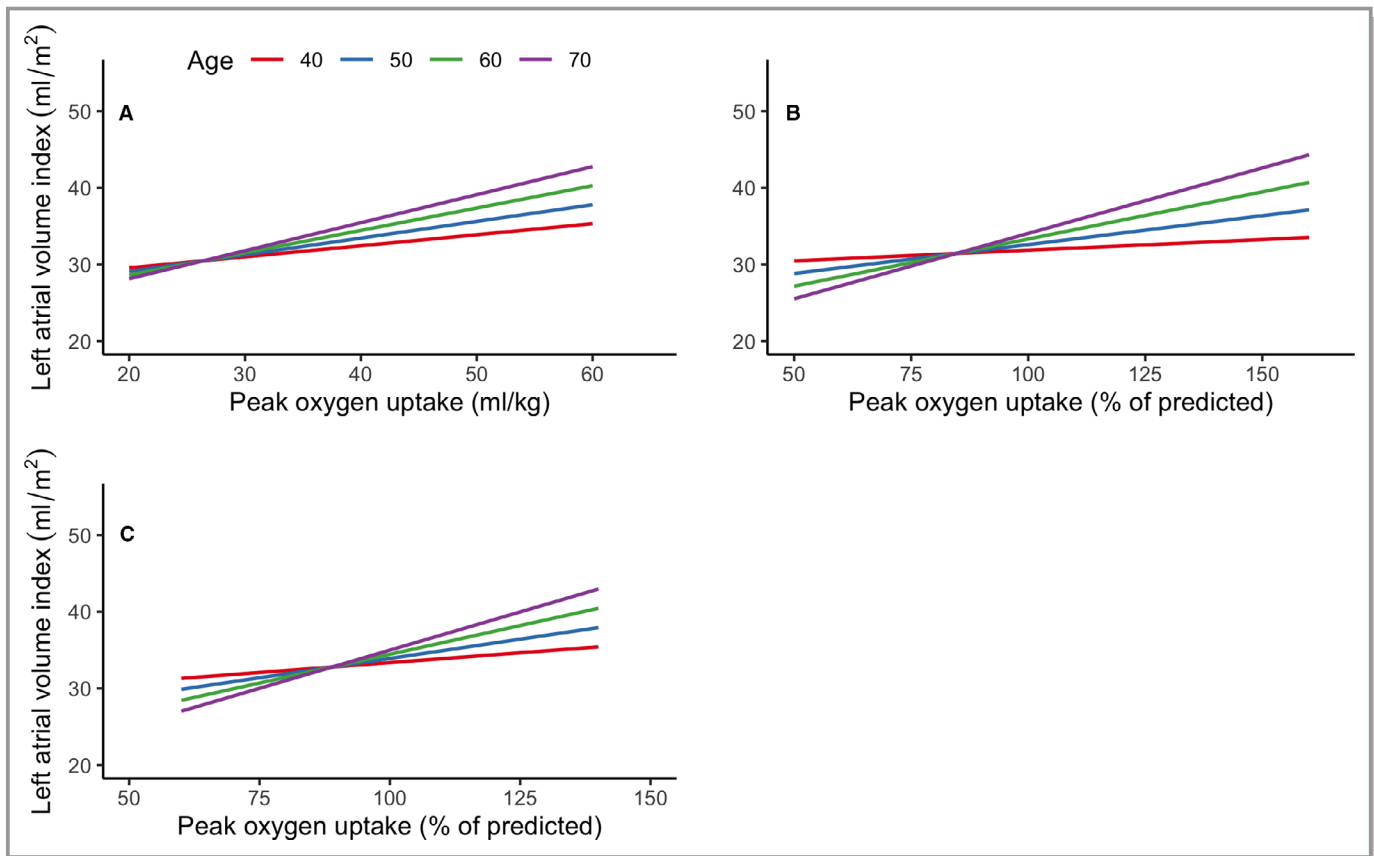
Figure 3. Prediction diagrams of left atrial volume index for ages 40, 50, 60, and 70 years by peak oxygen uptake (VO$_{2peak}$) (n=229) (**A**), percentage of age- and sex-predicted VO$_{2peak}$ (n=229) (**B**), and percentage of age- and sex-predicted VO$_{2peak}$ in men only (n=103) (**C**).

the effect is modified by age. In fact, participants aged ≥60 years with VO$_{2peak}$ as expected by age and sex were predicted to have LAVI at the threshold for pathological enlargement of 34 mL/m^2 (A–L method). Higher LAVI was not associated with other indexes of diastolic dysfunction. The main findings are summarized in Figure 4.

CRF, Diastolic Function, and LA Size

Although evidence on the associations between LAVI and CRF in healthy populations is lacking, the main finding from this study is supported by studies showing enlarged LAVI in competitive endurance athletes[7,8] and recreational runners.[9] Authors from a study comparing athletes and normal subjects argued that LAVI appears to be determined by a complex interplay between LV end-diastolic volume, PA level, and LV mass.[20] Sex was not an independent predictor in the latter study, which is in line with our results showing that LAVI was not different between sexes after adjusting for VO$_{2peak}$, a proxy of LV size. An interventional study randomizing adults to high-intensity exercise or yoga control showed that LA volume increased significantly more in the high-intensity exercise group,[21] although another study based on the same exercise

intervention showed that LA mechanical remodeling was more prominent than LV mechanical remodeling in the high-intensity exercise group.[22]

A modest proportion of the LAVI variance was explained by the VO$_{2peak}$/VO$_{2\%pred}$ models. However, the mean VO$_{2\%pred}$ of the study population was 10% lower than expected by age and sex, and few subjects had high VO$_{2\%pred}$ values, especially in women. In fact, only 16% of women had VO$_{2\%pred}$ higher than expected by age and sex, compared with 47% of the men. It is likely that this contributed largely to the lack of significant associations between LAVI and VO$_{2peak}$/VO$_{2\%pred}$ in women. The differences by sex for the association between CRF and LAVI should be investigated further.

Higher LAVI was not associated with diastolic dysfunction in our study, which is supported by a study from a US preventive health clinic showing that the association between LAVI and LV diastolic filling pressures measured by E/e' differs by CRF level.[11] Another study also showed that E/e' was associated with LAVI among normal subjects, but not among athletes.[20] In patients with LV diastolic dysfunction, low CRF is associated with enlarged LAVI,[23] and therefore it seems to be a U- (or at least J-) shaped relationship between LAVI and CRF, where enlarged LAVI and low CRF are
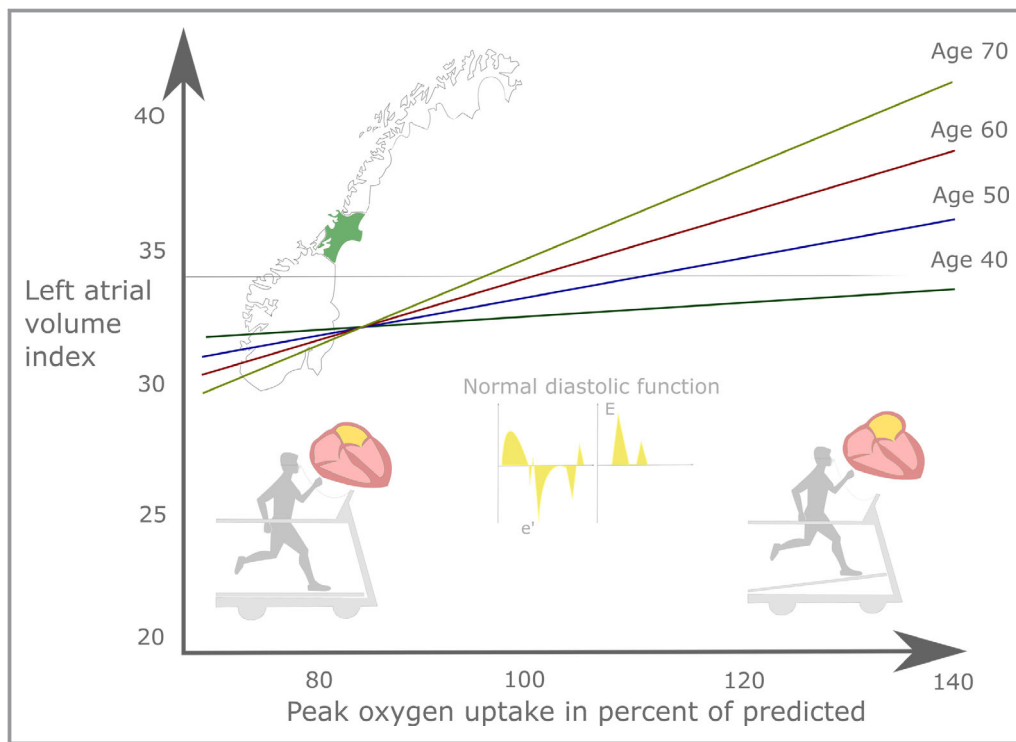
Figure 4. Take-home figure. Indexed left atrial volume was positively associated with cardiorespiratory fitness in healthy adults, and the effect was more pronounced with advanced age. Left atrial volume was not associated with other indexes of left ventricular diastolic dysfunction.

associated with diastolic dysfunction and a poor prognosis, whereas enlarged LAVI and high CRF probably are associated with a favorable prognosis. Higher prognostic value of diastolic dysfunction compared with enlarged LAVI has been shown in a study from the general population,[24] supporting that enlarged LAVI may convey other information than just as a marker of chronically elevated filling pressures.

The negative prognostic influence of LAVI is shown in high-risk populations, such as patients with type 2 diabetes mellitus and myocardial infarction.[1,2] However, longitudinal studies on the prognostic value of enlarged LAVI in fit populations are lacking, which should be evaluated in future studies. An interventional study did show LA mechanical remodeling in response to high-intensity exercise without significant electrical remodeling,[22] further supporting this notion.

A study investigating exercise capacity and LAVI in normal and diseased subjects showed that exercise capacity was negatively correlated to LAVI in systolic and diastolic dysfunction, but positively correlated to LAVI in normal subjects, supporting our findings,[25] as the population in our study was previously healthy.

It is likely that the physiological high blood flow obtained during PA may trigger LA remodeling in fit individuals in a similar way as the high-pressure states found in relation to LV pathological features. The number of years of endurance

exercise training has been shown to be an independent predictor of enlarged LAVI in athletes,[10] which is supportive of our finding of an effect modification between age and CRF on LAVI showing higher predicted LAVI by CRF with advanced age. Cumulative PA volume over years may therefore be an important stimulus to enlarged LAVI in healthy subjects from the general population as well. Animal models showing increased LA fibrosis in response to exercise training further support the possibility of cumulative, and possibly irreversible, changes to the LA over time.[26] Although data on cumulative PA over many years were not available in our study, it may be argued that LA enlargement caused by this stimulus may be less harmful as PA behavior generally is associated with lower cardiovascular risk. Thus, it may be hypothesized that LAVI is not a good marker of risk in a healthy and fit population.

Clinical Implications

Our study indicates that CRF should be considered when assessing LAVI, and as previously discussed it may be argued that LAVI is not a marker of risk in healthy and fit subpopulations. As Nistri et al previously stated,[20] a dichotomous classification of normal/pathological LAVI without taking variables such as athletic status into account increases risk of misclassification, further suggesting that specific cutoffs based on sporting activity should be proposed. Our

study supports these findings and further implies that CRF or exercise training status should be considered when assessing LAVI also in nonathletes. Our findings indicate that making such precautions is especially important among fit individuals of advanced age. In fact, one metabolic equivalent task (metabolic equivalent task=3.5 mL/kg per minute) higher VO_{2peak} translated to $\approx$1.3 mL higher predicted LAVI in 70-year-old patients in our study. Our results also suggest that briefly assessing patients' leisure-time PA could help clinicians in interpreting findings of enlarged LAVI. Another alternative to the somewhat resource-demanding ergospirometry is estimating CRF through nonexercise equations, which could be a feasible alternative in clinical practice.[12,19]

Strengths and Limitations

The study has several methodological strengths. CRF was measured by ergospirometry during incremental symptom-limiting exercise, dedicated echocardiographic recordings were obtained to assess LA volume, and leisure-time PA was measured by a validated questionnaire.

Although mean VO_{2peak} values were lower in our study population than in the reference population, CRF reference values from Norwegian populations in general are somewhat higher than in other populations.[27] Given the relationship between LAVI and CRF found in this study, this may partly explain the high LAVI values found in this study compared with a recent meta-analysis.[28] Another potentially important cause may be the inclusion of LAVI from studies assessing LAVI on the basis of one view only, and the meta-analyses did not take difference in length between 4- and 2-chamber view into account. The discrepancy between the recommendations, the large meta-analyses, and the present results reflects the need for high-quality echocardiographic studies from different populations. The A–L method for LA volume evaluation is known to yield higher values for LAVI compared with the summation of disc method, and the discrepancy in our material was similar to what was expected.[29] However, sensitivity analyses showed the same associations to CRF regardless of method of LAVI quantification.

The cross-sectional design limits conclusions about causation, and the selection of healthy individuals made echocardiographic diastolic dysfunction practically absent. Furthermore, we did not follow specific guidelines for examination of diastolic dysfunction when ejection fraction was reduced,[6] as the number of participants with reduced ejection fraction was negligible. Data on fat-free body mass were not available, and it is reasonable that fit individuals have a lower proportion of body fat that may influence the indexed LA volume. Obesity may also affect LAVI[30]; and although it is strongly related to CRF, it is possible that the presented associations could be different in populations of different body composition. As all participants were in sinus rhythm, the results should not be generalized to individuals with arrhythmias. However, although the participants answered to be free of any cardiovascular disease, it is possible that some participants may have had undiagnosed asymptomatic paroxysmal atrial fibrillation. This is especially important as previous studies have shown increased atrial fibrillation prevalence in populations with a long history of endurance exercise training,[31] and atrial fibrillation is associated with enlarged atria. However, it is less likely that subjects with high CRF are asymptomatic from their atrial fibrillation compared with subjects with low CRF. Furthermore, self-reported diagnoses of atrial fibrillation in HUNT3 have been validated, showing a negative predictive value of 98.4% for the self-reported questionnaire.[32] Thus, it is unlikely that confounding from atrial fibrillation has significantly affected the presented results.

Conclusions

In a healthy population, LA volume was positively associated with CRF, but not with diastolic dysfunction. On the basis of this study from a healthy population and earlier studies from diseased populations, there seems to be a U- or J-shaped relationship between CRF and LA size. Age-relative CRF should be considered when LA volume is included in clinical decision making. Enlarged LA volume may not be a marker of risk in fit subpopulations, which should be further studied.

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Disclosures

None.

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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.

	n	*β (95% CI)*	R²	p	*β (95% CI)*	R²	p
		Univariate model			**Age and sex-adjusted model**		
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.

|	n	Univariate model			Age and sex-adjusted model		
		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).
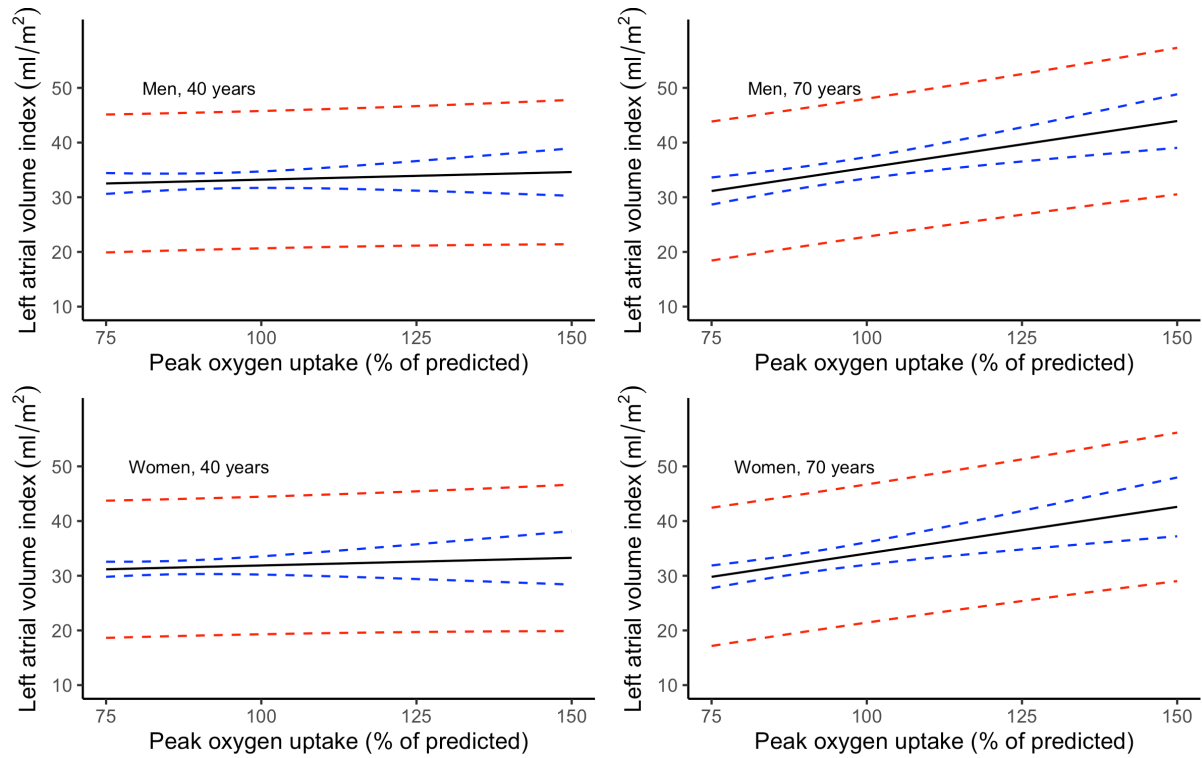
Figure S2. Prediction diagrams of left atrial volume index measured by biplane method of discs for different ages by a) VO$_{2peak}$ (n=209), b) percent of age and sex predicted VO$_{2peak}$ (n=209), and c) percent of age and sex predicted VO$_{2peak}$ in men only (n=96).
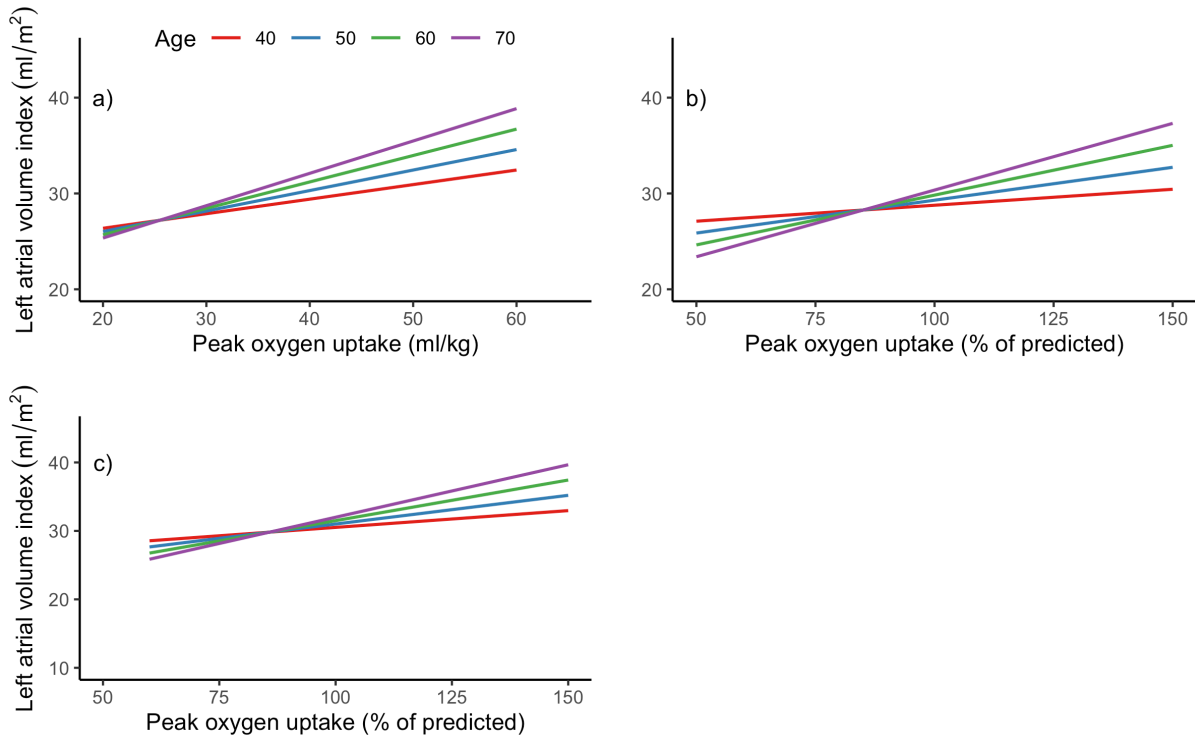
Figure S3. Prediction of left atrial volume index (A-L method) based on a restricted cubic spline model for percent of age and sex predicted VO$_{2peak}$ (n=229).
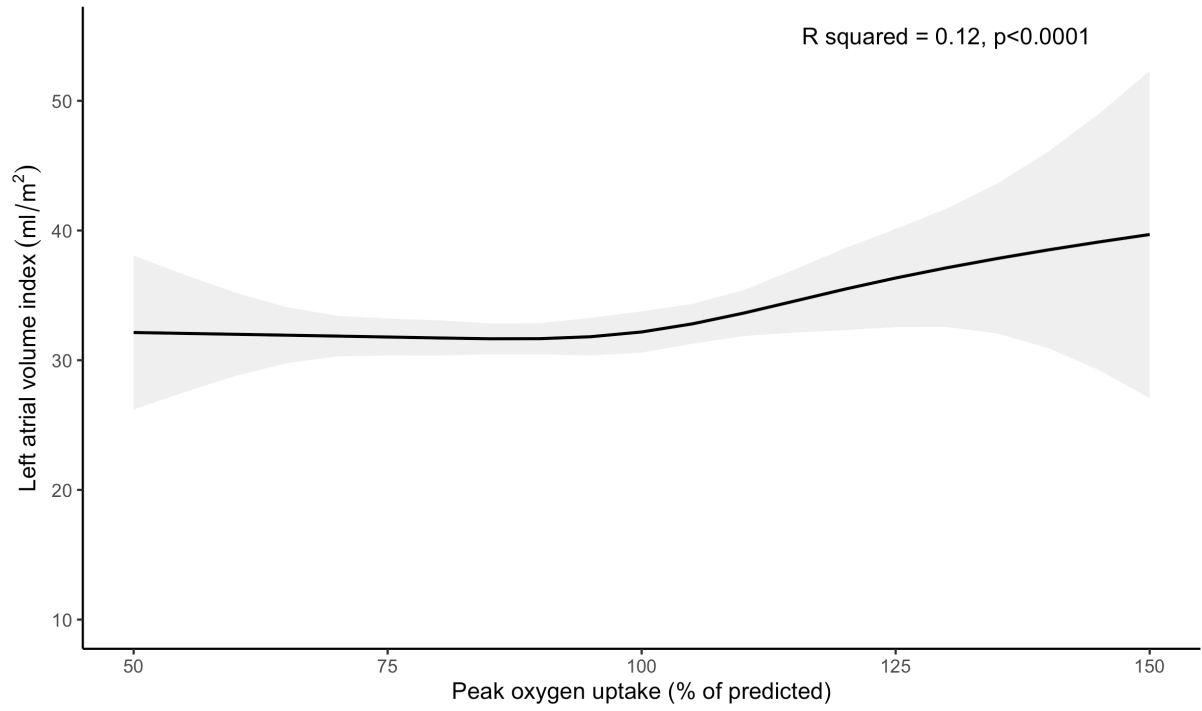
Figure S4. Prediction of left atrial volume index (A-L method) by percent of age and sex-predicted VO2peak based on a restricted cubic spline model for age.
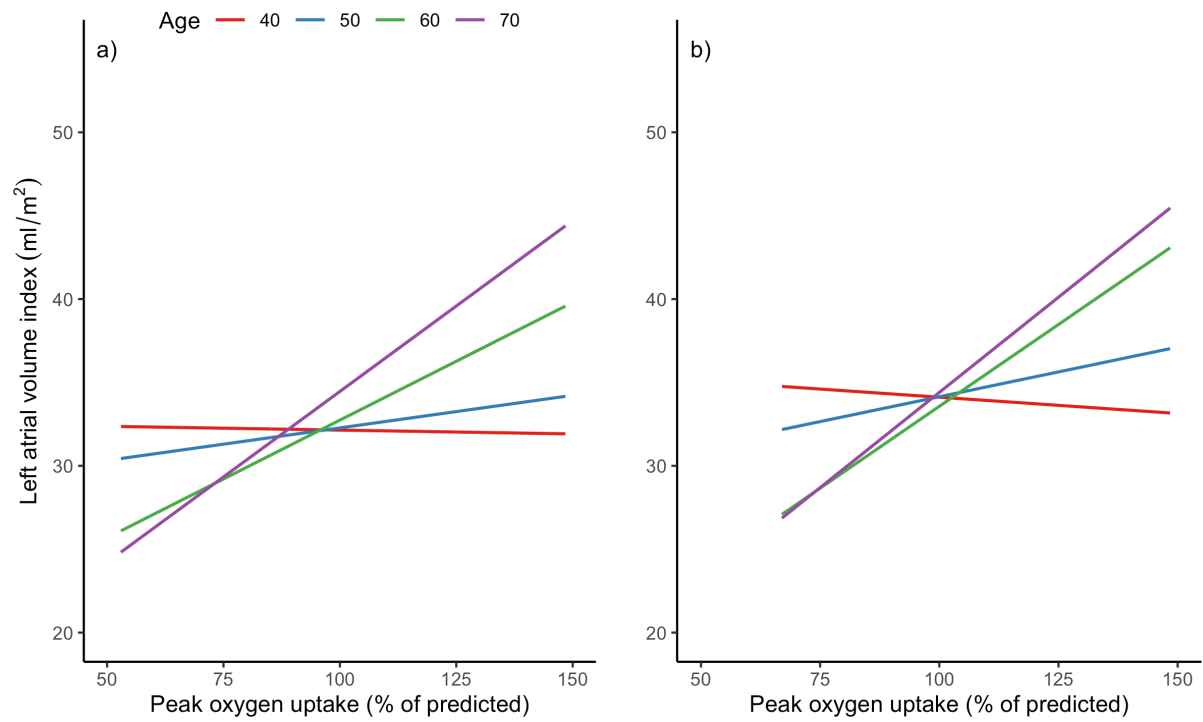
a) Sexes combined (n=229), b) men only (n=103).