RESEARCH ARTICLE

Cardio-Respiratory Reference Data in 4631 Healthy Men and Women 20-90 Years: The HUNT 3 Fitness Study

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Abstract

Purpose: To provide a large reference material on key cardio-respiratory variables in a healthy population of Norwegian men and women aged 20–90 years.

Methods: Sub maximal and peak levels of cardio-respiratory variables were measured using cardiopulmonary exercise testing during treadmill running.

Results: The highest peak ventilation among men (141.9 ± 24.5 L·min^{-1}) and women (92.0 ± 16.5 L·min^{-1}) was observed in the youngest age group (20–29 years, sex differences $p < 0.001$) with an average 7% reduction per decade. The highest tidal volumes were observed in the 30–39 and 40–49 year age groups among men (2.94 ± 0.46 L) and women (2.06 ± 0.32 L) (sex differences $p < 0.001$), with a subsequent average 6% reduction per decade. Ventilatory threshold and respiratory compensation point were observed at approximately 77% and 87% of peak oxygen uptake (VO_{2peak}) among men and women, respectively. The best ventilatory efficiency ($EqVCO_{2Than}$) was observed in the youngest age group (20–29 years) in both men (26.2 ± 2.8) and woman (27.5 ± 2.7) (sex differences $p < 0.001$) with an average 3% deterioration in ventilatory efficiency per decade.

Conclusion: This is the largest European reference material of cardio-respiratory variables in healthy men and women aged 20–90 years, establishing normal values for, and associations between key cardio-respiratory parameters. This will be useful in clinical decision making when evaluating cardiopulmonary health in similar populations.

Introduction

Cardiopulmonary exercise testing (CPET) is an underutilized clinical procedure [1], despite several published recommendations by international health organizations [2–5]. It is a good tool for evaluating mechanisms and limitations of exercise tolerance [6], and for the assessment of cardiopulmonary health [1]. Consequently, CPET is a valuable tool in clinical decision making [2]. There are numerous large studies establishing spirometry reference values [7–14]. However, studies containing a combination of principal cardio- respiratory variables, such as ventilation (V_E), tidal volume (V_T), breathing frequency (f_B), oxygen uptake (VO_2), expired carbon dioxide (VCO_2) and ventilatory efficiency ($EqVCO_2$) are limited. Previous research have included only a few of these key variables, are limited to selected age groups and fitness levels, or small populations e.g. [15–25]. The aim of this study was to establish a large reference material on submaximal and maximal cardiopulmonary variables in healthy men and women aged 20–90 years.

Methods

Participants

The HUNT 3 fitness study is the third wave of the Nord-Trøndelag Health Studies (ntnu.edu/hunt). Data were collected between October 2006 and June 2008. The entire population >20 years of age (n=94194) were invited to participate, 54% (n=50821) accepted. Eligible candidates had to be free from cardiovascular disease, respiratory symptoms, cancer, and the use of blood pressure medication. Based upon self-reported information, 30513 candidates presented as suitable for VO_{2max} testing. Out of these, 12609 candidates resided in the 3 municipals selected for VO_{2max} testing, and 5633 of them volunteered to participate. Subsequent the primary inclusion the medical interview excluded an additional 390 candidates not meeting medical inclusion criteria, leaving 5243 candidates. 4631candidates completed a VO_{2peak} test. These 3 locations were chosen due to geographical location to minimize travel distance for participants. We experienced technical difficulties with Cortex MetaMax Π, and during service at Cortex data was lost, thus, total sample sizes on tidal volume (V_T) and breathing frequency (f_B) was n=3667.

Ethics statement

The study was approved by the Regional committee for medical research ethics (2012/1672/REK nord), the Norwegian Data Inspectorate and the National Directorate of Health, and is in compliance with the Helsinki declaration. Written informed consent was obtained from all participants.

Cardio Pulmonary Exercise Test (CPET)

An individualized graded protocol [26] was used for measuring cardio-respiratory variables (Cortex MetaMax Π, Cortex, Leipzig, Germany). Before starting the testing procedure several MetaMax II apparatus were tested against Douglas-bag and iron lung (Cortex, Leipzig, Germany) and those finally used found reliable and valid [27]. Speed and angle of the test treadmills were calibrated prior to testing. The MetaMax II was calibrated prior to the first test each day using a standard two-point gas calibration procedure. The calibration included measurements of ambient air and a gas mix of known content (15.03% O_2 and 4.98% CO_2 in N_2), a calibration of the Triple-V volume transducer with a calibrated 3 L syringe (Calibration syringe D, SensorMedics, CareFusion, San Diego, CA, USA), and barometric pressure control. Volume calibration was performed every third test and the two-point gas calibration every fifth. Before each test the ambient room air was checked. Heart rate was measured by radio telemetry (Polar S610i, Polar Electro Oy, Kempele, Finland). Body mass was measured using the weighing scale Model DS-102 (Arctic Heating AS, Nøtterøy, Norway). Participants had a treadmill familiarization phase of 8–10 minutes during warm-up. They were instructed to avoid grabbing the handrails if not absolutely necessary. The individualized warm-up workload determined the initial speed/angle on the subsequent treadmill test. Candidates used a face mask (Hans Rudolph, Germany) of appropriate size linked to the MetaMax Π. When participant maintained a stable oxygen uptake >30seconds, velocity (0.5–1.0 kmh-1) or inclination (1–2%) was increased. Increased workload was if possible obtained with increased speed and keeping a fixed slope angle of the treadmill. If a participant was unable to increase speed, the angle was increased. Tests were ended when candidates reached volitional exhaustion (e.g. shortness of breath and leg fatigue). VO_{2max} was considered achieved if subjects reached a VO_2 plateau that remained stable even with increased work load [28], i.e. VO_2 did not increase more than 2 $mL\cdot kg^{-1}\cdot min^{-1}$ despite increased work load, and R≥1.05. Since 12.6% of the subjects failed to reach VO_{2max} we used the expression VO_{2peak}. Measurements were done at 3 different workloads, 2 submaximal and peak. Level 1: The individual initial workload was determined during warm-up, and stable VO_2 and heart rate were reached after 3 minutes. Level 2: Treadmill gradient was increased by 2% or speed increased 1 $km\cdot h^{-1}$, with steady state obtained after 2–3 minutes. Peak workload is described above.

Ventilatory anaerobic threshold (V_{Than}) and respiratory compensation point (RCP)

The transition point from aerobic to anaerobic metabolism denotes V_{Than} [29]. With increasing workload aerobic metabolism alone cannot provide the energy required, and energy production must increasingly depend upon anaerobic metabolism [30]. RCP marks the respiratory compensation for metabolic acidosis, beneath which V_E is strongly linked to VCO_2, whereas above V_E increases faster

relative to VCO_2 [31], hence, onset of hyperventilation [32]. Both V_{THan} and RCP were established by the V-slope method [31].

Ventilatory efficiency

We calculated the ventilatory equivalent $EqVO_2$ ($V_E \cdot VO_2^{-1}$) and $EqVCO_2$ ($V_E \cdot VCO_2^{-1}$) at VO_{2peak} and V_{Than}. The ventilatory equivalents describe the fraction of minute ventilation (V_E) to oxygen uptake (VO_2), or to expired carbon dioxide (VCO_2).

Statistical analysis

Parametric analysis was used and QQ-plots supported the assumption of normally distributed data. Data are presented as arithmetic mean $\pm$ standard deviation. Analysis of variance (Anova) was used to determine differences between age groups. If a significant F-ratio was achieved, post hoc evaluations were completed using Bonferroni tests. An Independent-Samples T-test was used for establishing level of significance between sexes. Linear regression and curve linear regression, with 95% confidence interval, were used to test associations between cardio-respiratory parameters. Multiple linear regressions were used to generate prediction models. All statistical tests were two-sided. SPSS 20.0 (Statistical package for Social Sciences, Chicago; Illinois, USA), and GraphPad Prism 4.01 (GraphPad Software, San Diego, California, USA) were used to analyze data. Correlations were done using data from Level 1, Level 2 and peak as described above. A p-value of <0.05 was considered statistically significant.

Results

Descriptive characteristics for men and women are presented in Table 1.

Peak ventilation (V_{Epeak}) and tidal volume (V_{Tpeak})

Women had a 34% ($p<0.001$) lower V_{Epeak} than men. V_{Epeak} was similar and highest in the two youngest age groups (20–29 and 30–39 years) in both men and women. In women V_{Epeak} became 8% ($p<0.01$) lower per decade from age 30–39 up to 60–69 years. Compared to men aged 20–39 years, men aged 40–49 years had 3.5% ($p<0.05$) lower V_{Epeak}, whereupon it decreased by 9% ($p<0.001$) per decade up to those aged 60–69 years. For both sexes we observed an average 16% ($p<0.001$) lower V_{Epeak} between the 2 most senior age groups (60–69 vs. +70 years) (Table 2).

Women had approximately 32% ($p<0.001$) lower V_{Tpeak} than men. For both sexes the highest V_{Tpeak} was found among those aged 30–49 years, despite no differences in stature compared to the youngest age groups. In both sexes we observed an average 4% ($p<0.05$) and 11% ($p<0.001$) drop in V_{Tpeak} per decade in age groups 40–69 years, and between the 2 most senior age groups, respectively

Table 1. Descriptive data for men and women in the HUNT 3 fitness study.

	Men	Women
	(n=2261)	(n=2370)
Age (yr.)	48.9 ± 13.5	48.0 ± 13.7
Anthropometrical data		
Height (cm)	179.2 ± 6.5	165.9 ± 5.9
Weight (kg)	85.6 ± 11.5	69.8 ± 11.2
BMI (kg•m^{-2})	26.6 ± 3.2	25.4 ± 3.9
Smoking status		
Never smoked/Quit smoking (%)	50.9/27.5	49.1/27.4
Daily smoker/Occasional smoker (%)	10.1/11.5	13.1/10.4

Data are presented as arithmetic mean ± SD. BMI: bod mass index.

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(Table 2). The highest breathing frequency (f_B) in both men and women, 50 ± 9 breaths·min^{-1} and 47 ± 7 breaths·min^{-1}, respectively, was found in the youngest age group (20–29 years), with an average 5% ($p < 0.05$) decrease per subsequent decade (Table 2).

Stratified by height an 11% ($p < 0.01$) rise in V_{Epeak} and V_{Tpeak} was observed per 10 cm increased height, in both sexes (Table 3).

Carbon dioxide (VCO_2) elimination

Women displayed roughly 34% ($p < 0.001$) lower VCO_{2peak} than men. Stratified by age the highest VCO_{2peak} was found in the youngest age groups. No significant differences in VCO_{2peak} were observed neither for men nor women between age groups 20–29 and 30–39 years, whereupon an approximate 6% ($p < 0.001$) and 5% ($p < 0.001$) decrease was observed between age groups 30–39 vs. 40–49 years, respectively. In subsequent age groups exponential reductions were observed, ending with an average 18% ($p < 0.001$) lower peak VCO_2 in the most senior age group compared with men and women aged 60–69 years (Table 2).

Ventilatory anaerobic threshold (V_{Than})

The highest V_{Than} was observed in the youngest age groups. No statistical differences in V_{Than} was observed between the 3 youngest age groups (20–49 years) among both sexes, whereupon we observed an approximate 10% ($p < 0.001$) lower V_{Than} per decade. V_{Than} was obtained at 75.2 ± 10.7 and $76.7 \pm 9.4\%$ of VO_{2peak} for men and women (20–29 years), respectively, which corresponds to approximately $88 \pm 7\%$ of peak heart rate (f_{cpeak}), with no major differences between age groups (Table 4).

Table 2. Physiological cardio-respiratory variables in the HUNT 3 Fitness study stratified by intensity levels, sex and age groups.

	Level 1 ($<V_{Than}$)		Level 2 ($<RCP$)		Peak	
	Men	Women	Men	Women	Men	Women
All	(n=999)	(n=1020)	(n=921)	(n=99)	(n=1758)	(n = 1754)
Workload (Watts)	99.2±24.2	68.6±19.0	115.1±24.8	81.7±19.9	177.2±37.0	119.0±25.0
f_c (beats·min^{-1})	141±19	149±19	153±19	160±18	180±16	179±15
%f_{cpeak}	78.8±8.0	83.3±7.5	85.6±7.3	89.6±6.5		
%VO_{2peak}	67.5±11.2	72.4±10.6	74.9±10.7	79.8±9.9		
f_B (1·min^{-1})	26±5.2	28±5	30±6	31±6	44±8	42±8
V_E (L·min^{-1})	60.8±14.6	45.1±10.7	73.7±19.6	54.6±14.2	123.7±25.7	81.8±17.6
V_T ($V_E·f_B^{-1}$)	2.32±0.46	1.61±0.32	2.51±0.47	1.76±0.33	2.84±0.49	1.94±0.33
VCO_2 (L·min^{-1})	2.14±0.50	1.54±0.36	2.54±0.58	1.82±0.41	4.22±0.92	2.76±0.62
VO_2 (L·min^{-1})	2.46±0.56	1.77±0.38	2.78±0.61	1.98±0.42	3.74±0.76	2.47±0.51
R ($CO_2·VO_2^{-1}$)	0.89±0.06	0.88±0.06	0.94±0.08	0.95±0.08	1.12±0.07	1.11±0.08
BMI	26.6±3.2	25.4±3.9				
20–29 years						
	(n=80)	(n=77)	(n=66)	(n=66)	(n=152)	(n = 160)
Workload (Watts)	109.5±24.0	78.1±15.0	125.5±22.9	90.9±13.3	197.2±40.2	126.3±24.4
f_c (beats·min^{-1})	158±20	164±20	172±14	176±16	196±11	194±9
%f_{cpeak}	80.8±8.8	85.0±8.3	87.8±5.4	0.7±6.5		
%VO_{2peak}	64.5±12.5	68.3±10.9	73.1±10.7	6.3±9.6		
f_B (1·min^{-1})	29±6	30±5	32±6	34±7	50±9	47±7
V_E (L·min^{-1})	61.3±15.7	45.4±10.8	75.1±19.3	57.9±15.9	141.9±24.5	92.0±16.5
V_T ($V_E·f_B^{-1}$)	2.14±0.41	1.53±0.31	2.39±0.46	1.73±0.31	2.84±0.52	1.91±0.31
VCO_2 (L·min^{-1})	2.31±0.60	1.62±0.39	2.87±0.66	1.98±0.40	4.94±0.87	3.17±0.57
VO_2 (L·min^{-1})	2.72±0.67	1.92±0.42	3.16±0.72	2.20±0.41	4.30±0.73	2.77±0.47
R ($CO_2·VO_2^{-1}$)	0.90±0.06	0.89±0.06	0.96±0.05	0.97±0.08	1.15±0.06	1.14±0.06
BMI	24.2±3.1	23.9±3.9				
30–39 years						
	(n=137)	(n=191)	(n=129)	(n=167)	(n=280)	(n=326)
Workload (Watts)	109.3±21.9	76.7±16.9	123.1±22.0	90.9±19.3	196.8±32.6	127.4±23.9
f_c (beats·min^{-1})	149±17	157±17	163±16	169±16	190±9	188±11
%f_{cpeak}	78.9±7.4	83.3±6.9	86.0±6.4	90.3±5.8		
%VO_{2peak}	62.1±10.1	69.1±10.1	71.0±10.1	78.1±9.9		
f_B (1·min^{-1})	26±5	29±5	30±7	32±6	47±8	45±7
V_E (L·min^{-1})	61.7±15.3	47.3±12.2	76.4±20.1	58.6±15.3	136.8±21.5	91.5±15.5
V_T ($V_E·f_B^{-1}$)	2.36±0.45	1.66±0.35	2.56±0.45	1.82±0.35	2.94±0.46	2.06±0.32
VCO_2 (L·min^{-1})	2.31±0.53	1.66±0.40	2.75±0.54	1.98±0.42	4.82±0.75	3.13±0.57
VO_2 (L·min^{-1})	2.63±0.52	1.91±0.40	2.98±0.52	2.16±0.44	4.20±0.65	2.74±0.50
R ($CO_2·VO_2^{-1}$)	0.89±0.06	0.88±0.06	0.95±0.08	0.96±0.08	1.14±0.06	1.14±0.06
BMI	27.3±3.5	25.2±4.0				
40–49 years						
	(n=267)	(n=258)	(n=253)	(n=240)	(n=469)	(n=441)
Workload (Watts)	106.2±21.5	74.2±15.1	123.0±21.8	87.7±16.0	187.5±32.9	124.2±22.5
f_c (beats·min^{-1})	144±18	151±16	157±18	163±15	183±12	182±11
%f_{cpeak}	78.6±7.7	83.1±7.1	85.7±7.3	90.0±6.0		

Table 2. Cont.

	Level 1 (<V_{Than})		Level 2 (<RCP)		Peak	
	Men	**Women**	**Men**	**Women**	**Men**	**Women**
%VO_{2peak}	65.6±10.5	70.1±10.3	74.0±10.2	78.8±9.8		
f_B (1·min^{-1})	27±5	29±5	30±7	32±6	44±8	44±8
V_E (L·min^{-1})	63.1±14.8	47.3±10.1	78.1±21.0	58.3±13.7	132.0±22.1	87.7±14.8
V_T (V_E·f_B^{-1})	2.41±0.46	1.67±0.30	2.63±0.47	1.83±0.31	2.97±0.49	2.02±0.31
VCO_2 (L·min^{-1})	2.26±0.45	1.62±0.34	2.70±0.51	1.95±0.41	4.54±0.73	2.96±0.53
VO_2 (L·min^{-1})	2.62±0.56	1.85±0.35	2.97±0.59	2.10±0.39	4.00±0.62	2.62±0.44
R (CO_2·VO_2^{-1})	0.89±0.05	0.88±0.06	0.95±0.07	0.95±0.08	1.13±0.06	1.13±0.07
BMI	26.8±3.3	25.5±3.9				
50–59 years						
	(n=246)	(n=267)	(n=227)	(n=230)	(n=441)	(n=444)
Workload (Watts)	98.8±19.9	66.8±17.5	116.5±21.2	79.1±18.2	171.4±28.5	116.7±23.0
f_c (beats·min^{-1})	139±16	145±16	151±16	156±15	176±13	176±11
%f_{cpeak}	78.3±7.7	82.2±7.1	85.2±7.3	88.4±6.4		
%VO_{2peak}	67.9±10.6	72.3±10.2	75.6±10.4	80.6±9.6		
f_B (1·min^{-1})	26±5	28±5	29±6	30±6	42±8	40±7
V_E (L·min^{-1})	62.0±14.4	44.3±9.9	75.0±18.5	52.6±13.2	118.7±21.6	77.2±14.0
V_T (V_E·f_B^{-1})	2.40±0.45	1.61±0.30	2.58±0.45	1.74±0.31	2.83±0.45	1.92±0.30
VCO_2 (L·min^{-1})	2.17±0.46	1.50±0.32	2.57±0.52	1.75±0.34	4.05±0.71	2.60±0.46
VO_2 (L·min^{-1})	2.46±0.48	1.72±0.31	2.78±0.52	1.90±0.33	3.61±0.60	2.35±0.38
R (CO_2·VO_2^{-1})	0.90±0.06	0.88±0.08	0.95±0.07	0.94±0.08	1.12±0.07	1.11±0.07
BMI	27.3±3.1	25.9±3.6				
60–69 years						
	(n=203)	(n=167)	(n=186)	(n=144)	(n=313)	(n=284)
Workload (Watts)	87.4±20.5	57.3±17.4	103.9±21.1	70.1±18.4	157.7±32.7	108.6±23.4
f_c (beats·min^{-1})	131±16	140±19	143±17	150±18	169±14	168±13
%f_{cpeak}	77.9±8.5	83.8±8.4	84.6±8.0	89.3±7.5		
%VO_{2peak}	68.4±11.1	74.2±9.7	76.5±11.0	81.5±9.1		
f_B (1·min^{-1})	26±5	28±5	29±6	30±5	41±7	38±6
V_E (L·min^{-1})	58.5±13.8	42.9±10.0	68.8±16.3	49.4±11.1	109.0±20.7	70.0±12.5
V_T (V_E·f_B^{-1})	2.27±0.46	1.57±0.31	2.42±0.43	1.68±0.33	2.70±0.47	1.85±0.30
VCO_2 (L·min^{-1})	1.95±0.43	1.43±0.31	2.26±0.49	1.65±0.35	3.57±0.68	2.32±0.42
VO_2 (L·min^{-1})	2.24±0.45	1.62±0.32	2.49±0.48	1.77±0.32	3.23±0.57	2.14±0.36
R (CO_2·VO_2^{-1})	0.88±0.05	0.88±0.06	0.93±0.09	0.93±0.10	1.10±0.07	1.08±0.08
BMI	26.9±2.9	26.2±3.7				
+70 years						
	(n=66)	(n=60)	(n=60)	(n=52)	(n=103)	(n=99)
Workload (Watts)	67.3±25.2	42.5±18.4	83.4±26.9	57.3±18.6	133.8±32.2	94.6±25.6
f_c (beats·min^{-1})	127±14	133±18	136±18	145±20	158±17	158±19
%f_{cpeak}	80.9±7.7	84.2±7.2	86.2±8.0	90.0±7.7		
%VO_{2peak}	70.4±10.9	74.4±9.9	77.6±11.0	81.4±9.1		
f_B (1·min^{-1})	26±5	28±5	28±6	30±5	37±7	36±5
V_E (L·min^{-1})	52.2±14.4	37.8±8.4	60.1±17.1	43.7±10.6	90.7±21.0	58.7±16.5
V_T (V_E·f_B^{-1})	2.01±0.39	1.37±0.25	2.14±0.42	1.47±0.28	2.46±0.38	1.62±0.41

Table 2. Cont.

	Level 1 ($<V_{Than}$)		Level 2 ($<$RCP)		Peak	
	Men	**Women**	**Men**	**Women**	**Men**	**Women**
VCO_2 (L·min^{-1})	1.64±0.43	1.19±0.25	1.92±0.50	1.38±0.32	2.90±0.67	1.89±0.42
VO_2 (L·min^{-1})	1.91±0.44	1.39±0.29	2.14±0.50	1.52±0.32	2.71±0.56	1.80±0.36
R (CO_2·VO_2^{-1})	0.88±0.06	0.88±0.05	0.92±0.06	0.93±0.08	1.06±0.08	1.04±0.07
BMI	26.0±2.7	26.2±3.9				

Data are presented as arithmetic mean ± SD. Workload: treadmill exercise load, fc: cardiac frequency, fB: breathing frequency, VE: minute ventilation, VT: tidal volume, VCO2: expired carbon dioxcide, VO2: oxygen uptake, R: respiratory exchange ratio, BMI: body mass index, VThan: ventilatory anaerobic threshold, RCP: respiratory compensation point.

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Respiratory compensation point (RCP)

The highest RCP was observed in the youngest age groups with roughly the same decline rate per decade as observed for V_{Than} (Table 4).

Ventilatory efficiency at VO_{2peak} and at V_{Than}

$EqVO_{2peak}$ were similar between sexes and age groups. $EqVCO_{2peak}$ was on average 1.2% ($p<0.05$) higher in women than in men. In men aged 20–59 years no differences were observed between subsequent age groups, upon which we observed a 4.4% ($p<0.001$) higher $EqVCO_{2peak}$ for men aged 60–69 years compared to those aged 50–59 years. No differences were shown between the two oldest male age groups. In women we observed no differences in $EqVCO_{2peak}$ between subsequent age groups throughout all decades. Comparing the youngest and oldest age groups an 8% ($p<0.001$) higher $EqVCO_{2peak}$ was observed in the oldest age group, in both men and women (Table 5).

$EqVO_{2Than}$ was on average 3% ($p<0.001$) higher in women than in men. $EqVO_{2Than}$ was similar and lowest in the two youngest male age groups (20–29 and 30–39 years). We observed a 5.2% ($p<0.05$) higher $EqVO_{2Than}$ for men aged 40–49 years compared to those aged 30–39 years, with no differences between the subsequently older male age groups (40–49 through +70 years). In women no differences were observed between subsequent age groups throughout all decades. When comparing the youngest and oldest age groups a 12% ($p<0.05$) higher $EqVO_{2Than}$ was observed in the oldest age group, among both men and women (Table 5).

$EqVCO_{2Than}$ was on average 2.5% ($p<0.001$) higher in women compared to men. $EqVCO_{2Than}$ was alike and lowest in the two youngest male age groups (20–29 and 30–39 years), whereas a 4.9% ($p<0.01$) higher $EqVCO_{2Than}$ was observed in men 40–49 years compared to the 30–39 years group. No differences were found between men aged 40–49 years and 50–59 years, whereupon an average 5.3% ($p<0.05$) higher $EqVCO_{2Than}$ was observed per decade between the three oldest male age groups. In women aged 20–69 years no differences in $EqVCO_{2Than}$ was observed between subsequent age groups, upon which a 5.4% ($p<0.05$)

Table 3. Peak respiratory variables in the HUNT 3 fitness study stratified by sex and height.

	Men	Women
150–159 cm		
		(n=269)
V_E (L·min^{-1})		71.0 $\pm$ 15.8
V_T (V_E·f_B^{-1})		1.68 $\pm$ 0.29
f_B (1·min^{-1})		42 $\pm$ 8
160–169 cm		
	(n=128)	(n=1146)
V_E (L·min^{-1})	104.7 $\pm$ 22.4	81.0 $\pm$ 16.6
V_T (V_E·f_B^{-1})	2.40 $\pm$ 0.37	1.93 $\pm$ 0.30
f_B (1·min^{-1})	44 $\pm$ 9	42 $\pm$ 7
170–179 cm		
	(n=846)	(n=432)
V_E (L·min^{-1})	117.3 $\pm$ 23.8	90.1 $\pm$ 16.7
V_T (V_E·f_B^{-1})	2.71 $\pm$ 0.42	2.13 $\pm$ 0.31
f_B (1·min^{-1})	44 $\pm$ 8	42 $\pm$ 8
180–189 cm		
	(n=740)	(n=13)
V_E (L·min^{-1})	132.0 $\pm$ 23.6	92.5 $\pm$ 21.6
V_T (V_E·f_B^{-1})	3.00 $\pm$ 0.46	2.12 $\pm$ 0.61
f_B (1·min^{-1})	44 $\pm$ 8	44 $\pm$ 16
190–200 cm		
	(n=93)	
V_E (L·min^{-1})	144.7 $\pm$ 26.6	
V_T (V_E·f_B^{-1})	3.32 $\pm$ 0.50	
f_B (1·min^{-1})	43 $\pm$ 9	

Data are presented as arithmetic mean $\pm$ SD. VE: ventilation, VT: tidal volume, fB: breathing frequency.

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higher $EqVCO_{2Than}$ was observed in the oldest age group compared to those 60–69 years. Comparing the youngest and the oldest age groups showed a 16% ($p<0.001$) higher $EqVCO_{2Than}$ in the oldest group, in both men and women (Table 5).

$EqVCO_{2VThan}$, among the 3 oldest age groups, stratified by fitness quartiles

In those aged 50–59 years there was a 7.2% ($p<0.05$) and 8.2% ($p<0.001$) increase between the most fit (Q_1) and least fit (Q_4), men and women, respectively. The middle (60–69 years) and the most senior groups (+70 years) had increases of 13.4% ($p<0.001$; men) vs. 13.1% ($p<0.001$; women), and 16.4% ($p<0.01$; men) with no significant differences among women, between the fittest (Q_1) and least fit (Q_4), respectively (Table 6).

Table 4. Cardiorespiratory variables in the HUNT 3 Fitness study stratified by sex, age groups.

	N	VO_{2peak} (L·min^{-1})	VO_{2peak} (mL·kg·min^{-1})	V_{Than} (L·min^{-1})	V_{Than}(%VO_{2peak})	RCP (L·min^{-1})	RCP (%VO_{2peak})
All							
Men	1050	3.74±0.76	44.2±9.3	2.83±0.67	76.4±10.4	3.24±0.71	86.4±10.9
Women	1013	2.47±0.51	35.8±7.7	1.90±0.43	77.6±9.7	2.21±0.50	89.2±10.4
20–29 years							
Men	101	4.30 ±.73	54.0±8.8	3.20±0.75	75.2±10.7	3.59±0.69	85.6±10.3
Women	92	2.77±0.47	42.8±7.6	2.08±0.44	76.7±9.4	2.48±0.43	90.9±8.3
30–39 years							
Men	172	4.20±0.65	48.6±7.9	3.17±0.62	75.6±10.3	3.57±0.65	85.4±10.5
Women	203	2.74±0.50	39.6±7.0	2.07±0.45	75.6±9.8	2.44±0.52	88.9±12.3
40–49 years							
Men	264	4.00±0.62	46.6±8.0	3.04±0.63	76.6±11.0	3.44±0.67	85.5±11.0
Women	249	2.62±0.44	37.8±7.0	2.02±0.40	77.6±9.7	2.36±0.45	88.5±9.9
50–59 years							
Men	267	3.61±0.60	41.9±7.6	2.71±0.53	76.2±10.1	3.19±0.62	86.9±11.4
Women	259	2.35±0.38	33.7±5.7	1.82±0.36	78.2±9.4	2.12±0.42	89.1±11.2
60–69 years							
Men	182	3.23±0.57	38.4±6.9	2.48±0.49	77.5±10.1	2.85±0.54	88.4±10.8
Women	152	2.14±0.36	30.5±5.1	1.68±0.34	78.9±9.3	1.94±0.34	90.8±8.2
+70 years							
Men	64	2.71±0.56	34.2±7.1	2.05±0.48	77.4±9.8	2.37±0.49	87.4±9.6
Women	58	1.80±0.36	26.8±5.1	1.44±0.33	79.8±10.7	1.59±0.33	87.3±10.1

Data are presented as arithmetic mean ± SD. VO2peak: peak oxygen uptake, VThan: Ventilatory anaerobic threshold, RCP: respiratory compensation point.

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Estimating key cardio pulmonary parameters from non-exercise prediction models

Prediction equations for V_{Epeak}, VCO_{2peak} and V_{Than} were derived from non-exercise variables, including weight, height, age and sex. Weight and age proved negligible in predicting V_{Tpeak}, as did weight and height in predicting $EqVCO_{2VThan}$ and $EqVO_{2VThan}$, hence these variables were excluded from the respective models. For all models gender should be substituted with 1 or 2 for men and women, respectively. The final regression models are presented in table 7. Non-exercise prediction models for VO_{2peak} are previously published from the HUNT 3 fitness material [33].

Association between $EqVCO_{2VThan}$ and age

Figure 1 displays the relationship between $EqVCO_{2VThan}$ and age, with relative low, but statistical strong correlations r=0.27 (p<0.0001) and r=0.18 (p<0.001) among men and women, respectively.

Table 5. Ventilatory equivalents at peak exercise and at ventilatory anaerobic threshold in the HUNT 3 fitness study.

	Men	Women
20–29 years		
	(n=207)	(n=246)
EqVO$_{2peak}$ (V$_{Epeak}$·VO$_{2peak}$$^{-1}$)	33.2±4.1	33.5±5.0
EqVCO$_{2peak}$ (V$_{Epeak}$·VCO$_{2peak}$$^{-1}$)	29.0±3.3	29.3±4.0
	(n=69)	(n=75)
EqVO$_{2VThan}$ (V$_{EVThan}$·VO$_{2VThan}$$^{-1}$)	24.9±3.6	26.3±3.5
EqVCO$_{2VThan}$ (V$_{EVThan}$·VCO$_{2VThan}$$^{-1}$)	26.2±2.8	27.5±2.7
30–39 years		
	(n=342)	(n=417)
EqVO$_{2peak}$ (V$_{Epeak}$·VO$_{2peak}$$^{-1}$)	32.9±4.3	33.8±4.6
EqVCO$_{2peak}$ (V$_{Epeak}$·VCO$_{2peak}$$^{-1}$)	28.6±3.4	29.6±3.7
	(n=134)	(n=181)
EqVO$_{2VThan}$ (V$_{EVThan}$·VO$_{2VThan}$$^{-1}$)	25.0±2.9	26.9±4.2
EqVCO$_{2VThan}$ (V$_{EVThan}$·VCO$_{2VThan}$$^{-1}$)	26.7±2.4	28.5±3.6
40–49 years		
	(n=593)	(n=604)
EqVO$_{2peak}$ (V$_{Epeak}$·VO$_{2peak}$$^{-1}$)	33.2±4.4	33.8±4.6
EqVCO$_{2peak}$ (V$_{Epeak}$·VCO$_{2peak}$$^{-1}$)	29.3±3.6	29.9±3.8
	(n=265)	(n=259)
EqVO$_{2VThan}$ (V$_{EVThan}$·VO$_{2VThan}$$^{-1}$)	26.3±3.8	27.5±4.6
EqVCO$_{2VThan}$ (V$_{EVThan}$·VCO$_{2VThan}$$^{-1}$)	28.0±3.3	29.3±3.9
50–59 years		
	(n=579)	(n=592)
EqVO$_{2peak}$ (V$_{Epeak}$·VO$_{2peak}$$^{-1}$)	33.1±4.8	33.1±4.8
EqVCO$_{2peak}$ (V$_{Epeak}$·VCO$_{2peak}$$^{-1}$)	29.5±4.0	30.0±4.1
	(n=241)	(n=245)
EqVO$_{2VThan}$ (V$_{EVThan}$·VO$_{2VThan}$$^{-1}$)	26.6±3.9	27.0±3.5
EqVCO$_{2VThan}$ (V$_{EVThan}$·VCO$_{2VThan}$$^{-1}$)	28.3±3.6	29.0±3.1
60–69 years		
	(n=401)	(n=373)
EqVO$_{2peak}$ (V$_{Epeak}$·VO$_{2peak}$$^{-1}$)	33.9±5.3	33.0±5.0
EqVCO$_{2peak}$ (V$_{Epeak}$·VCO$_{2peak}$$^{-1}$)	30.8±4.5	30.6±4.5
	(n=203)	(n=158)
EqVO$_{2VThan}$ (V$_{EVThan}$·VO$_{2VThan}$$^{-1}$)	27.5±4.1	27.4±3.6
EqVCO$_{2VThan}$ (V$_{EVThan}$·VCO$_{2VThan}$$^{-1}$)	29.7±4.1	29.4±3.3
+70 years		
	(n=137)	(n=134)
EqVO$_{2peak}$ (V$_{Epeak}$·VO$_{2peak}$$^{-1}$)	33.7±5.4	32.8±8.4
EqVCO$_{2peak}$ (V$_{Epeak}$·VCO$_{2peak}$$^{-1}$)	31.6±4.5	31.4±7.8
	(n=69)	(n=56)
EqVO$_{2VThan}$ (V$_{EVThan}$·VO$_{2VThan}$$^{-1}$)	28.6±3.9	28.5±3.9
EqVCO$_{2VThan}$ (V$_{EVThan}$·VCO$_{2VThan}$$^{-1}$)	31.3±4.0	31.0±3.0

Data are presented as arithmetic mean $\pm$ SD. EqVO2 and EqVCO2: ventilatory efficiency.

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Associations between V_E and VCO_2

Figure 2 show the relationship between V_E and VCO_2 from start of test until V_{Than}, with strong correlations (men: r=0.94; women: r=0.93).

Discussion

This is the largest European cardio-respiratory reference material in healthy men and women aged 20–90 years. Previous papers mostly present smaller, selected age groups [15, 18, 34–40], or only male populations [23, 25, 41]. Hence, this study will serve as a useful addition to previous research.

Sex and age group differences in peak ventilation (V_{Epeak}) and tidal volume (V_{Tpeak})

In this study women had approximately 34% and 32% lower V_{Epeak} and V_{Tpeak}, respectively, and a 4% lower peak f_{Bpeak} than men. This is in agreement with other population-based studies on V_{Epeak} [39, 42–44], V_{Tpeak} and f_{Bpeak} [22, 45], and as expected as women have smaller lung size and dynamic lung function volumes than men, also after adjusting for differences in stature [46]. We observed 6–30% higher V_{Epeak} among men and women compared to that seen in Brazilian [42] (n=3992), American [43] (n=988) and French [44] (n=150) populations, as well as in small sample size studies [22, 45, 47, 48]. Yet, a Norwegian study [49] (n=759) displays V_{Epeaks} fairly consistent with ours. Hence, there might be population differences, which highlight the need of reference data in different populations.

Lower V_{Epeak} with increasing age is consistent with findings in Brazilian [42] (n=3992), Israeli [23] (male =1424), Canadian [39] (n=100), [25] (male =816) and French [44] (n=150) studies, and in line with an age attenuation in dynamic lung function largely attributed to decreased elastic recoil [50, 51].

In this study the highest V_{Tpeak} was observed among the 30–49 year groups, in both men and women, with a decrease in subsequent age groups. These findings are unexpected, since the highest V_T should be in the youngest age group, with deterioration between subsequently older age groups [50, 51]. Our findings could be explained by the relative low sample size in the youngest age group. Contrary to us a Canadian [39] (n=100) and Israeli [23] (n=1424) study presented their highest V_{Tpeak} in the youngest age groups (15–25 yrs). Interestingly, while the Canadian study displayed the same male average V_{Tpeak} as us, they have significantly lower V_{Epeak}, signaling a necessarily lower f_{Bpeak} (not displayed).

Association between V_T and V_E below and above V_{Than}

On the initial sub maximal workloads the V_T vs. V_E slope displays a steeper gradient than towards test termination. This is to be expected, since it is well established that V_T increases steeper than f_B below V_{Than}, whereas f_B mostly accounts for the increase in V_E at workloads above V_{Than} [47, 52].

Table 6. Ventilatory efficiency and oxygen uptake presented in fitness quartiles: The HUNT 3 fitness study.

	Men		Women	
	$V_{EVThan} \cdot VCO_{2VThan}^{-1}$	VO_{2peak} (mL·kg·min^{-1})	$V_{EVThan} \cdot VCO_{2VThan}^{-1}$	VO_{2peak} (mL·kg·min^{-1})
50–59 years				
	(n=241)		(n=242)	
Q_1	27.6±3.8	51.8±4.3	28.2±2.8	41.3±2.9
Q_2	27.5±2.9	44.0±2.9	28.1±2.8	35.1±1.3
Q_3	28.5±3.0	39.2±1.5	29.1±2.5	31.5±1.1
Q_4	29.6±4.4	32.6±3.0	30.5±3.5	26.8±2.4
60–69 years				
	(n=202)		(n=158)	
Q_1	28.4±2.6	47.6±4.1	28.2±2.9	37.1±3.0
Q_2	29.5±3.7	40.2±1.4	29.5±3.0	32.1±0.9
Q_3	29.5±3.8	35.5±1.2	28.7±2.7	28.7±1.0
Q_4	32.2±5.5	30.3±3.0	31.9±3.9	24.2±2.4
+70 years				
	(n=69)		(n=56)	
Q_1	29.2±3.8	43.5±4.4	30.1±3.0	33.4±3.7
Q_2	31.0±3.1	35.9±1.4	30.8±2.6	27.9±0.9
Q_3	30.7±3.6	31.4±1.4	30.9±2.3	24.8±0,8
Q_4	34.0±4.2	25.6±2.5	32.7±3.4	20.8±2.0

Data are presented as arithmetic mean ± SD. VEVThan•VCO2VThan-1: ventilatory efficiency at ventilatory anaerobic threshold. Q1-4: quartiles of ventilatory efficiency and oxygen uptake.

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Sex and age group differences in V_{Than} and RCP

We observed V_{Than} at an average 77% of VO_{2peak}, in both sexes, and in line with other studies (n=204–3992) [24, 40, 42, 53, 54] minor sex differences. Previous studies report V_{Than} at significantly lower fractions (49–70% of VO_{2peak}) [23, 24, 40, 42, 53, 54], or more consistent to that observed by us [25, 55, 56]. Differences are most likely caused by use of different methods and analyzing

Table 7. Multiple linear regression models for predicting key cardio respiratory variables from non-exercise variables: The HUNT 3 fitness study.

Equations	R^2	SEE
V_{Epeak} (L•min^{-1}) =16.843+ (0.178 x weight) + (0.876 x height) − (0.762 x age) − (28.171 x gender)	0.67	17.5
VCO_{2peak} (L•min^{-1}) =1.264+ (0.012 x weight + (0.025 x height − (0.031 x age) − (0.981 x gender)	0.70	0.59
V_{Than} (L•min^{-1} of VO_2) =(0.01 x weight) + (0.016 x height) − (0.017 x age) − (0.581 x gender) +0.514	0.59	0.47
V_{Tpeak} (L) = (0.032 x height) − (0.468 x gender) −2.379	0.64	0.37
$EqVCO_{2VThan}$ =23.897+ (0.072 x age) + (0.826 x gender)	0.08	3.47
$EqVO_{2VThan}$ =23.148+ (0.050 x age) + (0.808 x gender)	0.04	3.91

VEpeak: peak ventilation, VECO2: peak expiration of carbon dioxide, VThan: ventilatory anaerobic threshold, VTpeak: peak tidal volume, EqVCO2VThan and EqVO2VThan: ventilatory efficiency at ventilatory anaerobic threshold, R2: coefficient of variation, SEE: standard error of the estimate.
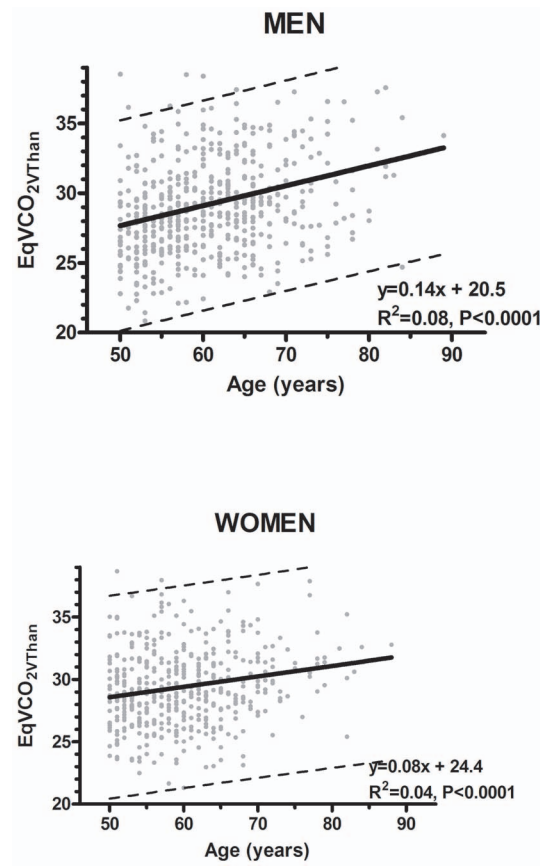
doi:10.1371/journal.pone.0113884.t007

Figure 1. Correlations between EqVCO2VThan (ventilatory efficiency at ventilator anaerobic threshold) and age groups: The HUNT 3 fitness study.

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approaches applied in the different studies, which makes direct comparisons difficult [23, 25, 42, 55, 56].

In this study V_{Than} was observed at $\approx75\%$ in the youngest age groups and at $\approx80\%$ of VO_{2peak} in the oldest age groups, in both men and women, with significant differences ($p<0.05$) between the youngest and the 60–69 year age group. Age related increase in V_{Than} (as percent of VO_{2peak}) is reported in previous studies as well [23–25, 42, 44, 53, 54, 57]. This is to be expected since V_{Than} ($L \cdot min^{-1}$) declines at a slower rate than VO_{2peak} ($L \cdot min^{-1}$) with increasing age [58, 59], and consequently occurs at a higher percent of $VO_{2max/peak}$ [60]. This is suggested to be, at least partly, due to changes in skeletal muscle composition associated with increasing age, with the selective loss of type II fibers and therefore a relative increase in type I fibers [61]. Contrary to this Lenti and colleagues [34] report a decrease in percent V_{Than} in a trained senior group (n=16), compared to their young trained, whereas the untrained groups are consistent with our findings (n=16). The small sample size taken into account, their data must be interpreted with caution.
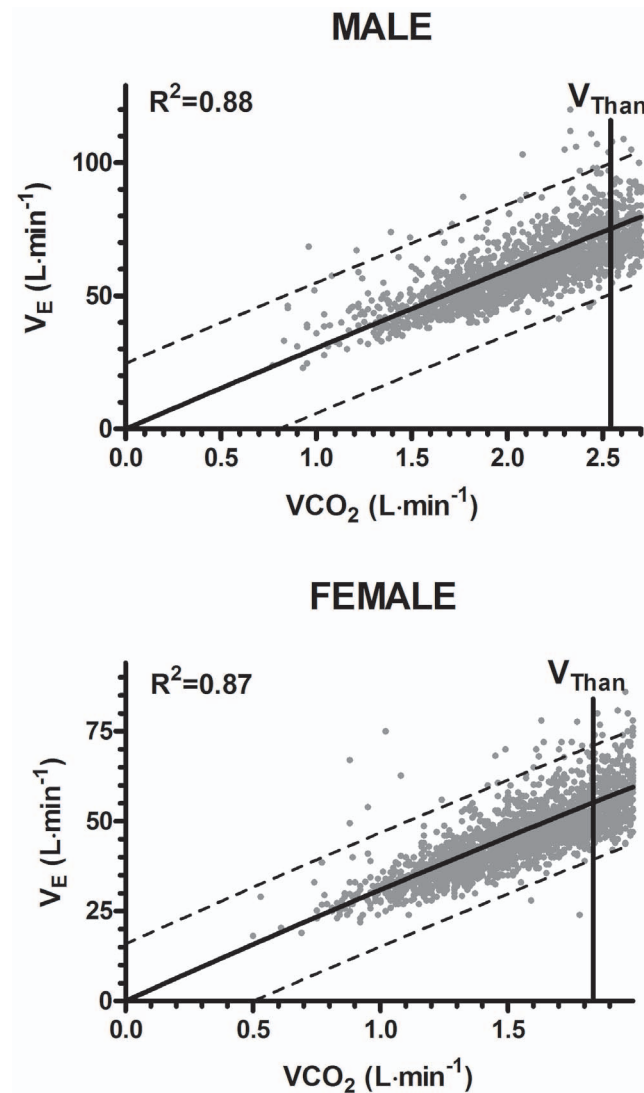
MALE

FEMALE

Figure 2. Correlations between V_E and VCO_2 from test start up to V_{Than}: The HUNT 3 fitness study.

RCP was observed at 86% and 90% of VO_{2peak}, among men and women, respectively. This is consistent with the findings of several other studies [18, 35, 37]. However, direct comparisons are difficult due to their small sample sizes (n=9–22) and the use of different measuring methods.

Ventilatory efficiency stratified by sex

In line with previous studies [17, 22] we observed similar $EqVO_{2peak}$ in men and women. Wasserman [52] suggests that $EqVCO_2$ should be determined at V_{Than}, or between V_{Than} and RCP as V_E is least variable in this range. Our submaximal level 2 measurements are close to V_{Than} and we observed slightly higher (p<0.001)

$EqVCO_{2VThan}$ in women than men, hence indicating less efficient ventilation in women. These observations are in agreement with previous studies [19, 20, 62]. Women's lower ventilatory efficiency might be explained by differences in ventilatory stimuli (e.g. $[H^+]$, $[K^+]$), metaboreceptors, and central command [63, 64].

Ventilatory efficiency at V_{Than} stratified by age groups

We observed deterioration in ventilatory efficiency, both in $EqVO_{2Than}$ ($p < 0.05$) and $EqVCO_{2Than}$ ($p < 0.001$), between the youngest and oldest age groups. This is in agreement with the findings of other studies (n=69–474) [19, 20, 57, 62]. It is presently uncertain which factors are responsible for diminished ventilatory efficiency during exercise with increasing age [65]. Clearly, increased dead space might be a major contributing factor, as well as the lung's mechanical limitation to airflow, which deteriorate as the lung loses elastic recoil with increasing age [66]. In women evidence points to decreased leg muscle strength as a contributing factor [65]. Other suggestions are factors linked to muscle afferent excitability as a result of fiber type shifts [67], and neuromuscular alterations with growing age [68].

$EqVCO_{2VThan}$ stratified by fitness quartiles

Individuals in the three oldest age groups (50–59, 60–69, +70 years) in the present study are more likely to be referred to clinical exercise testing than younger age groups, and have been studied in more depth than other age groups when it comes to $EqVCO_{2VThan}$. Interestingly, among individuals in these age groups approximately 25% had $EqVCO_{2VThan}$ higher than 30. $EqVCO_{2VThan} < 30$ is considered normal with a possible increase among older age groups [1]. In these age groups we observed minor differences in $EqVCO_{2VThan}$ between those that were among the three first quartiles of fitness (VO_{2peak} quartiles), whereupon we observed a significant drop in ventilatory efficiency (hence, an increase in $EqVCO_{2VThan}$) in those categorized as being least fit (Q_4) in both sexes and all three age groups. All fitness quartiles in the oldest age group (+70 years), and the least fit quartiles in the two younger age groups (50–59, 60–69 years) had $EqVCO_{2VThan} \approx > 30$, which could be caused by high dead space ventilation due to diminished alveoli perfusion [19]. More importantly, diminished ventilatory efficiency can reflect disease severity and prognosis in several patient groups including chronic obstructive pulmonary disease, pulmonary arterial hypertension, hypertrophic cardiomyopathy and interstitial lung disease [1, 15], and are displayed in the range 41–60 in more severe cases of congestive heart failure [15]. Although we cannot totally exclude the possibility of unknown diseases in some of our participants, the self-report and medical interview, adhering to our inclusion criteria, provides a healthy population. Therefore seen in context of our sample size our findings may represent normal ventilatory efficiency values for the oldest age groups and least fit population.

Non-exercise prediction models for key cardio-respiratory variables

There is a plethora of VO_{2peak} prediction models. However, models on other key cardio-respiratory variables are less abundant. The accuracy of previously published models on VO_{2peak} from the HUNT 3 fitness data (Men: 12.8%, Women: 14.3%) [33] is in fair agreement with previous large sample studies (Jurca 2005). Smaller sample studies [69–71] with uniform populations [72,73] show accuracies in the range ± 7–17%. Also V_{Than} accuracy ($\pm 19.9\%$) is approximately the same compared to 7 previous small-scale studies [40]. Our precision of V_{Epeak} prediction ($\pm 17.2\%$) is in agreement with a large study of males [23], contrasted by a small study [39] showing 28% accuracy. However, it was hard to compare our V_{Tpeak} accuracy ($\pm 15.5\%$) with others [23], since key data was not presented. The 12.1% accuracy in predicting $EqVCO_{2VThan}$ was similar to a small sample study [62]. Our prediction models will provide a rough estimation of these key variables, regardless of gender and age. Moreover, the models use non-exercise variables that are easy to measure, thus making these models easy to use in both clinical settings and for recreational athletes.

Association between ventilatory efficiency and workload

The slope of the ventilatory equivalent for oxygen ($EqVO_2 \cdot W^{-1}$) increases with rising workload (w), which demonstrates reduced ventilatory efficiency as the workload increases. This is supported by two former case studies [30,52]. More interestingly the $EqVCO_2 \cdot W^{-1}$ displays a gradient close to zero, which indicates a constant ventilatory efficiency throughout the incremental workload, and is in fair agreement with Wasserman and colleagues [52], yet, contradicted by another study [30] that presents an increase in $EqVCO_2$ as the workload approaches peak. However, it is noteworthy that these studies are based on single case observations, and thus difficult to compare with our findings.

Strengths and limitations

The large sample size, inclusion of men and women, wide age distribution and cardio-respiratory measurements up to the true VO_{2max} makes this study robust. The lack of spirometry data limits the assessment of ventilatory parameters. Also this study may be subject to bias due to self-selection caused by the low participation rate. However, almost all those invited to the current Fitness study from the large HUNT study agreed to participate in the fitness test. Due to limited capacity at the test sites resulting in long waiting lines, some potential participants chose to withdraw their participation from the study. Those who finally participated in the study could thus be healthier than those who quit or declined participation. However, a comparison of the participants in the fitness study with a healthy sample of the total HUNT population (i.e. free from cardiovascular or pulmonary diseases, cancer, or sarcoidosis) confirmed that the fitness participants did not considerably differ from other healthy HUNT participants [26].

Conclusions

The selection of key cardio-respiratory variables combined with an age and sex stratified large sample size makes this material unique. The inconsistencies between this and earlier research, and the scarce availability of large sample size materials support the usefulness of a large reference material as presented in this study. The HUNT 3 Fitness study presents the largest European reference material of cardio-respiratory variables in healthy men and women aged 20–90 years. Our material establishes normal values for, and associations between, as well as providing prediction models for these key cardio-respiratory parameters.

Acknowledgments

Author Contributions

Conceived and designed the experiments: UW. Performed the experiments: UW. Analyzed the data: HL SS UW. Contributed reagents/materials/analysis tools: HL SS UW. Wrote the paper: HL SS UW. Contributed substantially to design, analysis and interpretation of data, final approval of manuscript and was accountable for all aspects of the work: HL SS UW. Drafted manuscript: HL. Critical revision of manuscript for important intellectual content: SS UW. Conception and acquisition of work: UW.

References

1. **Guazzi M, Adams V, Conraads V, Halle M, Mezzani A, et al.** (2012) EACPR/AHA Scientific Statement. Clinical recommendations for cardiopulmonary exercise testing data assessment in specific patient populations. Circulation 126: 2261–2274.

2. **Balady GJ, Arena R, Sietsema K, Myers J, Coke L, et al.** (2010) Clinician's Guide to cardiopulmonary exercise testing in adults: a scientific statement from the American Heart Association. Circulation 122: 191–225.

3. **Task Force of the Italian Working Group on Cardiac Rehabilitation Prevention**, **Working Group on Cardiac Rehabilitation and Exercise Physiology of the European Society of Cardiology**, **Piepoli MF, Corra U, Agostoni PG, et al.** (2006) Statement on cardiopulmonary exercise testing in chronic heart failure due to left ventricular dysfunction: recommendations for performance and interpretation Part II: How to perform cardiopulmonary exercise testing in chronic heart failure. Eur J Cardiovasc Prev Rehabil 13: 300–311.

4. **Task Force of the Italian Working Group on Cardiac Rehabilitation Prevention**, **Working Group on Cardiac R, Exercise Physiology of the European Society of Cardiology**, **Piepoli MF, Corra U, et al.** (2006) Statement on cardiopulmonary exercise testing in chronic heart failure due to left ventricular dysfunction: recommendations for performance and interpretation. Part I: definition of cardiopulmonary exercise testing parameters for appropriate use in chronic heart failure. Eur J Cardiovasc Prev Rehabil 13: 150–164.

5. **American Thoracic S**, **American College of Chest P** (2003) ATS/ACCP Statement on cardiopulmonary exercise testing. Am J Respir Crit Care Med 167: 211–277.

6. (1997) Clinical exercise testing with reference to lung diseases: indications, standardization and interpretation strategies. ERS Task Force on Standardization of Clinical Exercise Testing. European Respiratory Society. Eur Respir J 10: 2662–2689.

7. **Hankinson JL, Kawut SM, Shahar E, Smith LJ, Stukovsky KH, et al.** (2010) Performance of American Thoracic Society-recommended spirometry reference values in a multiethnic sample of adults: the multi-ethnic study of atherosclerosis (MESA) lung study. Chest 137: 138–145.

8. **Koch B, Schaper C, Ewert R, Volzke H, Obst A, et al.** (2011) Lung function reference values in different German populations. Respir Med 105: 352–362.

9. **Dejsomritrutai W, Nana A, Maranetra KN, Chuaychoo B, Maneechotesuwan K, et al.** (2000) Reference spirometric values for healthy lifetime nonsmokers in Thailand. J Med Assoc Thai 83: 457–466.

10. **Loth DW, Ittermann T, Lahousse L, Hofman A, Leufkens HG, et al.** (2013) Normal spirometry values in healthy elderly: the Rotterdam Study. Eur J Epidemiol 28: 329–334.

11. **Mikulski MA, Gerke AK, Lourens S, Czeczok T, Sprince NL, et al.** (2013) Agreement Between Fixed-Ratio and Lower Limit of Normal Spirometry Interpretation Protocols Decreases With Age: Is There a Need for a New GOLD Standard? J Occup Environ Med 55: 802–808.

12. **Al Ghobain MO, Alhamad EH, Alorainy HS, Al Hazmi M, Al Moamary MS, et al.** (2013) Spirometric reference values for healthy nonsmoking Saudi adults. Clin Respir J.

13. **Ma YN, Wang J, Dong GH, Liu MM, Wang D, et al.** (2013) Predictive equations using regression analysis of pulmonary function for healthy children in Northeast China. PLoS One 8: e63875.

14. **Baur X** (2013) [Recommendation of new reference values for spirometry and body plethysmography]. Pneumologie 67: 401–405.

15. **Kleber FX, Vietzke G, Wernecke KD, Bauer U, Opitz C, et al.** (2000) Impairment of ventilatory efficiency in heart failure: prognostic impact. Circulation 101: 2803–2809.

16. **Sullivan MJ, Higginbotham MB, Cobb FR** (1988) Increased exercise ventilation in patients with chronic heart failure: intact ventilatory control despite hemodynamic and pulmonary abnormalities. Circulation 77: 552–559.

17. **Blackie SP, Fairbarn MS, McElvaney NG, Wilcox PG, Morrison NJ, et al.** (1991) Normal values and ranges for ventilation and breathing pattern at maximal exercise. Chest 100: 136–142.

18. **Pessoa Filho DM, Alves FB, Reis JF, Greco CC, Denadai BS** (2012) VO2 kinetics during heavy and severe exercise in swimming. Int J Sports Med 33: 744–748.

19. **Sun XG, Hansen JE, Garatachea N, Storer TW, Wasserman K** (2002) Ventilatory efficiency during exercise in healthy subjects. Am J Respir Crit Care Med 166: 1443–1448.

20. **Neder JA, Nery LE, Castelo A, Andreoni S, Lerario MC, et al.** (1999) Prediction of metabolic and cardiopulmonary responses to maximum cycle ergometry: a randomised study. Eur Respir J 14: 1304–1313.

21. **Davis JA, Frank MH, Whipp BJ, Wasserman K** (1979) Anaerobic threshold alterations caused by endurance training in middle-aged men. J Appl Physiol 46: 1039–1046.

22. **Kilbride E, McLoughlin P, Gallagher CG, Harty HR** (2003) Do gender differences exist in the ventilatory response to progressive exercise in males and females of average fitness? Eur J Appl Physiol 89: 595–602.

23. **Inbar O, Oren A, Scheinowitz M, Rotstein A, Dlin R, et al.** (1994) Normal cardiopulmonary responses during incremental exercise in 20- to 70-yr-old men. Med Sci Sports Exerc 26: 538–546.

24. **Sanada K, Kuchiki T, Miyachi M, McGrath K, Higuchi M, et al.** (2007) Effects of age on ventilatory threshold and peak oxygen uptake normalised for regional skeletal muscle mass in Japanese men and women aged 20–80 years. Eur J Appl Physiol 99: 475–483.

25. **Nelson MD, Petersen SR, Dlin RA** (2010) Effects of age and counseling on the cardiorespiratory response to graded exercise. Med Sci Sports Exerc 42: 255–264.

26. **Aspenes ST, Nilsen TI, Skaug EA, Bertheussen GF, Ellingsen O, et al.** (2011) Peak oxygen uptake and cardiovascular risk factors in 4631 healthy women and men. Med Sci Sports Exerc 43: 1465–1473.

27. **Loe H, Rognmo O, Saltin B, Wisloff U** (2013) Aerobic capacity reference data in 3816 healthy men and women 20–90 years. PLoS One 8: e64319.

28. **Hermansen L, Saltin B** (1969) Oxygen uptake during maximal treadmill and bicycle exercise. J Appl Physiol 26: 31–37.

29. **Nikooie R, Gharakhanlo R, Rajabi H, Bahraminegad M, Ghafari A** (2009) Noninvasive determination of anaerobic threshold by monitoring the %SpO2 changes and respiratory gas exchange. J Strength Cond Res 23: 2107–2113.

30. **Hopker JG, Jobson SA, Pandit JJ** (2011) Controversies in the physiological basis of the 'anaerobic threshold' and their implications for clinical cardiopulmonary exercise testing. Anaesthesia 66: 111–123.

31. **Beaver WL, Wasserman K, Whipp BJ** (1986) A new method for detecting anaerobic threshold by gas exchange. J Appl Physiol 60: 2020–2027.

32. **Meyer T, Faude O, Scharhag J, Urhausen A, Kindermann W** (2004) Is lactic acidosis a cause of exercise induced hyperventilation at the respiratory compensation point? Br J Sports Med 38: 622–625.

33. **Nes BM, Janszky I, Vatten LJ, Nilsen TI, Aspenes ST, et al.** (2011) Estimating V.O 2peak from a nonexercise prediction model: the HUNT Study, Norway. Med Sci Sports Exerc 43: 2024–2030.

34. **Lenti M, De Vito G, Scotto di Palumbo A, Sbriccoli P, Quattrini FM, et al.** (2011) Effects of aging and training status on ventilatory response during incremental cycling exercise. J Strength Cond Res 25: 1326–1332.

35. **Fabre N, Passelergue P, Bouvard M, Perrey S** (2008) Comparison of heart rate deflection and ventilatory threshold during a field cross-country roller-skiing test. J Strength Cond Res 22: 1977–1984.

36. **Marques-Neto SR, Maior AS, Maranhao Neto GA, Santos EL** (2012) Analysis of heart rate deflection points to predict the anaerobic threshold by a computerized method. J Strength Cond Res 26: 1967–1974.

37. **Rissanen AP, Tikkanen HO, Koponen AS, Aho JM, Hagglund H, et al.** (2012) Alveolar gas exchange and tissue oxygenation during incremental treadmill exercise, and their associations with blood O(2) carrying capacity. Front Physiol 3: 265.

38. **Kift J, Williams E** (2008) Ventilatory capacity and its utilisation during exercise. Lung 186: 345–350.

39. **Jones NL, Makrides L, Hitchcock C, Chypchar T, McCartney N** (1985) Normal standards for an incremental progressive cycle ergometer test. Am Rev Respir Dis 131: 700–708.

40. **Malek MH, Coburn JW** (2009) A new ventilatory threshold equation for aerobically trained men and women. Clin Physiol Funct Imaging 29: 143–150.

41. **Markovic G, Vucetic V, Nevill AM** (2007) Scaling behaviour of VO2 in athletes and untrained individuals. Ann Hum Biol 34: 315–328.

42. **Herdy AH, Uhlendorf D** (2011) Reference values for cardiopulmonary exercise testing for sedentary and active men and women. Arq Bras Cardiol 96: 54–59.

43. **Hollenberg M, Tager IB** (2000) Oxygen uptake efficiency slope: an index of exercise performance and cardiopulmonary reserve requiring only submaximal exercise. J Am Coll Cardiol 36: 194–201.

44. **Vogel T, Lepretre PM, Brechat PH, Lonsdorfer E, Benetos A, et al.** (2011) Effects of a short-term personalized Intermittent Work Exercise Program (IWEP) on maximal cardio-respiratory function and endurance parameters among healthy young and older seniors. J Nutr Health Aging 15: 905–911.

45. **Deruelle F, Brosbois JM, Mucci P, Bart F, Lensel G, et al.** (2004) Ventilatory threshold characterizations during incremental rowing and cycling exercises in older subjects. Can J Appl Physiol 29: 564–578.

46. **McArdle W, Katch F, Katch V** (2010) Exercise Physiology, Nutrition, Energy, and Human Performance: Lippincott Williams & Wilkins. 261 p.

47. **Kjelkenes I, Thorsen E** (2010) Anticipating maximal or submaximal exercise: no differences in cardiopulmonary responses. Clin Physiol Funct Imaging 30: 333–337.

48. **Jakovljevic DG, Popadic-Gacesa JZ, Barak OF, Nunan D, Donovan G, et al.** (2012) Relationship between peak cardiac pumping capability and indices of cardio-respiratory fitness in healthy individuals. Clin Physiol Funct Imaging 32: 388–393.

49. **Edvardsen E, Scient C, Hansen BH, Holme IM, Dyrstad SM, et al.** (2013) Reference values for cardiorespiratory response and fitness on the treadmill in a 20- to 85-year-old population. Chest 144: 241–248.

50. **Knudson RJ, Lebowitz MD, Holberg CJ, Burrows B** (1983) Changes in the normal maximal expiratory flow-volume curve with growth and aging. Am Rev Respir Dis 127: 725–734.

51. **Venturelli M, Schena F, Richardson RS** (2012) The role of exercise capacity in the health and longevity of centenarians. Maturitas 73: 115–120.

52. **Wasserman K, Hansen JE, Sue DY, Stringer WW, Sietsema K, et al.** (2012) Exercise Testing and Interpretation: Lippincott Williams & Wilkins. 167, 200–203 p.

53. **Itoh H, Ajisaka R, Koike A, Makita S, Omiya K, et al.** (2013) Heart rate and blood pressure response to ramp exercise and exercise capacity in relation to age, gender, and mode of exercise in a healthy population. J Cardiol 61: 71–78.

54. **Davis JA, Storer TW, Caiozzo VJ** (1997) Prediction of normal values for lactate threshold estimated by gas exchange in men and women. Eur J Appl Physiol Occup Physiol 76: 157–164.

55. **Helgerud J, Ingjer F, Stromme SB** (1990) Sex differences in performance-matched marathon runners. Eur J Appl Physiol Occup Physiol 61: 433–439.

56. **Helgerud J** (1994) Maximal oxygen uptake, anaerobic threshold and running economy in women and men with similar performances level in marathons. Eur J Appl Physiol Occup Physiol 68: 155–161.

57. **Meyer K, Hajric R, Samek L, Baier M, Lauber P, et al.** (1994) Cardiopulmonary exercise capacity in healthy normals of different age. Cardiology 85: 341–351.

58. **Paterson DH, Cunningham DA, Koval JJ, St Croix CM** (1999) Aerobic fitness in a population of independently living men and women aged 55–86 years. Med Sci Sports Exerc 31: 1813–1820.

59. **Stathokostas L, Jacob-Johnson S, Petrella RJ, Paterson DH** (2004) Longitudinal changes in aerobic power in older men and women. J Appl Physiol 97: 781–789.

60. **Cunningham DA, Nancekievill EA, Paterson DH, Donner AP, Rechnitzer PA** (1985) Ventilation threshold and aging. J Gerontol 40: 703–707.

61. **Posner JD, Gorman KM, Klein HS, Cline CJ** (1987) Ventilatory threshold: measurement and variation with age. J Appl Physiol 63: 1519–1525.

62. **Habedank D, Reindl I, Vietzke G, Bauer U, Sperfeld A, et al.** (1998) Ventilatory efficiency and exercise tolerance in 101 healthy volunteers. Eur J Appl Physiol Occup Physiol 77: 421–426.

63. **Dempsey JA** (2012) New perspectives concerning feedback influences on cardiorespiratory control during rhythmic exercise and on exercise performance. J Physiol 590: 4129–4144.

64. **Dempsey JA, Wagner PD** (1999) Exercise-induced arterial hypoxemia. J Appl Physiol (1985) 87: 1997–2006.

65. **Gonzales JU, Tucker SH, Kalasky MJ, Proctor DN** (2012) Leg strength is associated with ventilatory efficiency in older women. Int J Sports Med 33: 537–542.

66. **Johnson BD, Reddan WG, Pegelow DF, Seow KC, Dempsey JA** (1991) Flow limitation and regulation of functional residual capacity during exercise in a physically active aging population. Am Rev Respir Dis 143: 960–967.

67. **Yu F, Hedstrom M, Cristea A, Dalen N, Larsson L** (2007) Effects of ageing and gender on contractile properties in human skeletal muscle and single fibres. Acta Physiol (Oxf) 190: 229–241.

68. **Kamen G, Knight CA** (2004) Training-related adaptations in motor unit discharge rate in young and older adults. J Gerontol A Biol Sci Med Sci 59: 1334–1338.

69. **Malek MH, Housh TJ, Berger DE, Coburn JW, Beck TW** (2005) A new non-exercise-based Vo2max prediction equation for aerobically trained men. J Strength Cond Res 19: 559–565.

70. **Cao ZB, Miyatake N, Higuchi M, Ishikawa-Takata K, Miyachi M, et al.** (2009) Prediction of VO2max with daily step counts for Japanese adult women. Eur J Appl Physiol 105: 289–296.

71. **Bradshaw DI, George JD, Hyde A, LaMonte MJ, Vehrs PR, et al.** (2005) An accurate VO2max nonexercise regression model for 18–65-year-old adults. Res Q Exerc Sport 76: 426–432.

72. **George JD, Stone WJ, Burkett LN** (1997) Non-exercise VO2max estimation for physically active college students. Med Sci Sports Exerc 29: 415–423.

73. **Larsen GE, George JD, Alexander JL, Fellingham GW, Aldana SG, et al.** (2002) Prediction of maximum oxygen consumption from walking, jogging, or running. Res Q Exerc Sport 73: 66–72.