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Sex- and age-specific associations between cardiorespiratory fitness, CVD morbidity and all-cause mortality in 266.109 adults

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ABSTRACT

The aim was to investigate sex- and age-specific associations between cardiorespiratory fitness, all-cause and cause-specific mortality, and cardiovascular disease (CVD) morbidity. 266.109 participants (47% women, 18–74 years) free from CVD, participating in occupational health service screenings in 1995–2015 were included. CRF was assessed as estimated maximal oxygen consumption (estVO_2max) using a submaximal cycle test. Incident cases of first-time CVD event and death from any cause were ascertained through national registers. There were 4244 CVD events and 2750 cases of all-cause mortality during mean 7.6 years follow-up. Male gender, higher age and lower estVO_2max were associated with higher all-cause mortality and CVD morbidity incidence rates. Risk reductions with increasing estVO_2max were present in all age-groups of men and women. No obvious levelling off in risk was identified in the total cohort. However, women and older age-groups showed no further reduction in higher aggregated estVO_2max levels. CVD specific mortality was more associated with estVO_2max compared to tumor specific mortality. The risk for all-cause mortality and CVD morbidity decreased by 2.3% and 2.6% per increase in 1 ml·min^{-1}·kg^{-1} with no significant sex-differences but more pronounced in the three lower estVO_2max categories for all-cause mortality (9.1%, 3.8% and 3.3%, respectively). High compared to lower levels of estVO_2max was not related to a significantly elevated mortality or morbidity. In this large cohort study, CVD morbidity and all-cause mortality were inversely related to estVO_2max in both men and women of all age-groups. Increasing cardiorespiratory fitness is a clear public health priority.

1. Introduction

Cardiorespiratory fitness (CRF) assessed as maximal oxygen consumption (VO_2max) has long been recognized as a strong, independent predictor for cardiovascular disease (CVD) risk and mortality (Harber et al., 2017; Kodama et al., 2009). Men and younger age-groups have higher absolute (L·min^{-1}) and relative (mL·min^{-1}·kg^{-1}) VO_2max (Eriksen et al., 2016; Rapp et al., 2018), but little is known whether this translates to corresponding differences in sex- and age-related risk associations with CVD morbidity and all-cause mortality. The shape of such sex- and age-specific associations, from low to high CRF, is of great clinical importance for the development of individualized recommendations for improving CRF, as part of disease prevention and treatment.

A threshold level for all-cause mortality at CRF levels < 9 metabolic equivalents (METs) for women and 10 METs for men (where 1 MET corresponds to 3.5 ml·min^{-1}·kg^{-1}) is often used in clinical practice and health evaluations (Blair et al., 1989). The existence of such threshold has lately been challenged by results from larger studies reporting a graded inverse relationship between mortality and CVD from low to high levels of CRF with no evident plateau (Al-Mallah et al., 2016; Jensen et al., 2017; Mandsager et al., 2018). Importantly, the majority of previous studies has been conducted in men (Al-Mallah et al., 2018; Harber et al., 2017; Kodama et al., 2009), with only a few studies presenting sex- and age-specific results (Al-Mallah et al., 2016; Imboden et al., 2018; Kupsky et al., 2017; Mandsager et al., 2018; Nes et al.,

Abbreviations: VO_2max, maximal oxygen consumption; CRF, cardiorespiratory fitness; CVD, cardiovascular disease; METs, metabolic equivalents; HPA, health profile assessment

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2014; Qureshi et al., 2015; Stamatakis et al., 2013; Sui et al., 2007). In addition, some studies have used non-exercise testing methods (Nes et al., 2014; Stamatakis et al., 2013) and included selected populations referred for exercise testing (Al-Mallah et al., 2016; Kupsky et al., 2017; Mandsager et al., 2018; Qureshi et al., 2015).

The primary aim of this study was to investigate the sex- and age-specific associations between CRF, all-cause and cause-specific mortality, and CVD morbidity, in, as far as we known, the largest available sample of healthy men and women of different ages. Furthermore, the shapes of these associations were investigated, including any existence of a plateau or higher all-cause mortality or CVD morbidity associated with high CRF.

2. Methods

This study is based on the Health Profile Institute database, which contains data from Health Profile Assessments (HPAs) carried out in Swedish health services since the middle of the 1970s. The Health Profile Institute is responsible for the database, standardization of methods used, and education of the HPA coaches. Participation in the HPAs was free of charge, offered to all employees working for a company or an organisation connected to occupational or other health services in Sweden. All data were subsequently recorded in the database.

From January 1995 until December 2015, data from a total of 320.650 participants (aged 18–74 years) with a first-time HPA and an estimated VO_2max (estVO_2max) were stored in the central HPA database. Out of these, 1.579 had previous history of CVD, 2.934 had missing data on highest educational attainment, and 50.028 had missing data for exercise, diet, smoking and overall stress. Hence, 266.109 participants provided data for full sample analyses. During a follow-up, national registries derived data on first-time CVD event and mortality, and was included in the present analyses on an individual level using the unique Swedish personal identity number. The study was approved by the Stockholm Ethics Review Board (Dnr 2015/1864-31/2 and 2016/9-32), and adhered to the Declaration of Helsinki.

2.1. Assessment of cardiorespiratory fitness

VO_2max was estimated from the standardized submaximal Åstrand cycle ergometer test in $L{\cdot}min^{-1}$, and expressed in relative values ($ml{\cdot}min^{-1}{\cdot}kg^{-1}$) (Astrand, 1960). To minimize well-known errors with submaximal testing, participants were requested to refrain from vigorous activity the day before the test, consuming a heavy meal three hours and smoking/snuff use one hour before the test, and avoiding stress. Previous validation studies on adult population samples show small and non-significant mean differences on group level ($-0.07\ L{\cdot}min^{-1}$ 95% CI -0.21 to 0.06) between estimated VO_2max by the Åstrand protocol and direct measured VO_2max during treadmill running with an absolute error and coefficient of variance similar to other submaximal tests (SEE = $0.48\ L{\cdot}min^{-1}$, CV = 18.1%) (Bjorkman et al., 2016).

2.2. CVD event and mortality surveillance

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 ischemic stroke; ICD8, 410–414 and 430–438; ICD9, 401–405 and 410–414, 427, 429; ICD10, I10-I15 and I20-I25, I46) and death from any cause were ascertained through the Swedish national cause of death registry and the national in-hospital registry. For cause specific mortality analyses, ICD I00-I99 was used to define CVD, and C00-D48 to define tumor, as the main underlying cause of death.

2.3. Other measurements

Body mass was assessed with a calibrated scale in light-weight clothing to the nearest 0.5 kg. Body height was assessed using a wall-mounted stadiometer to the nearest 0.5 cm. Body mass index was subsequently calculated. Current exercise, diet, smoking and perceived overall stress were each self-reported through following statements a) *I exercise for the purpose of maintaining/improving my physical fitness, health and well-being* with the alternatives *Never, Sometimes, 1–2 times/week, 3–5 times/week,* or *At least 6 times/week*, b) *I consider my diet, regarding both meal frequency and nutritional content to be*…with the alternatives *Very poor, Poor, Neither good nor bad, Good,* or *Very good*, c) *I smoke*… with the alternatives *At least 20 cig/day, 11–19 cig/day, 1–10 cig/day, Occasionally,* or *Never*, and d) *I perceive stress in my life, both personally and at work*…with the alternatives *Very often, Often, Sometimes, Rarely,* or *Never*. Highest educational attainment at the time for the HPA, was obtained from Statistics Sweden, by linking the participant personal identity number and defined as length of education (< 9 years, 9–12 years, or > 12 years).

2.4. Statistical analysis

EstVO_2max is presented in continuous levels ($ml{\cdot}min^{-1}{\cdot}kg^{-1}$), per METs ($3.5\ ml{\cdot}min^{-1}{\cdot}kg^{-1}$), and in est$VO_2$max categories were arbitrarily derived by collapsing the METs into groups of three; ≤24.5, >24.5–35, >35–45.5, >45.5–56, $>56\ ml{\cdot}min^{-1}{\cdot}kg^{-1}$. Age-adjusted incidence rates per 10.000 person-years for CVD morbidity and all-cause mortality were computed by dividing the number of events with the total follow-up time, multiplied with the weight of the age group in the total sample. Furthermore, the relative estVO_2max on a continuous scale was analyzed as a spline function in a cox regression model, with knots at estVO_2max levels of 20, 30, 40, 50, and $60\ ml{\cdot}min^{-1}{\cdot}kg^{-1}$. Cox proportional hazard regression modelling was used to assess hazard ratios with 95% confidence interval (CI), with multi-variable adjustment for sex, age, year performed, exercise, smoking, diet and overall stress in all analyses (except for Fig. 1 and model 1 in Table 4). Proportional hazard assumption was checked using scaled Schönfelts residuals, with zero slopes on functions of time for all outcomes except a borderline significance for CVD morbidity in men. Because of this, we included an interaction term for time × estVO_2max, with no change of the results. To test for interaction between men and women, age-groups and relative estVO_2max strata for change in hazard ratio per increase in CRF (per $ml{\cdot}min^{-1}{\cdot}kg^{-1}$), an interaction term (sex/age-group/est-VO_2max strata*$ml{\cdot}min^{-1}{\cdot}kg^{-1}$) was introduced in the regression analyses, and significant interaction(s) were defined as $p < 0.05$ for the interaction term. Data were analyzed using SAS (version 9.4, SAS Institute Inc., NC, USA), and SPSS (version 24.0).

3. Results

A total of 141.074 men and 125.035 women (47.0%), 18–74 years of age, were included in the analyses (Table 1). The mean follow-up time for first CVD event and all-cause mortality was 7.1 (SD 4.5) years and 7.2 (SD 4.5) for men and 7.8 (4.5) years and 7.9 (4.5) for women, respectively. Men had higher absolute levels of estVO_2max compared to women, 3.1 (0.8) vs. 2.4 (0.6) $L{\cdot}min^{-1}$, and relative levels, 36.7 (9.9) vs. 36.1 (10.0) $ml{\cdot}min^{-1}{\cdot}kg^{-1}$. In age-adjusted Kaplan-Meier survival

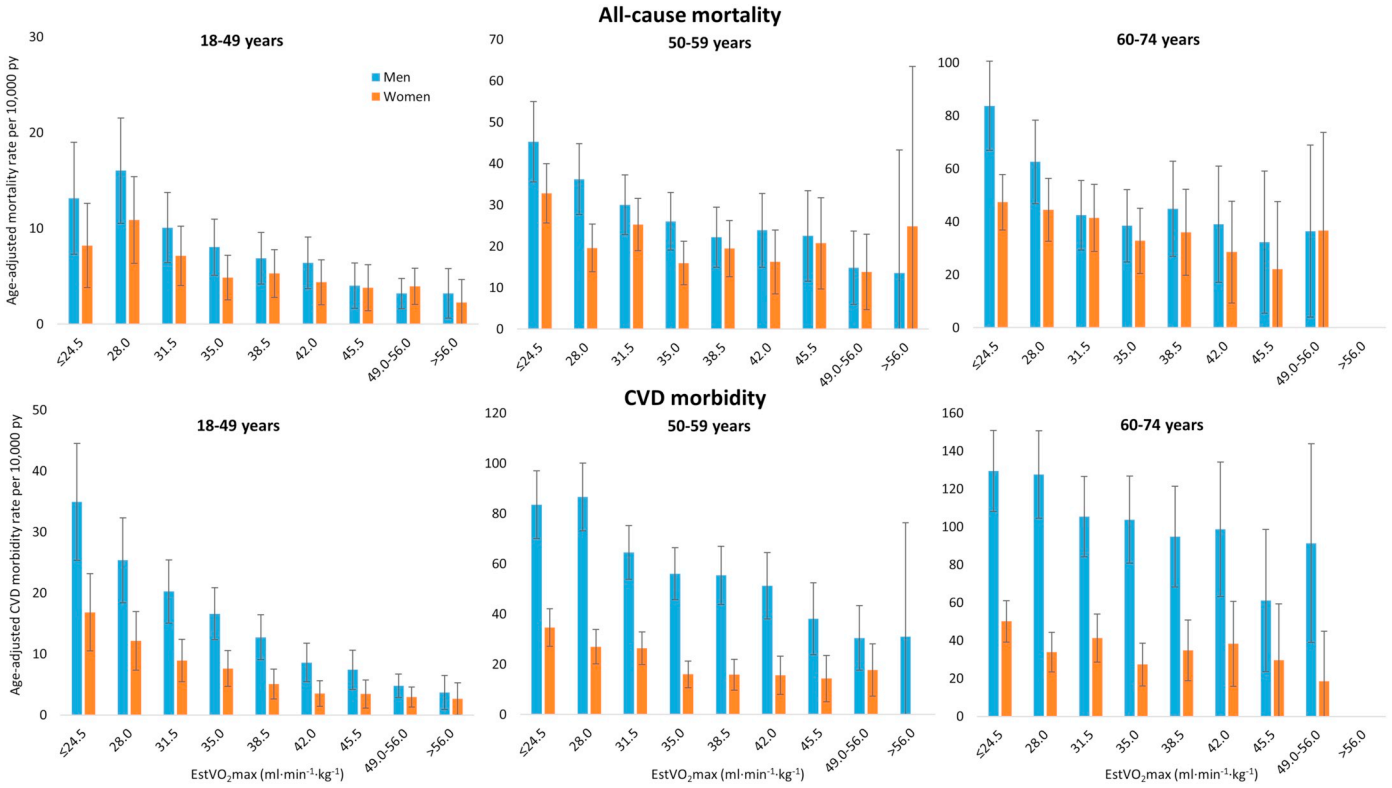


Fig. 1. Age-adjusted all-cause mortality rates (above) and CVD morbidity rates (below) by age- and estVO$_2$max (in 3.5 ml·min^{-1}·kg^{-1}) category in men and women.

curves, first-time CVD event incidence and mortality were higher in lower categories of estVO$_2$max for both men and women (Appendix Fig.A.1 and A.2).

Absolute incidence rates of both all-cause mortality and CVD morbidity were higher in older age-groups compared to younger, and decreased with increased estVO$_2$max in men and women, with some variation between different age-groups (Fig. 1). For example, women aged 50–59 years the linear decline for both all-cause mortality and CVD morbidity became flattened after 35.0 ml·min^{-1}·kg^{-1}. While CVD morbidity rates were significantly higher in men compared to women in all age-groups, and more pronounced in the lower end of the estVO$_2$max span, similar sex differences were less evident for all-cause mortality.

In multi-variable adjusted spline regression analysis there was a gradual decrease in risk with increasing estVO$_2$max levels up to 57.8 ml·min^{-1}·kg^{-1} for all-cause mortality and 59.3 ml·min^{-1}·kg^{-1} for CVD morbidity (above these values, 95% CI for the estimate included 1.00, Fig. 2). In higher estVO$_2$max levels, the spline function implies an increased **risk**, however non-significant, possibly due to a lack of cases in these categories. Tumor related cause of death was dominating in all aggregated categories with a stronger and steeper association between increasing category of estVO$_2$max and CVD related cause of death and CVD morbidity (Fig. 2 table).

3.1. Sex- and age-specific risks of all-cause mortality

In men, there was a gradual decrease in risk with higher aggregated estVO$_2$max category (Table 2) mainly driven by CVD related mortality. Women had a less pronounced association between estVO$_2$max and all-cause mortality, with only the lowest category being associated with higher risk. The cause specific analysis revealed a similar pattern for women and men.

In the youngest age-group, the lowest estVO$_2$max categories both in men and women were associated with a high risk compared to reference mainly driven by CVD mortality. In both older age-groups, only the lowest category was associated with a higher risk for both all-cause mortality and cause specific mortality, with a stronger association with CVD mortality.

In the sex- and age-specific analyses of Table 2, mainly the lowest category was associated with higher risk for all age-groups and again driven by CVD related mortality. However, the sex- and age-specific analyses should be interpreted cautiously due to a low number of cases and events in some sub-groups. In Appendix Fig. A.3, sex- and age-specific splines for all-cause mortality with increased levels of estVO$_2$max is presented.

3.2. Sex- and age-specific risks of CVD morbidity

Men and women had similar associations between the two lower categories of estVO$_2$max and increased risk for CVD morbidity, compared to reference (Table 3). While the higher aggregated category associated with significantly lower risk in men, no further reduction in risk was evident in women.

Younger age-groups experienced a steeper and stronger association between categories of estVO$_2$max and risk for CVD morbidity compared to the oldest age-group, with a possible levelling off in the oldest age-

Table 1
Characteristics of the study population, events, sum of follow-up years, and rate per 10.000 person-years for CVD morbidity and all-cause mortality (n = 266.109).

	Men				Women			
	< 50 years	50–59 years	60–74 years	Total	< 50 years	50–59 years	60–74 years	Total
N	102,076	30,704	8294	141,074	85,770	30,910	8355	125,035
Length of education (≥ 12 years)	24.3%	19.0%	20.9%	23.0%	35.0%	22.4%	21.2%	31.0%
Smoking (≥ 1 cig/day)	8.5%	11.0%	9.9%	9.1%	11.3%	13.8%	10.7%	11.9%
Exercise habits (≥ 1 time/week)	61.1%	60.3%	62.0%	61.0%	70.2%	73.6%	73.3%	71.2%
Overall stress (very often/often)	11.4%	7.4%	4.8%	10.1%	21.8%	13.4%	8.5%	18.8%
Diet habits (very poor/poor)	10.1%	5.4%	2.7%	8.6%	5.4%	2.6%	1.7%	4.4%
Height, cm	180.6 (6.7)	179.4 (6.5)	178.4 (6.2)	180.3 (6.6)	167.0 (6.1)	165.8 (5.8)	165.1 (5.7)	166.6 (6.0)
Weight, kg	84.9 (13.5)	85.6 (12.3)	83.8 (11.5)	85.0 (13.2)	68.7 (12.9)	69.9 (11.6)	69.6 (11.1)	69.1 (12.5)
BMI, kg/m^2	26.0 (3.8)	26.6 (3.4)	26.3 (3.2)	26.1 (3.7)	24.6 (4.4)	25.4 (4.0)	25.5 (3.9)	24.9 (4.3)
Estimated VO_2max								
Absolute, L·min^{-1}	3.2 (0.8)	2.7 (0.6)	2.5 (0.6)	3.1 (0.8)	2.6 (0.6)	2.2 (0.5)	2.0 (0.4)	2.4 (0.6)
Relative, mL·min^{-1}·kg^{-1}	38.6 (10.0)	32.1 (7.8)	29.6 (7.1)	36.7 (9.9)	38.5 (10.1)	31.4 (7.8)	28.8 (7.0)	36.1 (10.0)
Estimated VO_2max categories								
≤ 24.5 ml	5811 (5.7%)	5001 (16.3%)	2019 (24.3%)	12,831 (9.1%)	5491 (6.4%)	5919 (19.1%)	2479 (29.7%)	13,889 (11.1%)
24.5 < − 35 ml	33,138 (32.5%)	15,595 (50.8%)	4426 (53.4)	53,159 (37.7%)	28,612 (33.4%)	16,014 (51.8%)	4337 (51.9%)	48,963 (39.2%)
35 < − 45.5 ml	38,717 (37.9%)	8346 (27.3%)	1649 (19.9%)	48,712 (34.5%)	32,153 (37.5%)	7492 (24.2%)	1381 (16.5%)	41,026 (32.8%)
45.5 < − 56 ml	18,716 (18.3%)	1644 (5.4%)	190 (2.3%)	20,550 (14.6%)	14,891 (17.4%)	1361 (4.4%)	150 (1.8%)	16,402 (13.1%)
> 56 ml	5694 (5.6%)	118 (0.4%)	10 (0.1%)	5822 (4.1%)	4623 (5.4%)	124 (0.4%)	8 (0.1%)	4755 (3.8%)
CVD morbidity								
N events	1012 (1.0%)	1429 (4.7%)	567 (6.8%)	3008 (2.1%)	423 (0.5%)	581 (1.9%)	232 (2.8%)	1236 (1.0%)
Follow-up (years)	7.2 (4.6)	7.0 (4.5)	6.0 (3.8)	7.1 (4.5)	7.8 (4.5)	8.0 (4.4)	7.1 (3.9)	7.8 (4.5)
Incidence rate (95%CI)	13.8 (12.9–14.6)	66.1 (62.7–69.6)	113.4 (104.1–122.8)	30.0 (28.9–31.1)	6.3 (5.7–6.9)	23.5 (21.6–25.4)	38.9 (33.9–43.9)	12.7 (11.9–13.4)
All-cause mortality								
N cases	570 (0.6%)	688 (2.2%)	299 (3.6%)	1557 (1.1%)	378 (0.4%)	563 (1.8%)	252 (3.0%)	1193 (1.0%)
Follow-up (years)	7.3 (4.6)	7.2 (4.5)	6.3 (3.9)	7.2 (4.5)	7.8 (4.6)	8.1 (4.4)	7.3 (3.9)	7.9 (4.5)
Incidence rate (95%CI)	7.7 (7.1–8.3)	30.9 (28.6–33.2)	57.0 (50.5–63.4)	15.3 (14.6–16.1)	5.6 (5.1–6.2)	22.5 (20.6–24.3)	41.6 (36.4–46.7)	12.1 (11.5–12.8)
CVD related mortality								
N cases	107 (0.1%)	166 (0.5%)	70 (0.8%)	343 (0.2%)	33 (0.1%)	51 (0.2%)	28 (0.3%)	112 (0.1%)
Incidence rate (95%CI)	1.4 (1.2–1.7)	7.5 (6.3–8.6)	13.3 (10.2–16.5)	3.4 (3.0–3.7)	0.5 (0.3–0.7)	2.0 (1.5–2.6)	4.6 (2.9–6.3)	1.1 (0.9–1.4)
Tumor related mortality								
N cases	225 (0.2%)	354 (1.2%)	172 (2.1%)	751 (0.5%)	255 (0.3%)	427 (1.4%)	190 (2.3%)	872 (0.7%)
Incidence rate (95%CI)	3.0 (2.6–3.4)	15.9 (14.2–17.6)	32.8 (27.9–37.7)	7.4 (6.9–7.9)	3.8 (3.3–4.3)	17.0 (15.4–18.7)	31.3 (26.9–35.8)	8.9 (8.3–9.5)

Data is presented as n (%) or mean (SD). Incidence rate presented as cases per 10.000 person-years.

group. In the sex- and age-specific analyses of Table 3, lower category of estVO_2max was associated with a higher risk, with women of all ages and the older men showing no further obvious reduction in risk with higher estVO_2max. For sex- and age-specific splines for CVD morbidity and estVO_2max see Appendix Fig. A.4.

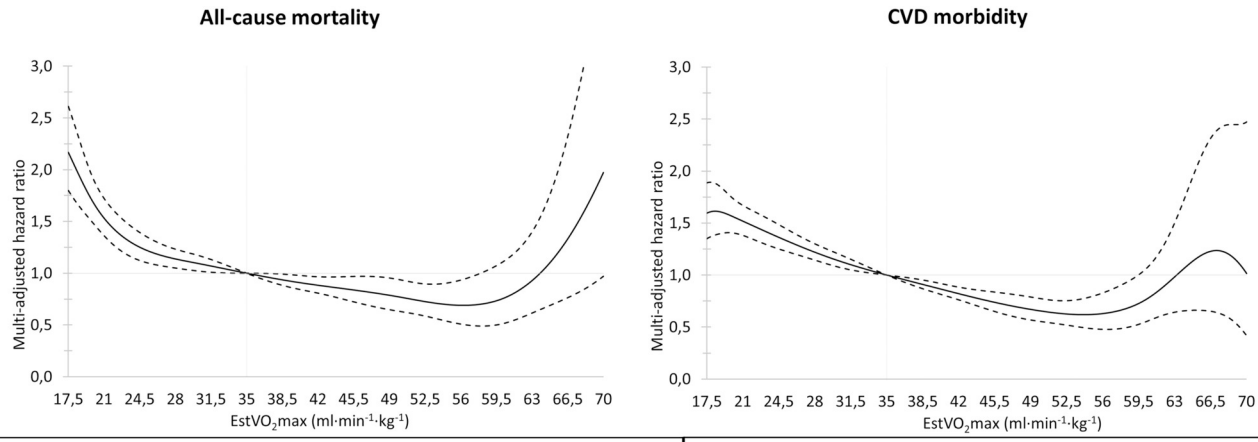
In a sensitivity analysis, we excluded participants with a follow-up time shorter than 2 years, which only marginally changed the association between aggregated categories of estVO_2max and risk for all-cause mortality and CVD morbidity, indicating a low degree of reversed causality (Appendix Tables A.1 and A.2).

3.3. Change in risk per increase in ml·min^{-1}·kg^{-1}

In the total population, multi-variable adjusted risk for all-cause mortality and CVD morbidity decreased with 2.3% and 2.6% per ml·min^{-1}·kg^{-1} increase (Table 4). There were no interaction between men and women (p = 0.133) nor between age-groups (p = 0.461) in risk reduction for all-cause mortality per ml·min^{-1}·kg^{-1} of higher estVO_2max. For CVD morbidity, there was no interaction between men and women (p = 0.914), however a significant interaction between age-groups (p = 0.001).

Risk reduction per ml·min^{-1}·kg^{-1} for all-cause mortality was significantly steeper in the lowest three estVO_2max categories (p < 0.001), with a significantly increased risk per ml·min^{-1}·kg^{-1} in the highest estVO_2max category. No similar interaction was seen for CVD morbidity (p = 0.268).

For all-cause mortality, further analyses revealed that there were no interaction between sex and ml·min^{-1}·kg^{-1} of estVO_2max (p-value for interaction term sex * ml·min^{-1}·kg^{-1} = 0.52 to 0.99) or age and ml·min^{-1}·kg^{-1} of estVO_2max (p-value for interaction term age * ml·min^{-1}·kg^{-1} = 0.17 to 0.60) in any of the aggregated estVO_2max categories after multi-variable adjustment. This indicates that the risk reduction with higher ml·min^{-1}·kg^{-1} of estVO_2max in the different aggregated estVO_2max categories may be interpreted similarly regardless of sex and age.



	≤24.5 ml	>24.5-35 ml	>35-45.5 ml	>45.5-56 ml	>56 ml	Total	≤24.5 ml	>24.5-35 ml	>35-45.5 ml	>45.5-56 ml	>56 ml	Total
Total, n (%)	*581 (2.2%)*	*1325 (1.3%)*	*663 (1.8%)*	*151 (1.4%)*	*30 (0.03%)*	*2750 (1.0%)*	*858 (3.3%)*	*2178 (2.2%)*	*982 (2.7%)*	*192 (1.8%)*	*34 (0.04%)*	*4244 (1.6%)*
HR (95% CI)	1.55 (1.38-1.75)	1.15 (1.04-1.26)	1.00 (ref)	0.85 (0.71-1.02)	0.97 (0.67-1.40)		1.60 (1.45-1.76)	1.28 (1.19-1.39)	1.00 (ref)	0.75 (0.64-0.87)	0.79 (0.56-1.12)	
Cause specific												
CVD, n (%)	*118 (20%)*	*237 (18%)*	*87 (13%)*	*8 (5%)*	*5 (17%)*	*455 (17%)*						
HR (95% CI)	2.30 (1.72-3.09)	1.49 (1.16-1.92)	1.00 (ref)	0.36 (0.18-0.75)	1.42 (0.57-3.54)							
Tumor, n(%)	*333 (57%)*	*771 (58%)*	*410 (62%)*	*95 (63%)*	*14 (50%)*	*1623 (59%)*						
HR (95% CI)	1.29 (1.11-1.50)	1.01 (0.90-1.15)	1.00 (ref)	0.94 (0.75-1.17)	0.87 (0.51-1.49)							

Fig. 2. Multi-variable adjusted hazard ratio for all-cause mortality and CVD morbidity by countinous estVO$_2$max level using spline function (solid line) with 95% CI (dashed lines). The reference level is set to median MET in the total population (35 ml·min^{-1}·kg^{-1}). Below the splines are HR (95% CI) for all-cause mortality and CVD morbidity presented in relation to aggregated categories of estVO$_2$max. All analyses are adjusted for sex, age, performed year, length of education, exercise, smoking, diet and overall stress.

4. Discussion

In the cohort including over 266.000 men and women with a wide age-span from the Swedish working population, male gender, higher age and lower estVO$_2$max was associated with higher all-cause mortality and CVD morbidity incidence rates. However, risk reductions with increasing estVO$_2$max were shown in both men and women of all age-groups. CVD specific mortality was more strongly associated with estVO$_2$max compared to tumor specific mortality.

No obvious levelling off in risk of either all-cause mortality or CVD morbidity in relation to estVO$_2$max was identified in the total cohort. Men experienced a gradually decrease in risk over the estVO$_2$max span, while women showed no further obvious risk reduction over the median aggregated estVO$_2$max category. A levelling off was shown in the oldest age-group for CVD morbidity and in all age-groups for all-cause mortality.

The risk for all-cause mortality and CVD morbidity decreased by 2.3% and 2.6% per increase in ml·min^{-1}·kg^{-1}, with no significant interaction between men and women. While younger age-groups experienced a steeper decrease in risk for CVD morbidity per ml·min^{-1}·kg^{-1}, no similar difference was seen for all-cause mortality. On the contrary, there was a steeper decrease in risk per ml·min^{-1}·kg^{-1} in the lower three aggregated categories of estVO$_2$max for all-cause mortality (9.1%, 3.8% and 3.3%, respectively). High estVO$_2$max was not related to a significantly elevated mortality or morbidity compared to lower levels.

4.1. CRF, all-cause mortality and CVD morbidity in relation to sex and age

Our findings are partly in concordance with previous data on the associations between CRF and all-cause mortality (Harber et al., 2017; Kodama et al., 2009) and CVD morbidity (Al-Mallah et al., 2018), also using direct measurements of VO$_2$max (Imboden et al., 2018; Khan et al., 2014; Laukkanen et al., 2016). Men had significantly higher absolute incident rates of CVD morbidity compared to women in all age-groups for the same level of estVO$_2$max, with less pronounced sex-differences for all-cause mortality. This is in line with a previous study in men and women referred for exercise testing (Al-Mallah et al., 2016), which concluded that men's survival was equivalent to what women demonstrated at a CRF of 2.6 METs (9.1 ml·min^{-1}·kg^{-1}) lower, with no further analyses of differences between different age-groups. Similar conclusions can roughly been drawn in the two youngest age-groups, with almost no overlapping in absolute rates between men and women for CVD morbidity. Interestingly, despite the differences in *absolute* incidence rates between men and women, as well as between age-groups, the decreased *relative* risk per ml·min^{-1}·kg^{-1} was similar. This has previously been shown in two of the few previous studies with sex-specific analyses in men and women referred for exercise testing (Al-Mallah et al., 2016; Kupsky et al., 2017; Qureshi et al., 2015) and general population using non-exercise testing (Nes et al., 2014).

While previous studies report that higher CRF in younger ages ($\leq$45 or $\leq$ 60 years) confers significantly greater survival benefits compared to older ages in men (Kokkinos et al., 2014) as well as in men and women (Nes et al., 2014), the present study revealed no significant interaction between the age-groups for all-cause mortality but for CVD morbidity. Similar trends were reported in asymptomatic men and women ($<$55 vs. $\geq$55 years) for nonfatal cardiovascular events (Sui et al., 2007) and in men and women referred for testing ($<$40 vs. $\geq$40 years) for incident heart failure (Kupsky et al., 2017), however with no difference between age-groups for atrial fibrillation (Qureshi et al., 2015).

Table 2
Multi-variable adjusted hazard ratio (95%CI) of all-cause mortality and cause specific mortality in aggregated estVO$_2$max categories in relation to sex, age-group and sex-and age-group, respectively.

	≤24.5	EstVO$_2$max (ml·min^{-1}·kg^{-1})		>45.5–56	>56	p-trend
		>24.5–35	>35–45.5			
Men						
All-cause mortality	1.64 (1.40–1.92)	1.18 (1.04–1.34)	1.00	0.78 (0.61–0.99)	0.88 (0.54–1.44)	**<0.001**
Cause specific						
CVD	2.22 (1.58–3.11)	1.44 (1.08–1.92)	1.00	0.46 (0.22–0.96)	1.48 (0.53–4.11)	**<0.001**
Tumor	1.34 (1.07–1.69)	1.04 (0.87–1.24)	1.00	0.82 (0.58–1.15)	0.78 (0.34–1.77)	**0.005**
Women						
All-cause mortality	1.47 (1.23–1.75)	1.11 (0.96–1.29)	1.00	0.96 (0.73–1.26)	1.09 (0.62–1.92)	**<0.001**
Cause specific						
CVD	2.67 (1.45–4.89)	1.72 (1.00–2.95)	1.00	–	1.24 (0.16–9.42)	**<0.001**
Tumor	1.27 (1.03–1.56)	1.00 (0.84–1.19)	1.00	1.04 (0.77–1.41)	0.96 (0.47–1.96)	**0.083**
18–49 years						
All-cause mortality	1.39 (1.07–1.76)	1.25 (1.08–1.46)	1.00	0.85 (0.68–1.06)	0.93 (0.62–1.39)	**<0.001**
Cause specific						
CVD	2.69 (1.55–4.66)	1.70 (1.13–2.57)	1.00	0.47 (0.20–1.13)	1.56 (0.55–4.48)	**<0.001**
Tumor	0.93 (0.62–1.38)	1.20 (0.97–1.47)	1.00	1.05 (0.79–1.41)	0.90 (0.49–1.63)	**0.426**
50–59 years						
All-cause mortality	1.52 (1.28–1.80)	1.07 (0.93–1.24)	1.00	0.82 (0.58–1.15)	1.09 (0.35–3.39)	**<0.001**
Cause specific						
CVD	2.02 (1.32–3.08)	1.38 (0.95–2.00)	1.00	0.32 (0.08–1.32)	3.02 (0.41–22.0)	**<0.001**
Tumor	1.27 (1.03–1.57)	0.89 (0.75–1.07)	1.00	0.70 (0.46–1.08)	0.94 (0.23–3.79)	**0.009**
50–74 years						
All-cause mortality	1.59 (1.22–2.09)	1.14 (0.88–1.47)	1.00	0.96 (0.48–1.92)	–	**<0.001**
Cause specific						
CVD	2.17 (1.14–4.13)	1.25 (0.67–2.31)	1.00	–	–	**0.002**
Tumor	1.41 (1.01–1.96)	1.09 (0.80–1.47)	1.00	1.10 (0.50–2.42)	–	**0.029**
Men						
18–49 years	≤24.5	>24.5–35	>35–45.5	>45.5–56	>56	
All-cause mortality	1.43 (1.04–1.96)	1.27 (1.05–1.54)	1.00	0.73 (0.54–0.98)	0.87 (0.52–1.46)	**<0.001**
Cause specific						
CVD	2.63 (1.38–5.00)	1.73 (1.08–2.79)	1.00	0.70 (0.29–1.70)	1.90 (0.56–6.44)	**0.002**
Tumor	0.86 (0.46–1.60)	1.21 (0.90–1.63)	1.00	0.79 (0.50–1.24)	0.85 (0.37–1.98)	**0.184**
50–59 years						
All-cause mortality	1.60 (1.26–2.01)	1.16 (0.96–1.41)	1.00	0.90 (0.58–1.40)	0.80 (0.11–5.69)	**<0.001**
Cause specific						
CVD	1.71 (1.05–2.78)	1.34 (0.90–2.01)	1.00	0.36 (0.09–1.49)	3.65 (0.50–26.8)	**0.009**
Tumor	1.37 (1.00–1.88)	0.97 (0.75–1.26)	1.00	0.85 (0.48–1.53)	–	**0.046**
60–74 years						
All-cause mortality	1.74 (1.22–2.48)	1.03 (0.74–1.44)	1.00	0.87 (0.35–2.20)	–	**<0.001**
Cause specific						
CVD	2.52 (1.21–5.23)	1.03 (0.50–2.12)	1.00	–	–	**0.001**
Tumor	1.43 (0.91–2.27)	0.98 (0.64–1.49)	1.00	0.84 (0.26–2.75)		**0.070**
Women						
18–49 years						
All-cause mortality	1.32 (0.89–1.95)	1.24 (0.97–1.57)	1.00	1.05 (0.75–1.47)	1.03 (0.55–1.93)	**0.124**
Cause specific						
CVD	2.93 (1.02–8.47)	1.57 (0.70–3.53)	1.00	–	0.95 (0.12–7.60)	**0.006**
Tumor	1.00 (0.59–1.68)	1.20 (0.89–1.60)	1.00	1.32 (0.90–1.93)	0.92 (0.40–2.14)	**0.953**
50–59 years						
All-cause mortality	1.45 (1.13–1.86)	0.97 (0.78–1.20)	1.00	0.70 (0.40–1.22)	1.31 (0.32–5.30)	**0.001**
Cause specific						
CVD	3.68 (1.36–9.96)	1.85 (0.70–4.86)	1.00	–	–	**0.001**
Tumor	1.22 (0.92–1.61)	0.84 (0.66–1.06)	1.00	0.57 (0.30–1.09)	1.47 (0.36–5.97)	**0.069**
60–74 years						
All-cause mortality	1.46 (0.96–2.22)	1.28 (0.87–1.90)	1.00	1.06 (0.37–3.02)	–	**0.069**
Cause specific						
CVD	1.37 (0.35–5.40)	1.90 (0.55–6.49)	1.00	–	–	**0.592**
Tumor	1.42 (0.88–2.29)	1.21 (0.77–1.90)	1.00	1.41 (0.49–4.08)	–	**0.185**

All analyses are adjusted for sex, age, performed year, length of education, exercise, smoking, diet and overall stress. A dash indicates ≤1 case in the strata, and HR with 95% CI cannot be calculated.

Table 3
Multi-variable adjusted hazard ratio (95%CI) of CVD morbidity in aggregated estVO$_2$max categories in relation to sex, age-group and sex-and age-group, respectively.

	EstVO$_2$max (ml·min^{-1}·kg^{-1})					p-Trend
	≤24.5	>24.5–35	>35–45.5	>45.5–56	>56	
Men	1.52 (1.35–1.71)	1.28 (1.17–1.40)	1.00	0.71 (0.59–0.86)	0.77 (0.51–1.16)	**<0.001**
Women	1.84 (1.54–2.20)	1.34 (1.15–1.56)	1.00	0.83 (0.62–1.12)	0.85 (0.45–1.62)	**<0.001**
18–48 years	1.98 (1.65–2.37)	1.41 (1.25–1.60)	1.00	0.81 (0.66–0.99)	0.97 (0.66–1.40)	**<0.001**
50–59 years	1.51 (1.32–1.74)	1.23 (1.10–1.38)	1.00	0.70 (0.53–0.94)	0.67 (0.21–2.08)	**<0.001**
60–74 years	1.37 (1.10–1.70)	1.08 (0.88–1.32)	1.00	0.98 (0.57–1.67)	1.45 (0.20–10.4)	**<0.001**
Men						
18–49 years	1.84 (1.48–2.30)	1.37 (1.18–1.58)	1.00	0.75 (0.59–0.96)	0.88 (0.56–1.39)	**<0.001**
50–59 years	1.46 (1.24–1.73)	1.24 (1.09–1.42)	1.00	0.66 (0.47–0.93)	0.92 (0.30–2.88)	**<0.001**
60–74 years	1.36 (1.04–1.76)	1.12 (0.89–1.42)	1.00	1.14 (0.64–2.04)	1.99 (0.28–14.3)	**0.040**
Women						
18–49 years	2.43 (1.77–3.35)	1.59 (1.26–2.01)	1.00	0.97 (0.67–1.40)	1.15 (0.60–2.20)	**<0.001**
50–59 years	1.64 (1.27–2.12)	1.23 (0.98–1.54)	1.00	0.81 (0.46–1.42)	–	**<0.001**
60–74 years	1.37 (0.91–2.05)	0.95 (0.65–1.41)	1.00	0.47 (0.11–1.98)	–	**0.017**

All analyses are adjusted for sex, age, performed year, length of education, exercise, smoking, diet and overall stress.

4.2. The shape of the association between CRF, all-cause mortality and CVD morbidity

We could not confirm the existence of a threshold value above which no further risk reduction was present for either all-cause mortality or CVD morbidity in the total cohort. This is in line with previous studies in adults free from CVD (Al-Mallah et al., 2016) and cancer (Jensen et al., 2017) as well as in patients referred for exercise testing (Mandsager et al., 2018). Though, in the present study, there was some variation between sex- and age-specific sub-groups, which has not been presented before.

Importantly, no increased risk at high levels of estVO$_2$max (<56 ml·min^{-1}·kg^{-1}) compared to lower levels was identified, neither in men and women nor in any of the three age-groups. A U-shaped association has previously been proposed between all-cause mortality and dose of jogging in healthy adults (Schnohr et al., 2015) and in individuals with an underlying CVD (Mons et al., 2014). Though, the previous studies included too few cases in the highly active group to support a significant higher risk. The different findings may be explained by that these studies refer to the habit of exercise, i.e. jogging, while the present study refers to a physiological outcome. Two previous studies have focused on mortality in former elite athletes, showing that French Olympians saved on average 6.5 years of life (Antero-Jacquemin et al., 2018) and elite Finnish endurance athletes had a 2.4 higher age at death, compared to general population (Kontro et al., 2018). This may indicate that in samples with high statistical power, based on low-risk populations, high CRF is not associated with increased mortality compared to lower levels.

Table 4
All-cause mortality and CVD morbidity risk per 1 ml·min^{-1}·kg^{-1} increase in estVO$_2$max in the total population and across sub-groups.

	All-cause mortality		CVD morbidity	
	Model 1	Model 2	Model 1	Model 2
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Total population	0.972 (0.967–0.977)	0.977 (0.972–0.982)	0.968 (0.965–0.972)	0.974 (0.969–0.978)
Men	0.966[a] (0.960–0.972)	0.973 (0.966–0.980)	0.969 (0.965–0.974)	0.974 (0.969–0.979)
Women	0.980 (0.973–0.987)	0.981 (0.974–0.989)	0.966 (0.959–0.973)	0.971 (0.963–0.978)
18–49 years	0.976 (0.969–0983)	0.979 (0.972–0.987)	0.965[b] (0.959–0.971)	0.972[b] (0.965–0.978)
50–59 years	0.971 (0.964–0.979)	0.978 (0.970–0.986)	0.969 (0.963–0.975)	0.973 (0.967–0.979)
60–74 years	0.962 (0.949–0.974)	0.966 (0.954–0.979)	0.976 (0.967–0.986)	0.981 (0.971–0.992)
≤24.5 ml	0.909 (0.878–0.940)[c]	0.909 (0.878–0.940)[c]	0.977 (0.949–1.006)	0.976 (0.947–1.005)
>24.5–35 ml	0.954 (0.937–0.972)[c]	0.962 (0.944–0.980)[c]	0.957 (0.944–0.971)	0.964 (0.950–0.978)
>35–45.5 ml	0.965 (0.939–0.991)[c]	0.967 (0.941–0.994)[c]	0.971 (0.950–0.993)	0.975 (0.953–0.997)
>45.5–56 ml	0.987 (0.932–1.046)[c]	0.989 (0.933–1.049)[c]	1.016 (0.966–1.069)	1.017 (0.967–1.071)
>56 ml	1.090 (1.024–1.162)[c]	1.094 (1.027–1.166)[c]	1.054 (0.986–1.126)	1.059 (0.990–1.133)

Model 1; adjusted for performed year, sex (when not stratified for) and age.
Model 2; as Model 1 + adjusted for length of education, exercise, smoking, diet and overall stress.
[a] Significantly different between women and men.
[b] Significantly different across age-groups.
[c] Significantly different across estVO$_2$max strata.

There was an increased risk of all-cause mortality *within* the highest estVO2max category ($\geq 56\ ml{\cdot}min^{-1}{\cdot}kg^{-1}$). However, in this sub-group, the total mortality was very low (0.03%) compared to the other aggregated categories of estVO$_2$max, with limited, absolute number of cases (30 fatalities, including 5 CVD, 14 tumor and 11 external/other causes). This prevents further interpretations of risk variation within this group. Thus, the question still remains, whether there is a cut-off for CRF, above which no more health benefits are achieved. In clinical practice, however, the individual risk-factor assessment, for prescribing the most suitable exercise as part of individualized exercise prescription, may be the way forward for achieving the maximal health benefits at minimal risk for the individual (Vanhees et al., 2012a; Vanhees et al., 2012b; Vanhees et al., 2012c).

The studied cause-specific mortality had a varying pattern in relation to CRF. While the frequency of tumor related mortality was relatively higher, compared to CVD, the association between increased estVO$_2$max and reduced risk for all-cause mortality was mainly driven by CVD related mortality. The risk of tumor related mortality was only significantly elevated in the lowest aggregated estVO$_2$max category ($\leq 24.5\ ml{\cdot}min^{-1}{\cdot}kg^{-1}$) in men and women, and in the oldest age-groups. This is contrary to previous findings, showing that each METs increment increase in CRF was associated with a 14.0% reduction in cancer mortality (Imboden et al., 2018). Although previous epidemiological studies have indicated a beneficial effect of physical activity on cancer related mortality (especially breast- and colon cancer), the magnitude of the risk reduction is smaller compared to the risk reduction seen for all-cause and CVD mortality, with mechanistic pathways being more unclear (Barry et al., 2018; Lynch and Leitzmann, 2017).

4.3. Implications for clinicians and policymakers

In a previous publication from the present cohort, we reported a decrease of $4.2\ ml{\cdot}min^{-1}{\cdot}kg^{-1}$ in estVO$_2$max over almost 25 years in this large cohort (Ekblom-Bak et al., 2019), with male gender, young age, short education and living in a rural area were predictive of greater reductions. Low CRF has been shown to be one of the most powerful modifiable risk factors (in comparison to smoking, overweight/obesity and diabetes) for prediction of both mortality and morbidity in both healthy adults (Blair, 2009) and in patients referred for exercise testing (Mandsager et al., 2018). The results in table 4 may be used as a simple summary tool in clinical practice for a more individually adapted communication and implementation of the results. This may be more relevant and motivating for the individual.

4.4. Study strengths and limitations

The main strength of the present study is the large study sample, enabling highly clinically relevant analyses of variations in the associations across sub-groups. A possible limitation to our results is that the cohort may be somewhat selected as participation was not mandatory. Though similar results of the highest risk reduction were found in extremely high CRF-values in a high risk population (Mandsager et al., 2018). Moreover, the validity of results from these types of association studies are less influenced by selected population. Although the number of CVD morbidity and all-cause mortality cases were relatively high in the total population, the analyses in some of the most specific sub-groups would have benefited from more cases. A limitation is the use of a submaximal test to estimated VO$_2$max. However, measuring actual VO$_2$max during maximal performance would not have been feasible in this large non-athletic population. No further adjustments were made for other risk factors (such as blood pressure or lipids) as these variables are considered to be mediators explaining a large part of the effect/association of cardiorespiratory fitness on morbidity and mortality risk and would falsely diminish the role of fitness, with such results theoretically only relying on the variables that are not adjusted for or a result of residual confounding. Moreover, valid data on co-morbidities like hypertension, diabetes and dyslipidemia or medications at baseline was not available, which may have influenced the point estimates.

5. Conclusion

This study includes, to our knowledge, the largest sample of men and women of different ages study from the general population to investigate the sex- and age-specific associations between CRF, all-cause and cause-specific mortality, and CVD morbidity. There were an inverse relation between CRF, CVD morbidity and all-cause mortality in both men and women of all age-groups. No obvious plateau in risk reduction with higher CRF was evident in the total cohort, however, with some variation between sex- and age groups. High estVO$_2$max was not related to a significantly elevated mortality or morbidity compared to lower levels. The results in table 4 could be used in clinical practice for a more individually relevant and motivating communication and implementation of the results. In the light of the recently published trends of decreased estVO$_2$max in this population, and similar findings of lower overall physical activity in the general population, preventive actions for increased CRF is a clear public health priority, especially for vulnerable groups.

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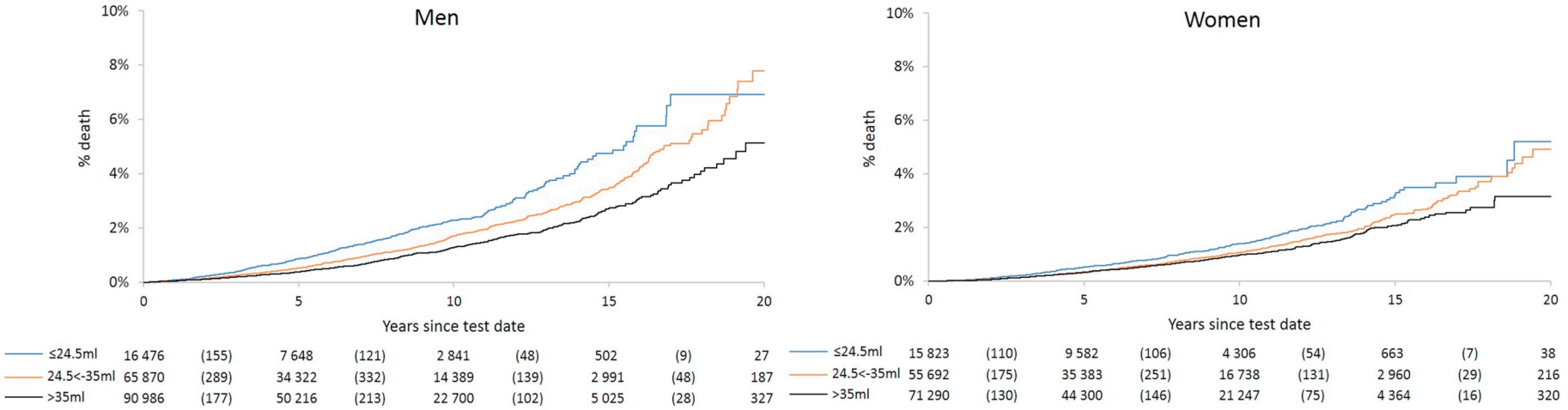
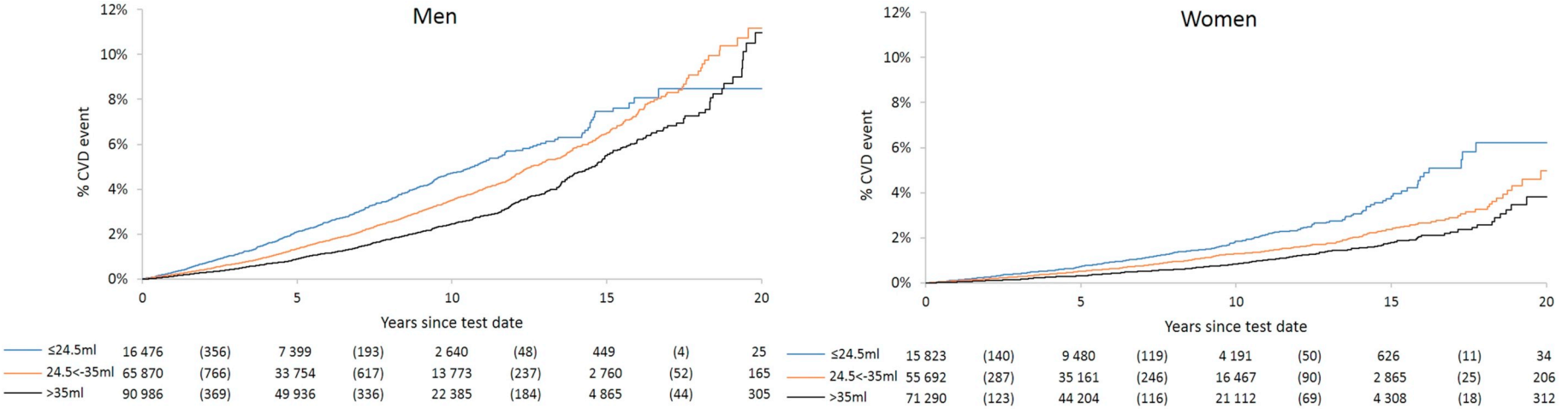
Declaration of competing interest

GA (responsible for research and method) and PW (CEO and responsible for research and method) are employed at HPI Health Profile Institute. JS reports personal fees from HPI Health Profile Institute during the conduct of the study.

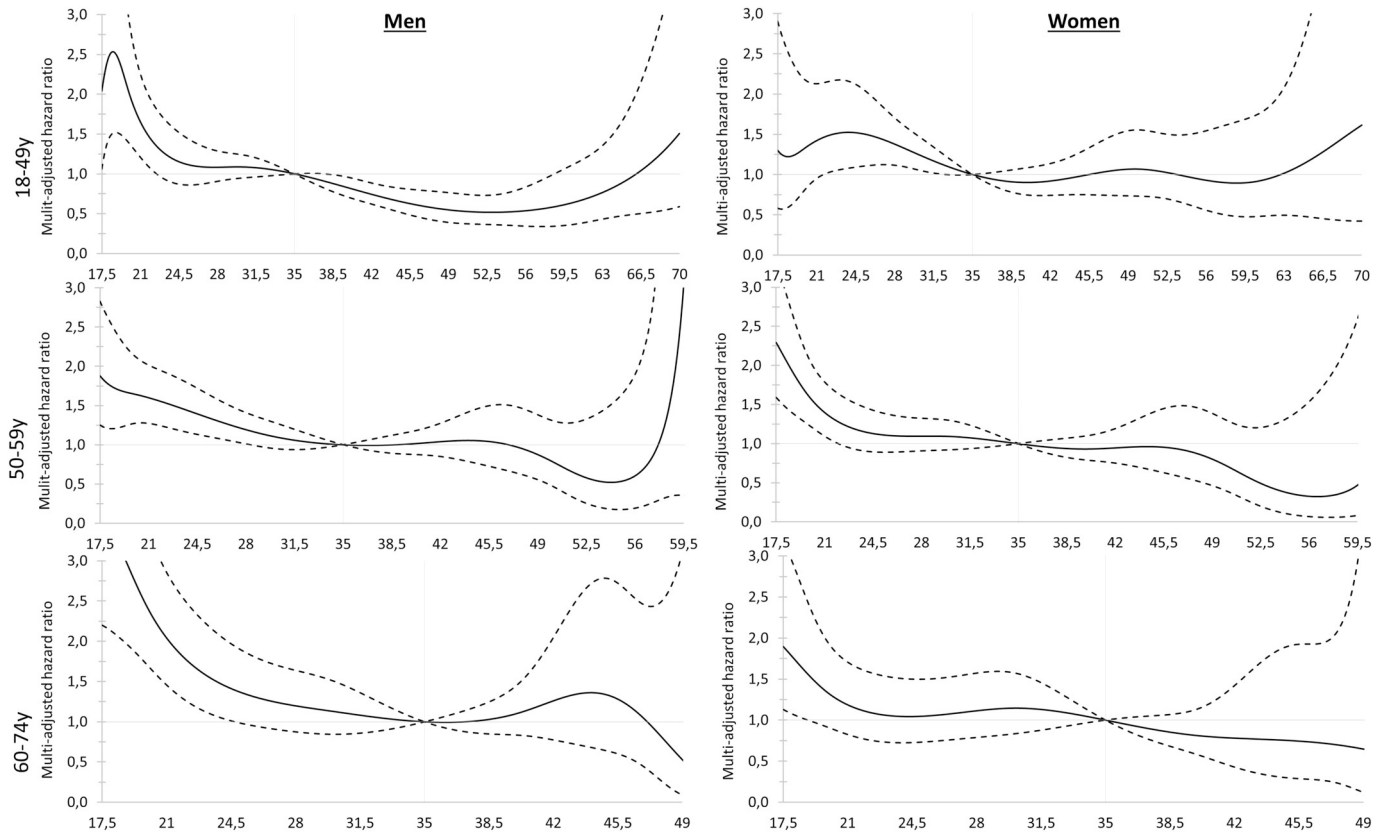
Appendix A. Appendix



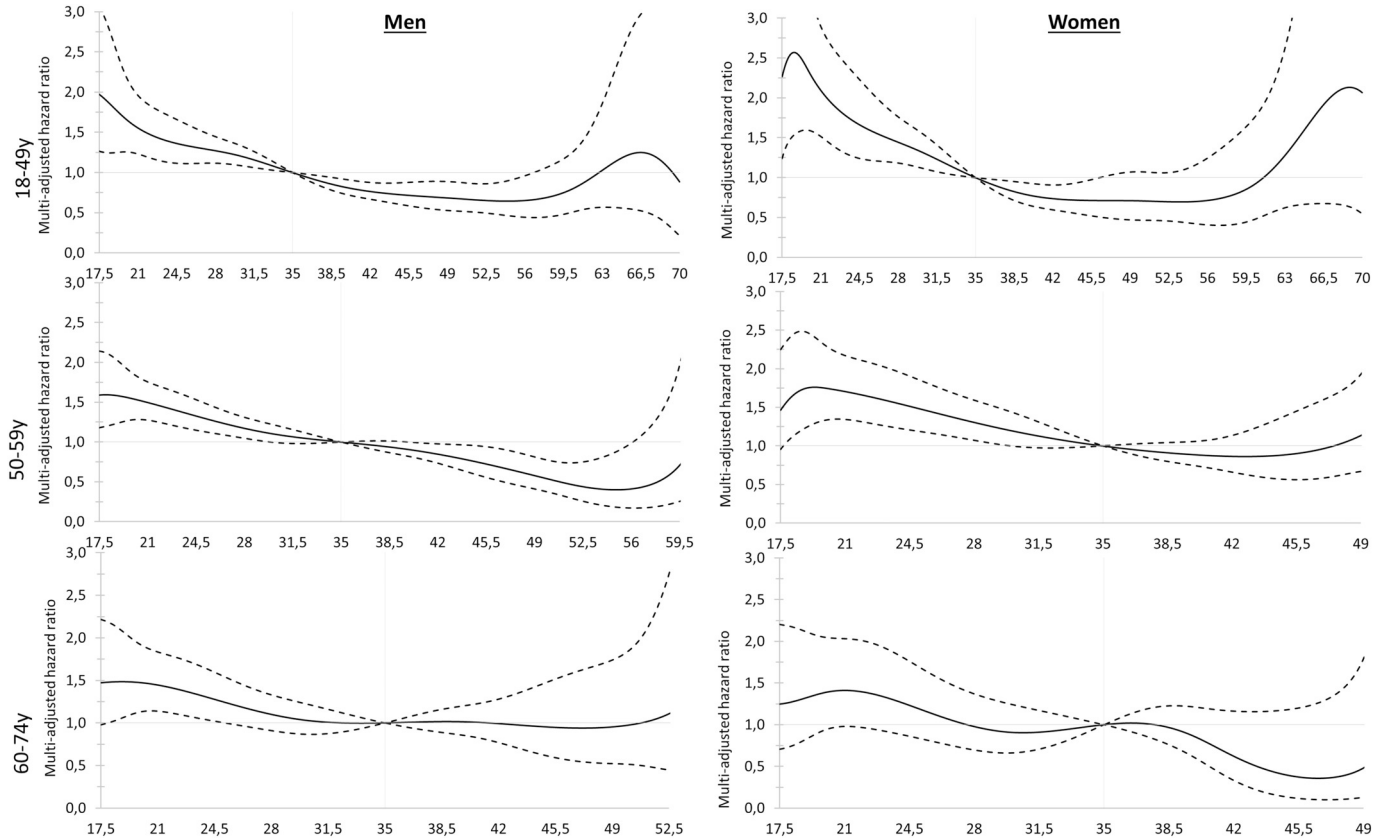
Appendix Fig. A.1.



Appendix Fig. A.2.



Appendix Fig. A.3.



Appendix Fig. A.4.

Appendix Table A.1
Hazard ratio (95% CI) of all-cause mortality in aggregated estVO$_2$max categories, with during first 2 years of follow-up excluded.

	≤24.5 ml	>24.5–35 ml	>35–45.5 ml	>45.5–56 ml	>56 ml
All (n = 2750)	1.55 (1.38–1.75)	1.15 (1.04–1.26)	1.00 (ref)	0.85 (0.71–1.02)	0.97 (0.67–1.40)
First 2 years follow-up excluded (n = 2477)	1.47 (1.30–1.67)	1.12 (1.02–1.24)	1.00 (ref)	0.82 (0.68–1.00)	0.88 (0.58–1.32)
Men					
18–49 years					
All	1.42 (1.03–1.96)	1.27 (1.05–1.54)	1.00 (ref)	0.73 (0.54–0.98)	0.87 (0.52–1.46)
First 2 years follow-up excluded	**1.20 (0.83–1.73)**	1.27 (1.04–1.56)	1	**0.73 (0.53–1.01)**	0.80 (0.44–1.45)
50–59 years					
All	1.60 (1.26–2.01)	1.16 (0.96–1.41)	1.00 (ref)	0.90 (0.58–1.40)	0.79 (0.11–5.68)
First 2 years follow-up excluded	1.50 (1.18–1.92)	1.11 (0.91–1.36)	1.00 (ref)	0.83 (0.52–1.33)	0.88 (0.12–6.31)
60–74 years					
All	1.75 (1.23–2.49)	1.03 (0.74–1.44)	1.00 (ref)	0.87 (0.35–2.19)	–
First 2 years follow-up excluded	1.85 (1.26–2.71)	1.08 (0.75–1.55)	1.00 (ref)	1.00 (0.40–2.55)	–
Women					
18–49 years					
All	1.32 (0.89–1.95)	1.24 (0.97–1.57)	1.00 (ref)	1.05 (0.75–1.47)	1.03 (0.55–1.93)
First 2 years follow-up excluded	1.15 (0.75–1.75)	1.19 (0.93–1.52)	1.00 (ref)	0.98 (0.69–1.39)	0.90 (0.45–1.80)
50–59 years					
All	1.45 (1.13–1.86)	0.97 (0.78–1.20)	1.00 (ref)	0.70 (0.40–1.22)	1.31 (0.32–5.30)
First 2 years follow-up excluded	1.42 (1.10–1.83)	0.96 (0.77–1.20)	1.00 (ref)	0.68 (0.38–1.21)	1.39 (0.34–5.64)
60–74 years					
All	1.46 (0.96–2.22)	1.28 (0.87–1.90)	1.00 (ref)	1.06 (0.37–3.02)	–
First 2 years follow-up excluded	1.40 (0.91–2.17)	1.25 (0.83–1.88)	1.00 (ref)	0.84 (0.26–2.77)	–

Bold text indicates change in significance between full sample and after exclusion of first two years of follow-up.
Adjusted sex, age, year performed, length of education, exercise, diet, smoking, overall stress.

Appendix Table A.2
Hazard ratio (95%CI) of CVD morbidity in aggregated estVO$_2$max categories, with during first 2 years of follow-up excluded.

	≤24.5 ml	>24.5–35 ml	>35–45.5 ml	>45.5–56 ml	>56 ml
All (n = 4244)	1.60 (1.45–1.76)	1.28 (1.19–1.39)	1.00 (ref)	0.75 (0.64–0.87)	0.79 (0.56–1.12)
Cases first 2 years follow-up excluded (n = 3534)	1.52 (1.37–1.70)	1.28 (1.18–1.40)	1.00 (ref)	0.79 (0.67–0.93)	0.70 (0.47–1.04)
Men					
18–49 years					
All	1.84 (1.48–2.30)	1.37 (1.18–1.58)	1.00 (ref)	0.75 (0.59–0.96)	0.88 (0.56–1.39)
First 2 years follow-up excluded	1.67 (1.30–2.14)	1.39 (1.19–1.62)	1.00 (ref)	**0.78 (0.61–1.01)**	0.76 (0.45–1.28)
50–59 years					
All	1.46 (1.24–1.73)	1.24 (1.09–1.42)	1.00 (ref)	0.66 (0.47–0.93)	0.92 (0.30–2.88)
First 2 years follow-up excluded	1.39 (1.16–1.67)	1.21 (1.05–1.40)	1.00 (ref)	0.65 (0.45–0.94)	0.74 (0.18–2.98)
60–74 years					
All	1.36 (1.04–1.76)	1.12 (0.89–1.42)	1.00 (ref)	1.14 (0.64–2.04)	1.99 (0.28–14.3)
First 2 years follow-up excluded	**1.31 (0.97–1.78)**	1.20 (0.92–1.56)	1.00 (ref)	1.14 (0.59–2.21)	2.74 (0.38–19.82)
Women					
18–49 years					
All	2.43 (1.77–3.35)	1.59 (1.26–2.01)	1.00 (ref)	0.97 (0.67–1.40)	1.15 (0.60–2.20)
First 2 years follow-up excluded	2.08 (1.45–2.98)	1.53 (1.19–1.97)	1.00 (ref)	1.03 (0.71–1.51)	0.99 (0.45–2.04)
50–59 years					
All	1.64 (1.27–2.12)	1.23 (0.98–1.54)	1.00 (ref)	0.81 (0.46–1.42)	–
First 2 years follow-up excluded	1.73 (1.30–2.29)	1.23 (0.96–1.59)	1.00 (ref)	1.01 (0.57–1.78)	–
60–74 years					
All	1.37 (0.91–2.05)	0.95 (0.65–1.41)	1.00 (ref)	0.47 (0.11–1.98)	–
First 2 years follow-up excluded	1.36 (0.87–2.13)	1.03 (0.68–1.58)	1.00 (ref)	0.59 (0.14–2.49)	

Bold text indicates change in significance between full sample and after exclusion of first two years of follow-up.
All analyses adjusted for sex, age, year performed, length of education, exercise, diet, smoking, overall stress.

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