


# Scaling $\text{VO}_2\text{max}$ to body size differences to evaluate associations to CVD incidence and all-cause mortality risk

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## ABSTRACT

**Objective** To evaluate and compare ratio and allometric scaling models of maximal oxygen consumption ( $\text{VO}_2\text{max}$ ) for different body size measurements in relation to cardiovascular disease (CVD) incidence and all-cause mortality.

**Methods** 316 116 individuals participating in occupational health screenings, initially free from CVD, were included.  $\text{VO}_2\text{max}$  was estimated using submaximal cycle test. Height, body mass and waist circumference (WC) were assessed, and eight different scaling models (two evaluated in a restricted sample with WC data) were derived. Participants were followed in national registers for first-time CVD event or all-cause mortality from their health screening to first CVD event, death or 31 December 2015.

**Results** Increasing deciles of  $\text{VO}_2\text{max}$  showed lower CVD risk and all-cause mortality for all six models in the full sample ( $p < 0.001$ ) as well as with increasing quintiles in the restricted sample (eight models) ( $p < 0.001$ ). For CVD risk and all-cause mortality, significantly weaker associations with increasing deciles for models 1 ( $\text{L}\cdot\text{min}^{-1}$ ) and 5 ( $\text{mL}\cdot\text{min}^{-1}\cdot\text{height}^{-2}$ ) were seen compared with model 2 ( $\text{mL}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$ ), (CVD,  $p < 0.00001$ ;  $p < 0.00001$ : all-cause mortality,  $p = 0.008$ ;  $p = 0.001$ ) and in some subgroups. For CVD, model 6 ( $\text{mL}\cdot\text{min}^{-1}\cdot(\text{kg}^1\cdot\text{height}^{-1})^{-1}$ ) had a stronger association compared with model 2 ( $p < 0.00001$ ) and in some subgroups.

In the restricted sample, trends for significantly stronger associations for models including WC compared with model 2 were seen in women for both CVD and all-cause mortality, and those under 50 for CVD.

**Conclusion** In association to CVD and all-cause mortality, only small differences were found between ratio scaling and allometric scaling models where body dimensions were added, with some stronger associations when adding WC in the models.

## INTRODUCTION

Cardiorespiratory fitness assessed as maximal oxygen consumption ( $\text{VO}_2\text{max}$ ) is a strong independent predictor for cardiovascular disease (CVD).<sup>1 2</sup> Absolute  $\text{VO}_2\text{max}$  level ( $\text{L}\cdot\text{min}^{-1}$ ) is mainly dependent on genetic

## What are the new findings?

- ▶ In 316 116 men and women, eight ratio or allometric scaling models of maximal oxygen consumption ( $\text{VO}_2\text{max}$ ) to body size differences for association to cardiovascular disease (CVD) incidence and all-cause mortality were evaluated.
- ▶ All models of  $\text{VO}_2\text{max}$  scaled for body size differences were associated with lower CVD risk and all-cause mortality.
- ▶ There were small differences between the models.
- ▶ However, including only height as body measurement provided a less powerful discrimination for CVD risk, while inclusion of waist circumference showed a stronger association to CVD risk.

## How might it affect clinical practice in the future?

- ▶ Maximal oxygen consumption ( $\text{VO}_2\text{max}$ ) level is considered a clinical vital sign, and the present study adds new important knowledge of how clinical practitioners may consider intraindividual size differences in  $\text{VO}_2\text{max}$  for best prediction of CVD incidence and all-cause mortality.

contribution, moderate-to-vigorous intensity levels of physical activity and body size. To enable intraindividual comparisons in terms of both performance-related and health-related aspects,  $\text{VO}_2\text{max}$  is traditionally scaled for body size differences using ratio scaling ( $Y=bX$ ). Most commonly, body mass in kg is used (expressed as  $\text{mL}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$ ). However, a growing body of evidence indicates that the linear, per-ratio standard way of expressing  $\text{VO}_2\text{max}$  can lead to several types of errors and misinterpretations, including larger subjects being penalised and lighter subjects favoured.<sup>3-5</sup>

The theory of geometric similarity states that when comparing biological functions between humans of different sizes, the



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**Table 1** Characteristics of participants**A: Characteristics of all participants (316 116)**

	Men		Women	
	Age ≤50	Age >50	Age ≤50	Age >50
No	130 723	42 407	103 260	39 726
Age (mean±SD)	37±8	57±4	38±8	57±4
Height (cm) (mean±SD)	181±7	179±7	167±6	166±6
Body mass (kg)	86±14	86±12	70±13	71±12
<i>Estimated, VO<sub>2</sub>max</i>				
Relative, mL·min <sup>-1</sup> ·kg <sup>-1</sup>	37.9±9.9	31.2±7.6	37.9±10.1	30.3±7.7
Absolute, L·min <sup>-1</sup>	3.2±0.8	2.7±0.6	2.6±0.6	2.1±0.5

**B: Characteristics of participants, restricted sample (63 380)**

	Men		Women	
	Age ≤50	Age >50	Age ≤50	Age >50
No	28 877	9 800	18 141	6 562
Age (mean±SD)	37±8	57±4	38±8	57±4
Height (cm) (mean±SD)	181±7	179±7	167±6	166±6
Body mass (kg)	86±14	86±12	70±13	71±12
Waist circumference (cm)	94±11	99±10	83±12	88±11
<i>Estimated, VO<sub>2</sub>max</i>				
Relative, mL·min <sup>-1</sup> ·kg <sup>-1</sup>	37.9±9.9	31.2±7.6	37.9±10.1	30.3±7.7
Absolute, L·min <sup>-1</sup>	3.2±0.8	2.7±0.6	2.6±0.6	2.1±0.5

VO<sub>2</sub>max, maximal oxygen consumption.

measures should be dimensionally homogenous. Static and dynamic functions are expressed as multiples of the linear dimension (L).<sup>6 7</sup> VO<sub>2</sub>max scaled for body size using traditional ratio scaling does not comply to the theory of geometric similarity, as absolute VO<sub>2</sub>max in L·min<sup>-1</sup>·kg<sup>-1</sup> in linear dimensions is expressed as L<sup>3</sup> divided by minutes (L) and body mass (L<sup>3</sup>), which does not result in dimensional homogeneity (≠ 1). Allometric scaling, on the other hand, is a model that follows the theory of geometric similarity and has been proposed to be more accurate, compared with ratio scaling, for intra-individual size-independent comparisons. The allometric scaling model equation reads  $Y=aX^b$ . In this context,  $Y$  is VO<sub>2</sub> (litre = L<sup>3</sup>),  $a$  is the constant,  $X$  is the body size variable and  $b$  is the exponent parameter.<sup>7 8</sup> Height and body mass are two easy accessible measures of body size that can be used for allometric scaling of VO<sub>2</sub>. In heterogenic samples, theoretical suggested exponents for scaling for VO<sub>2</sub>max can be either height<sup>2</sup> or body mass<sup>2/3</sup> (both equal to L<sup>2</sup>).<sup>9</sup> Furthermore, body fat distribution, in particular excess fat in the abdominal region measured as waist circumference (WC), has a strong association with CVD risk.<sup>10 11</sup> Thus, also including an easy accessible measure of abdominal fat (eg, WC) would be clinically relevant.

Both ratio and allometric scaling of VO<sub>2</sub>max for body size differences have mainly been evaluated in terms of the performance-related aspect of cardiorespiratory

fitness, often using small sample sizes to enable intraindividual comparisons. To our knowledge, only two studies have evaluated scaling of VO<sub>2</sub>max for different body measurements in association with health-related aspects (CVD risk factors, all-cause mortality).<sup>12 13</sup> No previous study has compared different ways of scaling VO<sub>2</sub>max including different variables of body size, applying these, with the dimensional theory, to a health perspective. Thus, the aim of this study was to evaluate and compare different models scaling absolute VO<sub>2</sub>max for body size, in relation to CVD risk and all-cause mortality in a large sample of men and women of different ages.

## MATERIALS AND METHODS

### Procedure

Data were obtained for this study from the Health Profile Assessment (HPA) database managed by the HPI Health Profile Institute (Stockholm, Sweden). The institute has been responsible for standardising methods and educating the data collection staff since the late 1970s.<sup>14</sup> Participation is optional and cost-free for the individual and is offered to all employees working for a company or organisation connected to occupational or other health services. The HPA comprises an extensive questionnaire, anthropometric measurements, a submaximal cycle test for estimation of VO<sub>2</sub>max, and a person-centred dialogue. All data are subsequently recorded in the database. From January 1982 to December 2015, data from a total of 316

**Table 2** Description of the eight different models included in the analyses

Model	Expression of VO <sub>2</sub> max	In terms of linear dimensions (L)	Comment to model
1	L·min <sup>-1</sup>	L <sup>3</sup> ·L <sup>-1</sup> thus L <sup>2</sup>	Not scaled for body size
2	mL·min <sup>-1</sup> ·kg <sup>-1</sup>	L <sup>3</sup> ·L <sup>-1</sup> ·L <sup>-3</sup> thus L <sup>-1</sup>	The traditional scale ratio
3	mL·min <sup>-1</sup> ·kg <sup>-0.67</sup>	L <sup>3</sup> ·L <sup>-1</sup> ·L <sup>-2</sup> thus L <sup>0</sup>	Using the theoretical mass exponent of 2/3 based on dimensional analysis <sup>6,8</sup>
4	Women: mL·min <sup>-1</sup> ·kg <sup>-0.62</sup> Men: mL·min <sup>-1</sup> ·kg <sup>-0.76</sup>	L <sup>3</sup> ·L <sup>-1</sup> ·L <sup>-2</sup> thus L <sup>0</sup>	Using sex-specific exponents derived from large population samples <sup>9</sup>
5	mL·min <sup>-1</sup> ·height <sup>-2</sup>	L <sup>3</sup> ·L <sup>-1</sup> ·L <sup>-2</sup> thus L <sup>0</sup>	Using height as body size measure for scaling <sup>8,19</sup>
6	mL·min <sup>-1</sup> ·(kg <sup>1</sup> ·height <sup>-1</sup> ) <sup>-1</sup>	L <sup>3</sup> ·L <sup>-1</sup> ·(L <sup>3</sup> ·L <sup>-1</sup> ) <sup>-1</sup> thus L <sup>0</sup>	
7	mL·min <sup>-1</sup> ·WC <sup>-2</sup>	L <sup>3</sup> ·L <sup>-1</sup> ·L <sup>-2</sup> thus L <sup>0</sup>	Using waist circumference and height as body size measure for scaling
8	mL·min <sup>-1</sup> ·(WC <sup>3</sup> ·height <sup>-1</sup> ) <sup>-1</sup>	L <sup>3</sup> ·L <sup>-1</sup> ·(L <sup>3</sup> ·L <sup>-1</sup> ) <sup>-1</sup> thus L <sup>0</sup>	

VO<sub>2</sub>max, maximal oxygen consumption; WC, waist circumference.

116 participants with a valid estimated VO<sub>2</sub>max test and no previous CVD event were included in the analyses. WC was added as a measurement in 2001 so all analyses including WC are from this date. This subgroup consisted of 63 380 participants. Characteristics of the participants are shown in [table 1A,B](#) where they have been divided by sex as well as under and over 50 years of age. This cut-point of ages was an arbitrary decision.

### Assessment of VO<sub>2</sub>max

VO<sub>2</sub>max was estimated using the standardised submaximal Åstrand cycle ergometer test.<sup>15</sup> In order to minimise well-known errors with submaximal testing, participants were asked to abstain from vigorous activity 24 hours before the test, eating a heavy meal or smoking/using snuff 3 hours and 1 hour before the test, respectively, as well as avoiding stress. Tested for criterion validity, the Åstrand test shows no systematic bias and limited variation in mean differences between estimated and directly measured VO<sub>2</sub>max while treadmill running (mean difference 0.01 L·min<sup>-1</sup>, 95% CI -0.10 to 0.11),<sup>16</sup> with an absolute error and coefficient of variance similar to other submaximal tests (SEE=0.48 L·min<sup>-1</sup>, CV=18.1%).<sup>17</sup> The submaximal test is thus suitable for use in large unselected cohorts.

### Body size measurements

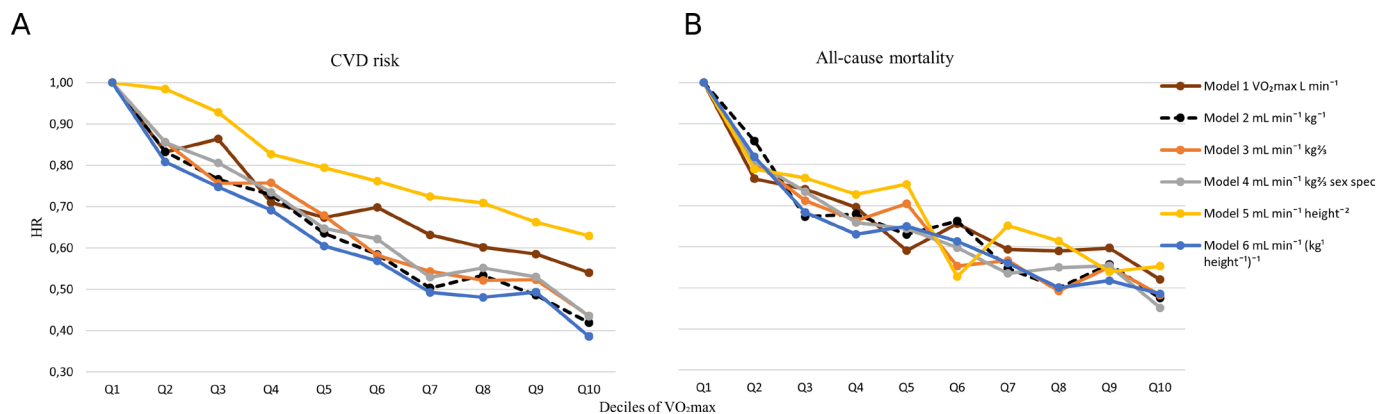
Body height and weight were assessed to the nearest 0.5 cm and 0.5 kg, respectively, by a calibrated scale and wall-mounted stadiometer. WC was measured with a tape measure to the nearest 0.5 cm at the midpoint between the top of the iliac crest and the lower margin of the last palpable rib in the mid-axillary line after normal exhalation.

### CVD event and mortality surveillance

Data on first-time CVD event or all-cause mortality were derived from Swedish national registers and included in the analyses on an individual level using the unique Swedish personal identity number. All participants were followed from their HPA to the first CVD event, death or until 31 December 2015. Incident cases of first-time CVD event after the HPA (fatal or non-fatal myocardial infarction, angina pectoris or ischaemic stroke; ICD8, 410–414 and 430–438; ICD9, 410–414, 427, 429 and 430–437; ICD10, I20–I25, I46 and I60–I66) and death from any cause were ascertained through the Swedish national cause of death registry and the national in-hospital registry.

### Models derived for scaling of VO<sub>2</sub>max

Eight different models for scaling of VO<sub>2</sub>max were derived, one not using any body measurements, six using body mass and/or height as measures of body size, and two using WC. Apart from models 1 and 2, which used litres per minute and the traditional ratio scaling of VO<sub>2</sub>max by body mass in kg, respectively, for comparative purposes, all models were derived to be dimensionally correct according to the theory of geometric similarity.



**Figure 1** HRs for CVD risk (left) and all-cause mortality (right) per decile for models 1–6 in the total sample (n=316 116). CVD, cardiovascular disease; VO<sub>2</sub>max, maximal oxygen consumption.

Model 4 uses sex-specific exponents for body mass derived from large population samples.<sup>9</sup> Six models<sup>1–6</sup> included data for all participants in the study population (n=316 116 participants), while only 63 380 cases provided data for WC and were included in models 7 and 8. The different models are described in [table 2](#).

### Statistical analyses

The range of values for each continuous model varied, hence, each model was further divided into sex-specific and age-specific (18–50 years; >50 years) specific deciles (comparison of models 1–6 in full sample, n=316 116), or quintiles (comparison of all models in a restricted sample of participants that provided WC data, n=63 380). Cox proportional hazard regression modelling was used to assess HR with 95% CI to predict first time CVD incidence and all-cause mortality in relation to the different models and in relation to the deciles and quintiles, respectively. To compare risk associations (HR) with increasing deciles or quintiles of scaled VO<sub>2</sub>max between the different models in comparison to the method most commonly used for scaling (model 2; mL·min<sup>-1</sup>·kg<sup>-1</sup>), the procedure described by R Core Team was used<sup>18–20</sup> for dependent samples with Bonferroni adjustment for multiple comparison. P<0.01 was used as level of significance for comparisons between models 1–6 in the full sample, and p<0.007 for comparisons between models 1–8 in the restricted sample. Trends of significance were defined as p<0.05. Concordance statistics were calculated as a measure of goodness-of-fit for Cox regression models including continuous variables for the models. The proportionality assumption for Cox regression was examined using scaled Schönfeld residuals, and we found no violation of the proportionality assumption. Data were analysed using IBM SPSS, V.24.0.0, 2016, SPSS.

### Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

### RESULTS

A total of 316 116 participants (45% women) were included to compare models 1–6, where there were 4760 cases of CVD (28% women, mean follow-up time of 6.8±4.7 years), and 2936 deaths due to all causes (43% women a mean follow-up time of 6.8±4.7 years). In the restricted sample analyses comparing all models (1–8), a total of 63 380 participants (39% women) were included, with 391 cases of CVD (24% women, mean follow-up time of 3.5±2.5 years) and 185 deaths due to all causes (30% women, mean follow-up time 3.5±2.5 years).

Increasing deciles of VO<sub>2</sub>max were associated with lower CVD risk and all-cause mortality for models 1–6 in the full sample analyses (p<0.001) ([figure 1A,B](#)). For risk associations per each higher decile for each model compared with model 2 for CVD risk in the full sample analyses, model 1 (L·min<sup>-1</sup>) and model 5 (mL·min<sup>-1</sup>·height<sup>-2</sup>) had significantly weaker associations compared with model 2 (mL·min<sup>-1</sup>·kg<sup>-1</sup>) (p<0.00001; p<0.00001). Models 1 and 5 also had a significantly weaker association compared with model two in all subgroups (p<0.00001 for all subgroups). Models 3 (mL·min<sup>-1</sup>·kg<sup>-0.67</sup>) and 4 (mL·min<sup>-1</sup>·kg<sup>-0.76</sup> and -0.52) had a significantly weaker association compared with model 2 in the whole sample (p=0.0004; p<0.00006), women (p=0.0003; p=0.00009), and those under 50 years (p<0.00001; p=0.00001), as well as a trend for a weaker association for men (p=0.038; p=0.015). Model 6 (mL·min<sup>-1</sup>·(kg<sup>1</sup>·height<sup>-1</sup>)<sup>-1</sup>) had a stronger association compared with model 2 for the whole sample (p<0.00001), men (p<0.00001) and both age subgroups (p=0.0001; p<0.00002), ([table 3A](#) and [figure 1](#)).

For all-cause mortality, significantly weaker associations with increasing deciles of scaled VO<sub>2</sub>max were seen for model 1 (L·min<sup>-1</sup>) and model 5 (mL·min<sup>-1</sup>·height<sup>-2</sup>) in comparison to model 2 for the full sample (p=0.0008; p=0.001), men (p=0.003; 0.0005) and those under 50 (p<0.0001; p<0.00001), ([table 3A](#) and [figure 1](#)). Model 4 showed a significantly stronger association to model 2 for those over 50 (p=0.009).

In the restricted sample, all models were associated with lower CVD risk and all-cause mortality with increasing

**Table 3** HR (95% CI) and concordance for CVD risk and all-cause mortality for the different models

**A: HR (95% CI) per decile and concordance for CVD risk and all-cause mortality for model 1–6 in the full sample (n=316 116)**

	CVD risk		All-cause mortality	
	HR (95% CI)	Concordance	HR (95% CI)	Concordance
<b>All (n=316 116)</b>				
	<b>4760 events</b>		<b>2936 deaths</b>	
Model 1	0.937 (0.93 to 0.95)*	0.80 (SE=0.003)	0.940 (0.93 to 0.95)*	0.75 (SE=0.005)
Model 2	0.913 (0.90 to 0.92)	0.81 (SE=0.003)	0.927 (0.92 to 0.94)	0.75 (SE=0.005)
Model 3	0.917 (0.91 to 0.93)*	0.81 (SE=0.003)	0.927 (0.91 to 0.94)	0.75 (SE=0.005)
Model 4	0.919 (0.91 to 0.93)*	0.81 (SE=0.003)	0.927 (0.91 to 0.94)	0.75 (SE=0.005)
Model 5	0.948 (0.94 to 0.96)*	0.80 (SE=0.003)	0.939 (0.93 to 0.95)*	0.75 (SE=0.005)
Model 6	0.909 (0.90 to 0.92)*	0.81 (SE=0.003)	0.927 (0.91 to 0.94)	0.75 (SE=0.005)
<b>Men (n=173 130)</b>				
	<b>3411 events</b>		<b>1677 deaths</b>	
Model 1	0.934 (0.92 to 0.95)*	0.80 (SE=0.003)	0.925 (0.91 to 0.94)*	0.75 (SE=0.007)
Model 2	0.916 (0.90 to 0.93)	0.80 (SE=0.003)	0.911 (0.90 to 0.93)	0.75 (SE=0.007)
Model 3	0.918 (0.91 to 0.93)†	0.80 (SE=0.003)	0.911 (0.89 to 0.93)	0.75 (SE=0.007)
Model 4	0.918 (0.91 to 0.93)†	0.80 (SE=0.003)	0.910 (0.89 to 0.93)	0.75 (SE=0.007)
Model 5	0.946 (0.94 to 0.96)*	0.80 (SE=0.003)	0.927 (0.91 to 0.94)*	0.74 (SE=0.007)
Model 6	0.910 (0.90 to 0.92)*	0.80 (SE=0.003)	0.909 (0.89 to 0.92)	0.75 (SE=0.007)
<b>Women (n=142 986)</b>				
	<b>1349 events</b>		<b>1259 deaths</b>	
Model 1	0.945 (0.93 to 0.96)*	0.75 (SE=0.006)	0.961 (0.94 to 0.98)	0.75 (SE=0.008)
Model 2	0.907 (0.89 to 0.93)	0.76 (SE=0.006)	0.949 (0.93 to 0.97)	0.75 (SE=0.007)
Model 3	0.915 (0.90 to 0.93)*	0.76 (SE=0.006)	0.948 (0.93 to 0.97)	0.75 (SE=0.007)
Model 4	0.919 (0.90 to 0.94)*	0.76 (SE=0.006)	0.949 (0.93 to 0.97)	0.75 (SE=0.008)
Model 5	0.951 (0.93 to 0.97)*	0.75 (SE=0.006)	0.956 (0.94 to 0.97)	0.75 (SE=0.008)
Model 6	0.906 (0.89 to 0.92)	0.76 (SE=0.006)	0.952 (0.93 to 0.97)	0.75 (SE=0.007)
<b>Age ≤50 (n=233 983)</b>				
	<b>1822 events</b>		<b>1128 deaths</b>	
Model 1	0.869 (0.85 to 0.88)*	0.67 (SE=0.007)	0.896 (0.88 to 0.91)*	0.61 (SE=0.01)
Model 2	0.820 (0.81 to 0.83)	0.70 (SE=0.007)	0.863 (0.85 to 0.88)	0.62 (SE=0.01)
Model 3	0.827 (0.81 to 0.84)*	0.70 (SE=0.007)	0.866 (0.85 to 0.89)	0.62 (SE=0.01)
Model 4	0.829 (0.81 to 0.84)*	0.69 (SE=0.007)	0.867 (0.85 to 0.89)	0.62 (SE=0.01)
Model 5	0.879 (0.86 to 0.89)*	0.66 (SE=0.007)	0.898 (0.88 to 0.92)*	0.60 (SE=0.01)
Model 6	0.814 (0.80 to 0.83)*	0.70 (SE=0.007)	0.862 (0.84 to 0.88)	0.63 (SE=0.01)
<b>Age &gt;50 (n=82 133)</b>				
	<b>2938 events</b>		<b>1808 deaths</b>	
Model 1	0.921 (0.91 to 0.93)*	0.66 (SE=0.005)	0.912 (0.90 to 0.93)	0.59 (SE=0.008)
Model 2	0.911 (0.90 to 0.92)	0.67 (SE=0.005)	0.908 (0.89 to 0.92)	0.59 (SE=0.008)
Model 3	0.911 (0.90 to 0.92)	0.67 (SE=0.005)	0.904 (0.89 to 0.92)	0.60 (SE=0.008)
Model 4	0.912 (0.90 to 0.92)	0.67 (SE=0.005)	0.903 (0.89 to 0.92)*	0.60 (SE=0.008)
Model 5	0.933 (0.92 to 0.95)*	0.66 (SE=0.005)	0.911 (0.90 to 0.93)	0.59 (SE=0.008)
Model 6	0.906 (0.89 to 0.92)*	0.67 (SE=0.005)	0.907 (0.89 to 0.92)	0.59 (SE=0.008)

Continued

Table 3 Continued

**B: HR (95% CI) per quintile and concordance for CVD risk and all-cause mortality for models 1–8 in the restricted sample (n=63 380)**

	CVD risk			All-cause mortality		
	HR (95% CI)	P value trend	Concordance	HR (95% CI)	P value trend	Concordance
<b>All (n=63 380)</b>						
	<b>391 events</b>			<b>185 deaths</b>		
Model 1	0.842 (0.78 to 0.91)†	<0.001	0.81 (SE=0.01)	0.881 (0.79 to 0.98)	0.019	0.72 (SE=0.023)
Model 2	0.800 (0.74 to 0.86)	<0.001	0.81 (SE=0.01)	0.907 (0.82 to 1.01)	0.069	0.72 (SE=0.023)
Model 3	0.805 (0.75 to 0.87)	<0.001	0.81 (SE=0.01)	0.890 (0.80 to 0.99)	0.03	0.72 (SE=0.023)
Model 4	0.814 (0.76 to 0.88)	<0.001	0.81 (SE=0.01)	0.911 (0.82 to 1.01)	0.082	0.72 (SE=0.023)
Model 5	0.864 (0.80 to 0.93)‡	<0.001	0.81 (SE=0.01)	0.875 (0.79 to 0.97)	0.013	0.72 (SE=0.023)
Model 6	0.788 (0.73 to 0.85)	<0.001	0.82 (SE=0.01)	0.903 (0.81 to 1.00)	0.059	0.72 (SE=0.023)
Model 7	0.781 (0.72 to 0.84)	<0.001	0.82 (SE=0.01)	0.880 (0.79 to 0.98)	0.019	0.72 (SE=0.023)
Model 8	0.774 (0.72 to 0.84)	<0.001	0.82 (SE=0.01)	0.906 (0.81 to 1.01)	0.069	0.72 (SE=0.023)
<b>Men (n=38 677)</b>						
	<b>298 events</b>			<b>130 deaths</b>		
Model 1	0.823 (0.75 to 0.90)	<0.001	0.81 (SE=0.012)	0.841 (0.74 to 0.96)	0.008	0.69 (SE=0.031)
Model 2	0.807 (0.74 to 0.88)	<0.001	0.82 (SE=0.011)	0.874 (0.77 to 0.99)	0.037	0.69 (SE=0.031)
Model 3	0.805 (0.74 to 0.88)	<0.001	0.82 (SE=0.012)	0.859 (0.76 to 0.97)	0.018	0.69 (SE=0.031)
Model 4	0.814 (0.75 to 0.89)	<0.001	0.82 (SE=0.012)	0.882 (0.78 to 1.00)	0.05	0.69 (SE=0.031)
Model 5	0.848 (0.78 to 0.92)†	<0.001	0.81 (SE=0.012)	0.849 (0.75 to 0.96)	0.011	0.69 (SE=0.031)
Model 6	0.786 (0.72 to 0.86)†	<0.001	0.82 (SE=0.011)	0.868 (0.76 to 0.99)	0.028	0.69 (SE=0.031)
Model 7	0.794 (0.73 to 0.87)	<0.001	0.82 (SE=0.012)	0.877 (0.77 to 1.00)	0.043	0.69 (SE=0.031)
Model 8	0.796 (0.73 to 0.87)	<0.001	0.82 (SE=0.012)	0.912 (0.80 to 1.04)	0.157	0.69 (SE=0.031)
<b>Women (n=24 703)</b>						
	<b>93 events</b>			<b>55 deaths</b>		
Model 1	0.906 (0.78 to 1.05)‡	0.187	0.77 (SE=0.02)	0.973 (0.81 to 1.17)	0.773	0.77 (SE=0.032)
Model 2	0.776 (0.66 to 0.91)	0.001	0.78 (SE=0.018)	0.992 (0.82 to 1.20)	0.931	0.77 (SE=0.032)
Model 3	0.805 (0.69 to 0.94)	0.006	0.78 (SE=0.018)	0.970 (0.80 to 1.18)	0.753	0.77 (SE=0.032)
Model 4	0.814 (0.70 to 0.95)	0.008	0.78 (SE=0.018)	0.986 (0.81 to 1.19)	0.888	0.77 (SE=0.032)
Model 5	0.916 (0.79 to 1.06)‡	0.246	0.77 (SE=0.020)	0.943 (0.78 to 1.14)	0.549	0.77 (SE=0.032)
Model 6	0.793 (0.68 to 0.93)	0.003	0.79 (SE=0.018)	0.994 (0.82 to 1.20)	0.953	0.77 (SE=0.032)
Model 7	0.742 (0.63 to 0.87)	<0.001	0.79 (SE=0.017)	0.885 (0.73 to 1.08)†	0.225	0.77 (SE=0.032)
Model 8	0.705 (0.60 to 0.83)†	<0.001	0.79 (SE=0.017)	0.886 (0.73 to 1.08)†	0.23	0.77 (SE=0.032)
<b>Age ≤50 (n=47 018)</b>						
	<b>120 events</b>			<b>64 deaths</b>		
Model 1	0.735 (0.64 to 0.84)‡	<0.001	0.66 (SE=0.026)	0.846 (0.71 to 1.01)	0.065	0.62 (SE=0.037)
Model 2	0.641 (0.56 to 0.74)	<0.001	0.70 (SE=0.024)	0.825 (0.69 to 0.99)	0.034	0.62 (SE=0.036)
Model 3	0.640 (0.55 to 0.74)	<0.001	0.71 (SE=0.024)	0.809 (0.68 to 0.97)	0.02	0.62 (SE=0.037)
Model 4	0.651 (0.56 to 0.75)	<0.001	0.70 (SE=0.024)	0.817 (0.68 to 0.98)	0.026	0.62 (SE=0.036)
Model 5	0.763 (0.67 to 0.87)	<0.001	0.66 (SE=0.027)	0.832 (0.70 to 0.99)	0.041	0.63 (SE=0.037)
Model 6	0.621 (0.54 to 0.72)	<0.001	0.71 (SE=0.023)	0.811 (0.68 to 0.97)	0.022	0.62 (SE=0.035)
Model 7	0.579 (0.50 to 0.67)‡	<0.001	0.73 (SE=0.022)	0.770 (0.64 to 0.92)	0.005	0.63 (SE=0.037)
Model 8	0.565 (0.48 to 0.66)‡	<0.001	0.73 (SE=0.021)	0.807 (0.67 to 0.97)	0.02	0.62 (SE=0.035)

Continued

**Table 3** Continued

**B: HR (95% CI) per quintile and concordance for CVD risk and all-cause mortality for models 1–8 in the restricted sample (n=63 380)**

	CVD risk			All-cause mortality		
	HR (95% CI)	P value trend	Concordance	HR (95% CI)	P value trend	Concordance
<b>Age &gt;50 (n=16 362)</b>						
	<b>271 events</b>			<b>121 deaths</b>		
Model 1	0.806 (0.74 to 0.88)	<0.001	0.66 (SE=0.019)	0.815 (0.71 to 0.93)	0.002	0.60 (SE=0.032)
Model 2	0.789 (0.72 to 0.86)	<0.001	0.66 (SE=0.018)	0.856 (0.75 to 0.98)	0.019	0.57 (SE=0.032)
Model 3	0.792 (0.73 to 0.87)	<0.001	0.66 (SE=0.018)	0.838 (0.74 to 0.96)	0.008	0.58 (SE=0.032)
Model 4	0.799 (0.73 to 0.87)	<0.001	0.66 (SE=0.018)	0.865 (0.76 to 0.98)	0.028	0.57 (SE=0.031)
Model 5	0.823 (0.76 to 0.90)	<0.001	0.66 (SE=0.018)	0.819 (0.72 to 0.93)	0.003	0.59 (SE=0.03)
Model 6	0.779 (0.71 to 0.85)	<0.001	0.66 (SE=0.019)	0.856 (0.75 to 0.98)	0.02	0.57 (SE=0.032)
Model 7	0.780 (0.71 to 0.85)	<0.001	0.66 (SE=0.018)	0.833 (0.73 to 0.95)	0.006	0.58 (SE=0.031)
Model 8	0.782 (0.72 to 0.85)	<0.001	0.66 (SE=0.018)	0.852 (0.75 to 0.97)	0.016	0.57 (SE=0.031)

P value trend &lt;0.001 for all values.

 \*Sign. difference ( $p < 0.01$ ) from model 2 ( $\text{mL}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$ ).

 †Trend ( $p < 0.05$ ) from model 2.

 ‡Sign. difference ( $p < 0.007$ ) from model 2 ( $\text{mL}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$ ).

CVD, cardiovascular disease.

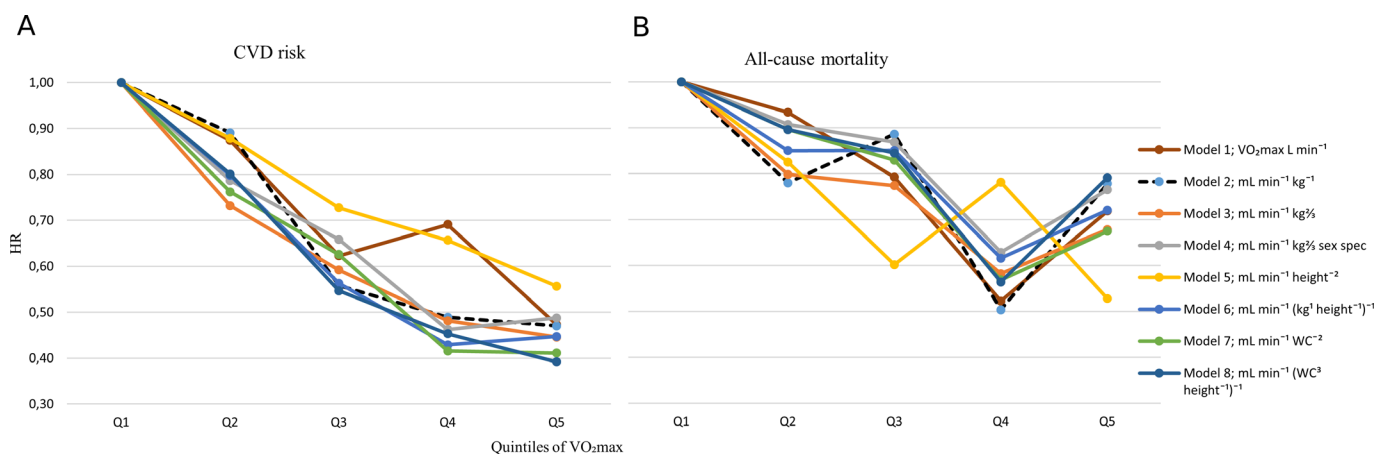
quintiles of  $\text{VO}_2\text{max}$  ( $p < 0.001$ ) (figure 2A,B). For CVD risk, model 5 ( $\text{mL}\cdot\text{min}\cdot\text{height}^{-2}$ ) had a significantly weaker association with increasing quintiles compared with model 2 ( $\text{mL}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$ ) for the whole sample ( $p = 0.0009$ ), and women ( $p = 0.001$ ). Model 1 ( $\text{L}\cdot\text{min}^{-1}$ ) had a significantly weaker association compared with model 2 ( $\text{mL}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$ ) for women ( $p = 0.003$ ) and those under 50 ( $p = 0.002$ ), and a trend towards a significantly weaker association in the whole sample ( $p = 0.025$ ) (table 3B). Model 5 showed a trend of a significantly weaker association ( $p = 0.031$ ) for men. There was a significantly stronger association to CVD risk for model 7 ( $\text{mL}\cdot\text{min}^{-1}\cdot\text{WC}^{-2}$ ) and model 8 ( $\text{mL}\cdot\text{min}^{-1}\cdot(\text{WC}^3\cdot\text{height}^{-1})^{-1}$ ) compared with model 2 for those under

50 ( $p = 0.002$  for both models) and a trend for women ( $p = 0.033$ ) for model 8.

For all-cause mortality, model 2 did not differ significantly from any of the other models (table 3B and figure 2). There was a trend towards a significantly stronger association for model 7 ( $\text{mL}\cdot\text{min}^{-1}\cdot\text{WC}^{-2}$ ) and model 8 ( $\text{mL}\cdot\text{min}^{-1}\cdot(\text{WC}^3\cdot\text{height}^{-1})^{-1}$ ) compared with model 2 for all-cause mortality in women ( $p = 0.012$ ;  $p = 0.033$ ).

## DISCUSSION

The main findings in this study are that all models of  $\text{VO}_2\text{max}$  scaled to different body measurements, both in the full sample and in the restricted sample, are



**Figure 2** HRs for CVD risk (left) and all-cause mortality (right) per quintile for models 1–8 in the restricted sample (n=63 380). CVD, cardiovascular disease;  $\text{VO}_2\text{max}$ , maximal oxygen consumption.

associated with lower CVD risk and all-cause mortality. In the full sample analyses, model 1 ( $\text{L}\cdot\text{min}^{-1}$ ) and model 5 ( $\text{mL}\cdot\text{min}^{-1}\cdot\text{height}^{-2}$ ) had less steep risk associations per increased deciles compared with reference model 2 ( $\text{mL}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$ ) for both CVD risk and all-cause mortality. This was seen in all subgroups for CVD risk, and in men and in those younger than 50 years for all-cause mortality. In the restricted sample, including scaling models with WC, there was an additional trend towards a significantly stronger association for model 7 ( $\text{mL}\cdot\text{min}^{-1}\cdot\text{WC}^{-2}$ ) and model 8 ( $\text{mL}\cdot\text{min}^{-1}\cdot(\text{WC}^3\cdot\text{height}^{-1})^{-1}$ ) in some subgroups for CVD risk and all-cause mortality.

Our results show that all the models examined here, except for model 1 and 5 that had a weaker association, and models 7 and 8 that partly had a trend of a stronger association, showed small differences in associations to CVD risk and all-cause mortality as compared with model 2 even if some p values were significant. That model 1 ( $\text{L}\cdot\text{min}^{-1}$ ) generally showed a weaker association to CVD and all-cause mortality is understandable as no body measurements were included in the model. The continual lack of agreement in the literature as to which body mass exponent is best for power function scaling of  $\text{VO}_2\text{max}$  has fuelled the continued use of the simple ratio scaling of  $\text{VO}_2\text{max}$  ( $\text{mL}\cdot\text{min}^{-1}\cdot\text{kg}$ ) which can almost be considered a criterion method. In spite of this lack of agreement, we used  $\text{mL}\cdot\text{min}^{-1}\cdot\text{kg}$  as the criterion method to compare the other models with. Surprisingly our results partly confirm that the simple ratio scaling may be adequate to use in spite of it not adhering to the dimensional theory. This is contrary to Heil and others<sup>7 8 21–23</sup> who suggest that the use of the simple ratio scaling of  $\text{VO}_2\text{peak}$  values should be discontinued in favour of body mass power exponents to powers between 0.65 and 0.75. However, our study concerns the use of different models of scaling in association to incidence of CVD and all-cause mortality, whereas most previous studies have studied performance-related aspects of cardiorespiratory fitness.<sup>24 25</sup> This could account for the small, if significant, differences between the models in this study as  $\text{VO}_2\text{max}$  levels are known to be associated to incidence of CVD and all-cause mortality.<sup>2 26</sup> Thus just including  $\text{VO}_2\text{max}$  in all the models may be enough to counteract the effect of the different body measurements in the models, including the traditional ratio scaling. However, this does not explain why model 5 ( $\text{mL}\cdot\text{min}^{-1}\cdot\text{height}^{-2}$ ) generally showed a weaker association to CVD incidence and all-cause mortality rate compared with model 2. The many different viable scaling exponents that have been reported in the literature concerning allometric scaling could also be due to the small sample sizes used in these studies.<sup>9 24 25</sup> The large sample size in our study could therefore be another reason for not finding similar differences.

Two previous studies have evaluated different scaling models in association with health-related aspects. Imboden *et al* showed a similar inverse relationship between  $\text{VO}_2\text{peak}$  and CVD risk as well as all-cause

mortality scaled to both total body mass and fat-free mass, but with a stronger relationship when normalising to fat-free mass rather than total body mass for all-cause mortality.<sup>13</sup> Unfortunately, we were not able to include scaling to fat-free mass as a model as we had no data for it. Fat-free mass is also a more difficult measurement to obtain than, for example, WC in most clinical environments. It might be calculated using weight and height measurements, however, with low validity. The possible added explanation of fat-free mass as a body measure for scaling of  $\text{VO}_2\text{max}$  should be evaluated in future studies.

The findings of less steep CVD risk association of model 5 ( $\text{mL}\cdot\text{min}^{-1}\cdot\text{height}^{-2}$ ) and a trend of more steep CVD risk association of model 7 ( $\text{mL}\cdot\text{min}^{-1}\cdot\text{WC}^{-2}$ ) and 8 ( $\text{mL}\cdot\text{min}^{-1}\cdot(\text{WC}^3\cdot\text{height}^{-1})^{-1}$ ) should be further discussed. Model 5 was the only model that included only height as a body measurement. Evidently, this did not discriminate individuals as powerfully as when including measurements of either body mass or WC for CVD risk assessment, which in turn might indicate (abdominal) overweight or obesity. Previous research has shown that both cardiorespiratory fitness and body fatness are strongly associated to CVD risk as well as all-cause mortality,<sup>2 12 27 28</sup> where those being obese and unfit are most at risk.<sup>29</sup> This implies that including both these measurements may be of importance to further discriminate individuals for CVD risk. The present analyses included only 391 CVD cases in the restricted sample analyses (0.6% of total n), and hence inclusion of more CVD cases in future analyses may provide significant associations.

### Strengths and weaknesses

A strength of this study is the sample size. Previous studies may have shown more diverging results due to the small samples they used. The heterogeneity of our sample is also a strength as it mirrors a normal population. A potential weakness is that the cohort may be slightly selective, as participation in the HPA was voluntary. However, the size and diversity of the cohort would weaken any selectivity, as well as the similarity of  $\text{VO}_2\text{max}$  levels to other population studies conducted in Sweden.<sup>16</sup> Another possible weakness is that  $\text{VO}_2\text{max}$  was estimated using the standardised submaximal Åstrand cycle ergometer test. It would not, however, have been feasible to measure  $\text{VO}_2\text{max}$  directly in this large and mainly non-athletic population.

A further limitation is that the association between  $\text{VO}_{2\text{max}}$  and incidence of CVD and all-cause mortality risk is dependent on many other risk factors such as obesity, dyslipidaemia, hypertension. We chose to only include age and sex as we had a limited amount of other risk factors in our data.

### CONCLUSIONS

In spite of the simple ratio scaling of  $\text{VO}_2\text{max}$  to body mass not following the dimensional theory, our results showed that it was associated to CVD and all-cause



mortality in a similar way to the other models where varying body dimensions were added to comply with the dimensional theory. However, including only height as a body measurement for scaling showed a weaker association to CVD risk compared with the criterion model 2 ( $\text{mL}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$ ). Inclusion of WC as body measurement for scaling showed a tendency for a stronger association to CVD risk in comparison to model 2. In times of low physical activity and  $\text{VO}_2\text{max}$  in the general population,<sup>30</sup> which may potentially accelerate vulnerability for chronic disease, it is highly clinically relevant to evaluate activity levels and  $\text{VO}_2\text{max}$ . The present study adds new important knowledge of how clinical practices may consider intra-individual size differences in  $\text{VO}_2\text{max}$  for association to CVD incidence and all-cause mortality. However, future studies with different outcomes are required to clarify this further.

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**Data availability statement** Data are available on reasonable request. Data are deidentified participant data. Available from Elin. EkblomBak@gih.se on reasonable request.

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