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Survival of the fittest? Peak oxygen uptake and all-cause mortality among older adults in Norway

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ABSTRACT

Objective: To determine the cardiorespiratory fitness (CRF) levels needed to avoid the Grim Reaper (Death) among older adults. We hypothesized that an above average peak oxygen uptake (VO_{2peak}) is needed for 70–77-year-old men and women to delay the encounter with Death.
Design: Prospective cohort study.
Setting: General population of older adults in Norway.
Participants: 788 women and 777 men aged 70–77 years.
Intervention: Clinical assessments, including a test of VO_{2peak}. Participants were categorised based on their baseline VO_{2peak} and changes after 1 year. This study explored associations between VO_{2peak} and 5-year all-cause mortality using Cox proportional hazard models.
Main outcome measure: All-cause mortality.
Results: Death caught up with 5.3 % of men and 3.7 % of women. Compared to unfit men and women, fewer men (Hazard Ratio [HR]: 0.34, 95 % Confidence Interval [CI] 0.15–0.78) and women (HR: 0.41, 95 % CI 0.17–0.98) classified as moderately fit encountered Death with no additional risk reduction among those classified as being more fit. It appears to be easier for the Grim Reaper to claim those in poorer physical condition, specifically VO_{2peak} levels <26.5 mL/kg/min for men and 22.2 mL/kg/min for women (corresponding to ≥85 % of the observed age- and sex-specific average).
Conclusion: The Grim Reaper typically targets individuals with VO_{2peak} levels <26.5 mL/kg/min/ and <22.2 mL/kg/min when chasing male and female souls aged 70–77 years, respectively, reflecting his penchant for limited CRF. These data underscore the importance of maintaining or enhancing CRF throughout life, providing clear targets for clinicians in assessing patient CRF levels.
Trial registration: ClinicalTrials.gov NCT01666340.

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List of Abbreviations

BALL ST	(Ball State Adult Fitness Program Longitudinal Lifestyle Study)
BMI	(Body mass index)
CI	(Confidence interval)
CPET	(Cardiopulmonary exercise test)
CRF	(Cardiorespiratory fitness)
CVD	(Cardiovascular disease)
HR	(Hazard ratio)
MET	(Metabolic equivalent of task)
PA	(Physical activity)
VO_{2peak}	(Peak oxygen uptake)

Introduction

The Grim Reaper, the personification of Death, is a prominent figure in mythology, representing the concept of mortality (Central Figure). We already know from an observational study of community-dwelling men, aged ≥70 years in Australia, published in the 2011 Christmas Issue of *The BMJ*, that the Grim Reaper's preferred walking speed is below 5 km/h under working conditions.[1]

Cardiorespiratory fitness (CRF) was established as a vital clinical vital sign in 2016,[2] and numerous studies have consistently demonstrated that it is a more robust predictor of longevity than physical activity (PA) alone.[3–7] It is therefore of interest to know: 1) how fit older men and women need to be in order to reduce their likelihood of being caught by the Grim Reaper; and 2) what happens to the risk of facing the Grim Reaper if CRF levels change over time?

We assessed whether there was a relationship between CRF level, directly measured as peak oxygen uptake (VO_{2peak}), and the risk of being caught by Death in 788 women and 777 men from the general population of older adults in Norway. We also tested whether changes in VO_{2peak} over one year influenced this association. We hypothesized that having a VO_{2peak} above the sex-specific average would be sufficient to reduce the risk of facing the Grim Reaper.

Methods

Study design and population

This study derived its data from the Generation 100 Study.[8] The study population was men and women 70–77 years of age, living in Trondheim, Norway, in 2012. In total, 1567 older adults (790 women) participated. The recruitment procedures have been described in detail previously,[8,9] and the inclusion and exclusion criteria are summarized in Box 1. Given the inherent risk of being in the presence of Death, the Grim Reaper was not invited to our clinical examinations. The study was approved by the Regional Committee for Medical Research Ethics (REK 2012/381 B). In the main study, participants were randomized into three groups (a control group recommended to follow the national PA guidelines, or to one of two exercise groups: structured high-intensity interval training or moderate continuous training). Here, we categorize participants according to their baseline VO_{2peak} value and their change in VO_{2peak} after one year of participation, regardless of group allocation. To maintain the integrity of the data, we excluded two women who met the Grim Reaper during the first year of follow-up – a total of 1565 (788 women) were included in this study.

Clinical examinations

A full description of the test protocol has been provided previously.[9] In brief, participants completed a questionnaire regarding their health, socioeconomic status, and lifestyle. From this, we obtained information on self-reported cohabitation, smoking status, history of cardiovascular disease (CVD), cancer, general health, and higher education.

A cardiopulmonary exercise test (CPET) was undertaken using ergospirometry with either Oxycon Pro (Erich Jaeger, Hoechberg, Germany, $n = 72$), or Cortex Metamax II (Leipzig, Germany, $n = 1483$) to measure VO_{2peak}; the same system was used consistently for each individual. After a warm-up phase, an individualized test protocol was used whereby the workload was increased gradually approximately every 1.5 min, or when VO_2 became stable. This procedure was maintained until voluntary exhaustion (VO_{2peak}), or until maximal oxygen uptake (VO_{2max}) was reached. Combined with a respiratory exchange ratio of ≥1.05, a maximal test was considered achieved when the participant continued until exhaustion and VO_2 did not increase >2 mL/kg/min between two 30 s epochs (i.e., a levelling-off of VO_2 despite increased workload). As about 40 % of the participants did not reach a true VO_{2max}, we use the term VO_{2peak} throughout this paper.

Mortality follow-up

Participants in the study were tracked for all-cause mortality through the Norwegian Population Registry and Norwegian Cause of Death Registry, which records cause of death according to the International

Box 1

Inclusion criteria:

Born during 1936–1942, with a permanent address in Trondheim, Norway.

Able to complete the exercise program (determined by the researchers).

Exclusion criteria:

Illness or disabilities that preclude exercise or hinder completion of the study.

Uncontrolled hypertension.

Symptomatic valvular, hypertrophic cardiomyopathy, unstable angina, primary pulmonary hypertension, heart failure or severe arrhythmia.

Diagnosed dementia.

Cancer that makes participation impossible or exercise contraindicated. Considered individually, in consultation with physician.

Chronic communicable infectious diseases.

Test results indicating that study participation is unsafe.

Participation in other studies conflicting with participation in Generation 100.

Classification of Diseases. The start of follow-up was defined as the date of attendance at the baseline clinical examination. This follow-up continued until the participant's death or until December 31, 2018, whichever occurred first.

Statistical analysis

Upon summarizing the baseline characteristics of 777 men and 788 women, we compared VO_{2peak} at baseline and the 1-year change in VO_{2peak} between participants caught up by Death and their surviving peers using Welch's *t*-test. Cox proportional hazards regression was used to analyze the association between VO_{2peak} and 5-year all-cause mortality. In the main analyses, participants were categorised into four CRF groups based on VO_{2peak} at baseline. Participants with a VO_{2peak} <85% of the sex-specific mean constituted the unfit reference group, as previously proposed.[10–12] Participants with 85-–99 %, ≥100–109 %, and ≥110 % of the sex-specific mean VO_{2peak} were categorised as *moderately*, *average*, and *highly* fit, respectively. First, we investigated the association between categorised VO_{2peak} and all-cause mortality. Second, we repeated the analyses using continuous VO_{2peak} at baseline (mL/kg/min). Third, we assessed whether change in VO_{2peak} over 1 year (calculated as VO_{2peak} at 1 year minus VO_{2peak} at baseline) was associated with all-cause mortality, and whether adding the 1-year change to the Cox proportional regression model modified the association between baseline VO_{2peak} and all-cause mortality. Fourth, based on the primary analyses, we selected one of the three pre-defined cut-offs in relative VO_{2peak} (≥85 %, 100 %, or 110 % of the sex-specific average) and examined the association between categorical changes in VO_{2peak} from baseline to 1-year follow-up, using four fitness categories of maintained, increased, decreased VO_{2peak} above or below the chosen cut-off (≥85 % of average VO_{2peak}). Lastly, we reassessed the association between continuous VO_{2peak} and all-cause mortality *within* the strata of those who maintained a VO_{2peak} below ("danger zone") and above ("safe zone") 85 % of the sex-specific average. All analyses were stratified by sex and adjusted for age and cohabitant status [live alone; live together spouse/partner/other people]. At this point, it may have been desirable to adjust for other potential confounders. However, considering the rule of thumb of ≥10 cases (deaths) per covariate,[13–15] and the 5-year observation of only 41 and 29 deaths among men and women, respectively, additional adjustment would not be appropriate here. Descriptive data are shown as mean (standard deviation) for continuous variables and frequency (percentage) for categorical variables. For the hazard ratios (HR), 95 % confidence intervals (CI) are reported where relevant.

Missing values of VO_{2peak} at baseline ($n = 29$) and 1 year ($n = 355$) were replaced using multiple imputation with 100 imputations and 10 iterations. The imputation model included all variables in the main analysis model with the addition of body mass index (BMI) at baseline and 1 year as two auxiliary variables. R 4.2.1 (The R foundation, Vienna, Austria) was used for all statistical analyses.

Patient and public involvement

Initial study ideas were presented to a large gathering of older adults in Trondheim, Norway, approximately two years prior to commencement of the study. This was followed by more focused discussions about the study details with smaller groups of participant representatives approximately six months prior to seeking approval from the regional ethical committee. The study's inception and initial research inquiries were developed by the authors in collaboration with user representatives and public entities, including the Norwegian Directorate of Health. While the core research questions remained unchanged after participant input, adjustments were made to the exercise training regimen based on their preferences. Participants specifically requested structured training guidance and designated meeting points for group exercises. As a result, we organized training sessions every six weeks at our facility, supplemented by two weekly sessions at various outdoor locations in Trondheim throughout the study period. We conducted annual interactive meetings with participants to assess the study's progress. As a result of participant feedback, we discontinued the requirement for daily training diaries after one year due to their perceived burden and its impact on motivation. In addition, we established a dedicated webpage offering weekly updates and provided continuous support through a designated contact reachable via email or phone for eight hours daily. Several participants (but not the Grim Reaper) have actively engaged in our regular meetings where we disseminate research findings to the wider community.

Equity, diversity, and inclusion statement

As the world's population is rapidly aging, and there exist few large long-term randomized trials including older men and women, we chose to initiate the largest such trial ever performed. Therefore, in 2012, we invited all inhabitants (to secure that all got a chance to partake) of Trondheim, Norway, aged 70–77 years to participate in the study. Participants that accepted to take part in the study were more physically active, had better overall health and more had higher education (50 % vs 32 %) than non-included participants. The inhabitants in central Norway from which the potential Generation 100 Study population was recruited from is predominantly Caucasian and it was, therefore, not possible to study potential differences in outcome in different ethnicities. However, we did include individuals with different chronic diseases, that will allow for in-depth analysis of outcome effects in these groups in the future (too few outcomes per 2024 to have enough power for main outcome analysis for these subgroups). We did also include approximately the same number of men and women that allows for gender specific analysis of outcomes. The author team is a truly transdisciplinary team with complementary academic backgrounds. The team is balanced with representatives from 4 different ethnicities, 6 women and 9 men with 4 talented junior researchers.

Results

The baseline characteristics of the 1565 participants are presented in Table 1. Mean (SD) age was 72.8 (2.1) and 72.9 (2.1) years, BMI 26.4 (3.3) and 25.5 (3.8) kg/m^2, and VO_{2peak} 31.2 (6.8) and 26.1 (4.9) mL/kg/min for men and women, respectively. Overall, men had 20 % higher VO_{2peak} and higher educational level than women. During a mean follow-up time of 4.9 (0.4; range: 1.4–5.0) years, 41 of 777 (5.3 %) men and 29 of 788 (3.7 %) women were caught up by Death.

CRF at baseline and 1-year changes among those facing Death versus survivors

Men caught by Death had lower VO_{2peak} at baseline [28.7 (8.1) mL/kg/min] than survivors outrunning the Grim Reaper [31.3 (6.6) mL/kg/min; $p = 0.044$] and had a smaller 1-year increase in VO_{2peak} [0.4 (3.4) mL/kg/min vs. 1.6 (3.3) mL/kg/min; $p = 0.032$]. Similarly, women

Table 1
Baseline characteristics of the participants in the Generation 100 Study.

	Women ($n = 788$)	Men ($n = 777$)
Age, years	72.9 (2.0)	72.8 (2.0)
BMI, kg/m^2	25.5 (3.8)	26.4 (3.3)
VO_{2peak}, mL/kg/min	26.1 (4.9)	31.2 (6.8)
Married/cohabitant, %	61.5	87.3
Current smoker, %	10.2	8.6
History of CVD, %	10.0	23.8
History of cancer, %	16.1	16.6
Self-reported good health, %	86.3	88.5
Higher Education, %	43.3	57.7

Data are presented as mean (standard deviation) and percentage. BMI, body mass index; CVD, Cardiovascular disease; Higher education, college/university.

caught by Death had a lower VO_{2peak} at baseline [23.8 (4.9) mL/kg/min] than survivors outrunning the Grim Reaper [26.2 (4.9) mL/kg/min; $p = 0.014$] but showed a comparable 1-year increase in VO_{2peak} [1.9 (1.5) mL/kg/min vs. 1.7 (2.9) mL/kg/min; $p = 0.649$].

CRF categories at baseline, changes in fitness, and risk of facing death

The absolute risk of facing Death among men having a baseline VO_{2peak} categorised as unfit (<85 % of the sex-specific average) was 10.1 %, a risk that decreased linearly ($p = 0.046$) across CRF groups to 3.7 % among those categorised as highly fit (≥110 % of the sex-specific average; Table 2). Compared to unfit men, fewer men classified as moderately fit (85–99 % of average VO_{2peak}) encountered Death (HR: 0.34, 95 % CI 0.15–0.78) with no additional risk reduction among those classified as average fit (100–109 % VO_{2peak}; HR: 0.43 95 % CI 0.16–1.16) or highly fit (≥110 % VO_{2peak}, HR: 0.38 CI 0.17–0.84).

The absolute risk of facing Death among women having a baseline VO_{2peak} categorised as unfit (<85 % of the sex-specific average) was 8.0 %, a risk that decreased linearly ($p = 0.025$) across CRF groups to 2.7 % among those categorised as highly fit (≥110 % of the sex-specific average; Table 2). Compared to unfit women, fewer women classified as moderately fit at baseline (85–99 % VO_{2peak}) encountered Death (HR: 0.41, 95 % CI 0.17–0.98), with no additional risk reduction among those classified as average fit (>100–109 % VO_{2peak}; HR: 0.16, 95 % CI 0.04–0.71) or highly fit (>110 % VO_{2peak}, HR: 0.38, 95 % CI 0.14–1.03). Fig. 1 presents the association between CRF groups at baseline and survival probability for men and women, respectively.

Each 1-mL/kg/min higher VO_{2peak} at baseline was associated with 6 % (HR: 0.94, 95 % CI 0.80–0.90) and 10 % (HR: 0.90, 95 % CI 0.83–0.98) lower risk of facing Death for men and women, respectively. In men, each 1-mL/kg/min increase in VO_{2peak} from baseline to 1-year corresponded to a 10 % (HR: 0.90, 95 % CI 0.82–0.99) reduction in all-cause mortality. By accounting for both VO_{2peak} at baseline and the 1-year change, the risk reduction associated with these measures increased to 7 % (HR: 0.93, 95 % CI 0.88–0.98) and 13 % (HR: 0.87, 95 % CI 0.79–0.96), respectively, and improved the fit of the Cox proportional hazards regression model ($p < 0.001$). In contrast, the increase in VO_{2peak} over one year was not associated with a reduced risk of being caught up by Death in women, neither with (HR: 1.02, 95 % CI 0.88–1.18) or without (HR: 1.04, 95 % CI 0.91–1.19) adjustment of VO_{2peak} at baseline. Adding the 1-year change in VO_{2peak} did not improve the fit of the model ($p = 0.824$), nor did it modify the association between baseline VO_{2peak} and all-cause mortality (HR: 0.90, 95 % CI 0.83–0.98). For conversion to per 1-metabolic equivalent of task, raise the HRs and CIs for 1 mL/kg/min to the power of 3.5.

Table 2
Peak oxygen uptake at baseline and risk of all-cause mortality in men and women in the Generation 100 Study.

	n	VO_{2peak} (mL/kg/min)	Deaths (n)	Absolute risk (%)	Hazard Ratio, 95 % CI
Women					
Unfit (<85 % of average VO_{2peak})	162	< 22.2	13	8.0	Reference
Moderately fit (85–99 %)	251	22.2–26.0	8	3.2	0.41, 0.17–0.98
Average fit (100–109 %)	153	26.1–28.7	2	1.3	0.16, 0.04–0.71
Fit (≥110 %)	222	≥28.7	6	2.7	0.38, 0.14–1.03
VO_{2peak}	788	Per 1 mL/kg/min	29	–	0.90, 0.83–0.98
MET (3.5 mL/kg/min)	788	Per 1 MET	29	–	0.69, 0.53–0.93
Men					
Unfit (<85 % of average VO_{2peak})	188	<26.5	19	10.1	Reference
Moderately fit (85–99 %)	229	26.5–31.2	8	3.5	0.34, 0.15–0.78
Average fit (100–109 %)	119	31.3–34.3	5	4.2	0.43, 0.16–1.16
Fit (≥110 % VO_{2peak})	241	≥34.4	9	3.7	0.38, 0.17–0.84
VO_{2peak}	777	Per 1 mL/kg/min	41	–	0.94, 0.90–0.99
MET (3.5 mL/kg/min)	777	Per 1 MET	41	–	0.81, 0.69–0.97

VO_{2peak}; Peak oxygen uptake; MET, Metabolic equivalent of task.

Death risk zones

Fig. 2 presents the relative VO_{2peak} at baseline and 1-year follow-up, as percentage of the sex-specific average, for men and women who either stayed alive or were caught up by the Grim Reaper during follow-up. Among 119 men maintaining a VO_{2peak} < 85 % of average (<26.5 mL/kg/min; hereinafter the "danger zone") from baseline to 1-year follow-up, the Grim Reaper caught up with 15 (12.6 %) compared to 21 (3.7 %) of 570 men maintaining a VO_{2peak} ≥ 85 % of average (hereinafter the "safe zone"; $p < 0.001$; Table 3). The remaining 88 men with a VO_{2peak} ≥ 85 % of average on *one* occasion (hereinafter collectively referred to as the "unsafe zone") had an absolute risk of facing Death in between those belonging to the danger- and safe zones. Four of 69 (5.8 %) men who increased their VO_{2peak} from below to ≥85 % of average died; and 1 of 19 (5.3 %) men who decreased their VO_{2peak} from above to <85 % of the average died ($p > 0.05$ for all comparisons). To outrun the Grim Reaper and prevent 1 death within 5 years, 12 and 15 men either need to maintain (HR: 0.29, 95 % CI 0.15–0.57) or increase (HR: 0.46, 95 % CI 0.15–1.40) to a VO_{2peak} ≥ 85 % of average within 1 year, respectively (Table 3).

Of the 86 women in the danger zone, with VO_{2peak} values consistently < 85 % of average (<22.5 mL/kg/min), the Grim Reaper caught up with 5 (5.6 %) compared to 15 out of the 604 (2.5 %) women who were in the safe zone, ≥85 % of average VO_{2peak} ($p = 0.149$; Table 3). Ninety-eight women were categorised in the collective unsafe zone, in which 8 of 76 (10.5 %) women who increased their VO_{2peak} from below to ≥85 % of average died, and 1 of 22 (4.5 %) women who decreased their VO_{2peak} from above to <85 % of average died ($p > 0.05$ for all comparisons). To outrun the Grim Reaper and prevent 1 death within 5 years, 31 women need to maintain (HR: 0.47, 95 % CI 0.17–1.31) a VO_{2peak} ≥ 85 % of average for 1 year, instead of maintaining a VO_{2peak} < 85 % of average (Table 3). However, increasing to a VO_{2peak} ≥ 85 % of average over 1 year, did not reduce the risk of being caught up by Death.

In men *within* the danger zone, every 1-mL/kg/min higher VO_{2peak} at baseline was associated with a 17 % (HR: 0.83, 95 % CI 0.70–0.99) lower risk of facing Death, and every 1-mL/kg/min increase from baseline to 1 year was associated with 29 % reduced risk (HR: 0.71, 95 % CI 0.59–0.87). In contrast, in men *within* the safe zone, baseline higher VO_{2peak} and increased VO_{2peak} at 1 year were not associated with all-cause mortality (baseline HR: 1.02. 95 % CI 0.94–1.10; 1-year change HR: 0.96, 95 % CI 0.84–1.10). In women, there was no association between change in VO_{2peak} and all-cause mortality ($p > 0.05$ for all comparisons).

Table 4 shows cause of death by baseline health status, CRF groups and risk zones for both men and women. Data show that cancer (23 men, 23 women) was the leading cause of death. Among men and women, 7 and 2 died from cardiovascular diseases, and 11 and 4 from other causes, respectively. Fig. 3 illustrates the Grim Reaper monitoring older men and women during their weekly outdoor exercise – looking for potential victims.

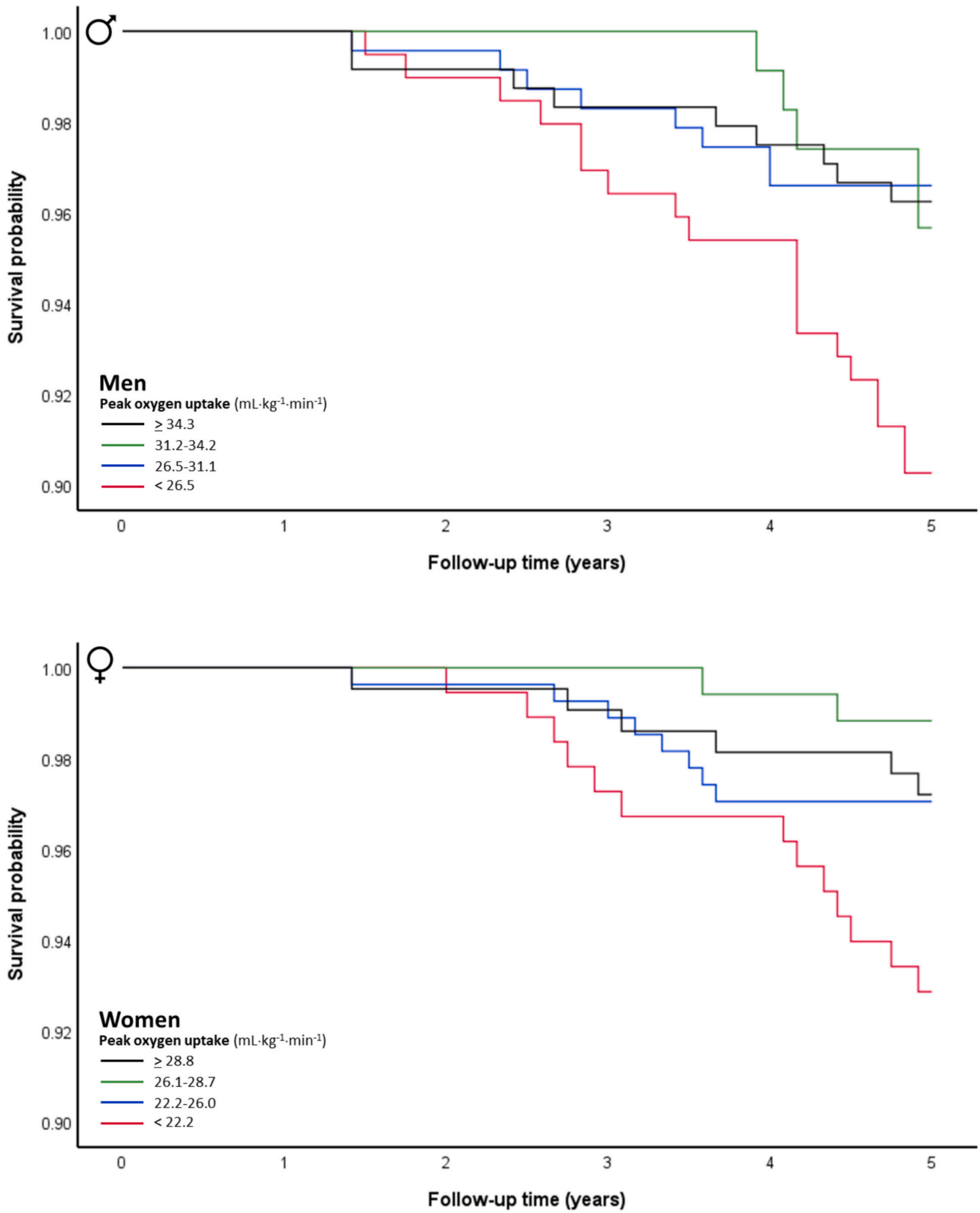

Fig. 1. Survival proportion of men for strata of peak oxygen uptake (VO_{2peak}) at baseline 1 in men (upper panel) and women. Based on Cox proportional hazards regression model adjusted for age and cohabitant status.

Discussion

To our knowledge, this is the first study to quantify the VO_{2peak} levels that older men and women should strive to reach to reduce risk of facing Death, which is of clear importance for public health. The main findings among men and women 70–77 years of age at baseline were that: 1) compared to having a VO_{2peak} < 85 % of the sex-specific average, a $VO_{2peak} \geq 85$ % lowers the risk of being caught by Death by 66 % in men and by 59 % in women, with no additional risk-reduction among those classified as being more fit; 2) each 1-mL/min/kg higher VO_{2peak} at baseline was associated with 6 % and 10 % lower risks of being caught by Death in men and women, respectively. For men, 3) maintaining a

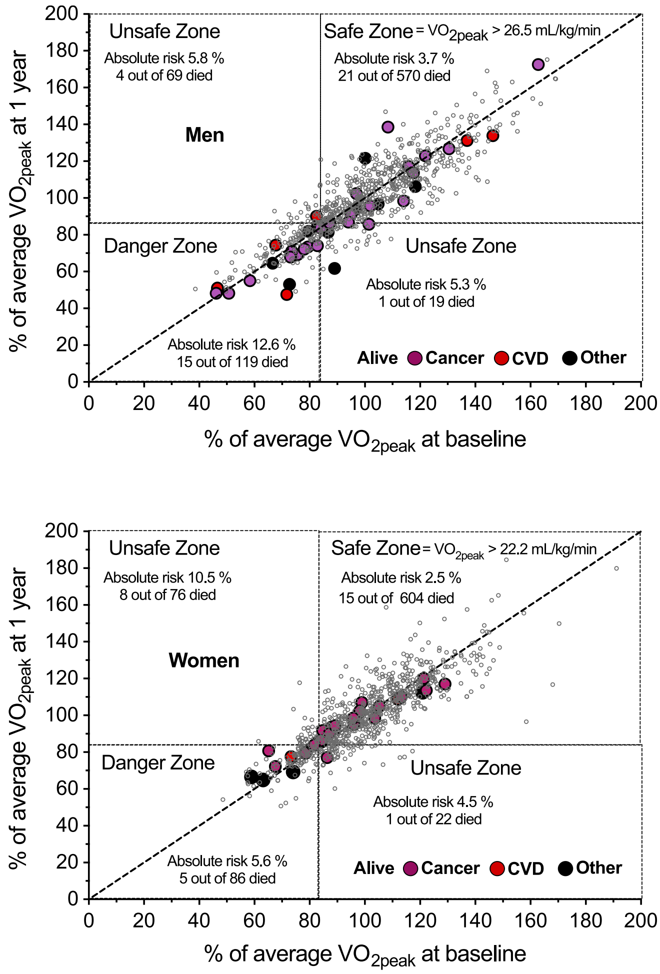

Fig. 2. VO_{2peak} for men (upper panel, average VO_{2peak} 31.2 mL/kg/min) and women (average VO_{2peak} 26.1 mL/kg/min) that died or stayed alive during the follow-up period.

$VO_{2peak} \geq 85$ % of average for one year constituted the "safe zone" with 71 % lower risk of being caught by Death compared to maintaining a $VO_{2peak} < 85$ % and being in the "danger zone"; 4) within the danger zone, every 1-mL/kg/min increase in VO_{2peak} from baseline to 1-year reduced the risk of Death by 29 %; 5) while chasing souls, the Grim Reaper tends towards men and women with a VO_{2peak}, <26.5 mL/kg/min and <22.2 mL/kg/min, respectively. These findings do not support our hypothesis that a higher-than-average VO_{2peak} is needed to reduce all-cause mortality, because older men and women with VO_{2peak} levels ≥85 % of the sex-specific average may outrun the Grim Reaper.

CRF at baseline and all-cause mortality

Our observation that men and women classified as moderately fit (85–99 % of the sex-specific average) had a significantly lower risk of facing Death than men and women categorised as unfit ($VO_{2peak} < 85$ % of average) aligns with findings from the Ball State Adult Fitness Program Longitudinal Lifestyle STudy (BALL ST),[16] including 4137 participants (mean age 42.8 years, 44 % women) with a mean follow-up of 24.2 years. The BALL ST showed that having moderate CRF levels, relative to one's age and sex, was associated with reduced all-cause mortality, as well as lower risk of death from CVD and cancer. Despite a 30-year age difference between the BALL ST cohort and our Generation 100 cohort, and 6 times longer follow-up time in the former, both studies underscore a similar conclusion; a single assessment of VO_{2peak} can effectively predict short- (this study) and long-term (BALL ST) mortality risk. The observed mortality rate of 10.1 % among men with <85 % of the sex-specific average VO_{2peak} is close to the expected 5-year mortality of around 10 % in the general older adult population in Norway.[17] Both men and women ≥85 % of VO_{2peak} at baseline were found to have a notably lower mortality risk than expected over five years (Table 2).

To aid the understanding of the relationship between VO_{2peak} and the risk of facing Death, we delved into more specific analyses. Building on the foundational insights mentioned above, which highlight the significant mortality risk-reduction associated with moderate CRF-levels in both men and women, we explored how incrementally higher VO_{2peak} values at baseline were associated with all-cause mortality risks. We found that for every 1-ml/kg/min higher VO_{2peak} at baseline, there was a corresponding decrease in risks of being caught by the Grim Reaper of 6 % and 10 % for men and women, respectively. These findings are in line with previous observational studies.[10,18–22] Our study adds to the literature that even small differences in VO_{2peak} modify all-cause mortality risk also in individuals aged ≥70 years.

CRF changes over one year of intervention

Previous studies report that an annual decrease in VO_{2peak} of approximately 2 % occurs in the age group we studied.[23,24] In contrast, over 1 year, we observed 5 % (1.6 mL/kg/min) and 7 % (1.7 mL/kg/min) increases in men and women, respectively. This confirms previous reports that older adults can improve their VO_{2peak}, even after the age of ≥70 years.[25]

Building on the observation of generally improved VO_{2peak} levels after 1 year, we proceeded to examine the effects of 1-year changes on the risk of being caught by Death. Among all men, every 1-mL/kg/min increase in VO_{2peak} at baseline and change in VO_{2peak} from baseline to 1 year, was associated with 7 % and 13 % risk-reductions, respectively. However, in men within the danger zone (i.e., maintaining $VO_{2peak} < 85$ % of average), each 1-mL/kg/min higher VO_{2peak} at baseline was associated with a 17 % lower risk of facing Death, and every 1-mL/kg/min increase from baseline to 1 year was associated with 29 % reduced

Table 3
Change in VO_{2peak} from baseline *to* 1-year and risk of all-cause mortality in men and women in the Generation 100 Study.

ZONES	n	Deaths (n)	Grim Reaper's Cause (n) Cancer	CVD	Other	Absolute risk (%)	Hazard Ratio, 95% CI
WOMEN							
Danger (<85% to <85% of average VO_{2peak})	86	5	1	1	3	5.8	Reference
Unsafe, decrease (≥85% to <85%)	22	1	1	0	0	4.5	0.77 (0.09-6.51)
Unsafe, increase (<85% to ≥85%)	76	8	8	0	0	10.6	2.01 (0.65-6.18)
Safe (≥85% to ≥85%)	604	15	13	1	1	2.5	0.47 (0.17-1.31)
MEN							
Danger (<85% to <85% of average VO_{2peak})	119	15	9	3	3	12.6	Reference
Unsafe, decrease (≥85% to <85%)	19	1	0	0	1	5.3	0.44 (0.05-3.35)
Unsafe, increase (<85% to ≥85%)	69	4	1	1	2	5.8	0.46 (0.15-1.40)
Safe (≥85% to ≥85%)	570	21	13	3	5	3.7	0.29 (0.15-0.57)

VO_{2peak}; Peak oxygen uptake. CVD; Cardiovascular Disease. The Grim Reaper refuses to give more information and refers to Stensvold et al.[8] for data supplement on "other causes" of death.

Table 4
Cause of death by baseline health status, fitness groups and risk zones.

Cause of Death VO_{2peak} at baseline	MEN (n = 777)								MEN WITH CANCER AT BASELINE (n = 131)								MEN WITH CVD AT BASELINE (n = 194)								MEN WITHOUT CANCER AND CVD AT BASELINE (n = 489)							
	n	†	Cancer, n		CVD, n		Other, n		n	†	Cancer, n		CVD, n		Other, n		n	†	Cancer, n		CVD, n		Other, n		n	†	Cancer, n		CVD, n		Other, n	
Unfit (<85 % of average VO_{2peak})	118	19	10	8.5 %	4	3.4 %	5	9.0 %	36	2	2	5.6 %	0	0.0 %	0	0.0 %	65	9	2	3.1 %	2	3.1 %	5	7.7 %	100	7	7	7.0 %	2	2.0 %	0	0.0 %
Moderately fit (85–99 %)	229	8	4	1.7 %	1	0.4 %	3	1.3 %	41	2	2	4.9 %	0	0.0 %	0	0.0 %	63	2	2	3.2 %	0	0.0 %	0	0.0 %	139	2	2	1.4 %	1	0.7 %	3	2.2 %
Average fit (100–109 %)	199	5	3	1.5 %	0	0.0 %	2	1.0 %	19	2	2	10.5 %	0	0.0 %	0	0.0 %	27	2	1	3.7 %	0	0.0 %	0	0.0 %	76	1	1	1.3 %	0	0.0 %	2	2.6 %
Highly fit (≥110 %)	241	9	6	2.5 %	2	0.8 %	1	0.4 %	25	3	3	8.6 %	0	0.0 %	0	0.0 %	39	1	1	2.6 %	0	0.0 %	0	0.0 %	174	3	3	1.7 %	2	1.1 %	1	0.6 %

Cause of Death VO_{2peak} at baseline	WOMEN (n = 788)								WOMEN WITH CANCER AT BASELINE (n = 131)								WOMEN WITH CVD AT BASELINE (n = 79)								WOMEN WITHOUT CANCER AND CVD AT BASELINE (n = 489)							
	n	†	Cancer, n		CVD, n		Other, n		n	†	Cancer, n		CVD, n		Other, n		n	†	Cancer, n		CVD, n		Other, n		n	†	Cancer, n		CVD, n		Other, n	
Unfit (<85 % of average VO_{2peak})	162	13	9	5.6 %	1	0.6 %	3	1.9 %	32	6	6	18.8 %	0	0.0 %	0	0.0 %	24	2	2	8.3 %	0	0.0 %	0	0.0 %	112	6	2	1.8 %	1	0.9 %	3	2.7 %
Moderately fit (85–99 %)	521	8	8	3.2 %	0	0.0 %	0	0.0 %	41	2	2	4.9 %	0	0.0 %	0	0.0 %	23	1	1	4.3 %	0	0.0 %	0	0.0 %	192	5	5	2.6 %	0	0.0 %	0	0.0 %
Average fit (100–109 %)	153	2	2	1.3 %	0	0.0 %	0	0.0 %	23	0	0	0.0 %	0	0.0 %	0	0.0 %	18	0	0	0.0 %	0	0.0 %	0	0.0 %	114	2	2	1.8 %	0	0.0 %	0	0.0 %
Highly fit (≥110 %)	222	6	4	1.8 %	1	0.5 %	1	0.5 %	35	3	3	8.6 %	0	0.0 %	0	0.0 %	14	0	0	0.0 %	0	0.0 %	0	0.0 %	175	3	1	0.6 %	1	0.6 %	1	0.6 %

Cause of Death VO_{2peak} from baseline to 1-year	MEN (n = 777)								MEN WITH CANCER AT BASELINE (n = 131)								MEN WITH CVD AT BASELINE (n = 194)								MEN WITHOUT CANCER AND CVD AT BASELINE (n = 489)							
	n	†	Cancer, n		CVD, n		Other, n		n	†	Cancer, n		CVD, n		Other, n		n	†	Cancer, n		CVD, n		Other, n		n	†	Cancer, n		CVD, n		Other, n	
Danger (<85 % to <85 % of avg. VO_{2peak})	119	15	9	7.6 %	3	2.5 %	3	5.0 %	22	1	1	4.5 %	0	0.0 %	0	0.0 %	46	6	2	4.3 %	1	2.2 %	3	6.5 %	60	9	7	11.7 %	2	3.3 %	0	0.0 %
Unsafe, decrease (≥85 % to <85 %)	19	1	0	0.0 %	0	0.0 %	1	5.3 %	2	0	0	0.0 %	0	0.0 %	0	0.0 %	7	0	0	0.0 %	0	0.0 %	0	0.0 %	11	1	0	0.0 %	0	0.0 %	1	9.1 %
Unsafe increase (<85 % to ≥85 %)	69	4	1	1.4 %	1	1.4 %	2	2.9 %	14	1	1	7.1 %	0	0.0 %	0	0.0 %	19	3	0	0.0 %	1	5.3 %	2	10.5 %	40	0	0	0.0 %	0	0.0 %	0	0.0 %
Safe (≥85 % to ≥85 %)	570	21	13	2.3 %	3	0.5 %	5	0.9 %	93	7	7	7.5 %	0	0.0 %	0	0.0 %	122	4	4	3.3 %	0	0.0 %	0	0.0 %	378	14	6	1.6 %	3	0.8 %	5	1.3 %

Cause of Death VO_{2peak} from baseline to 1-year	WOMEN (n = 788)								WOMEN WITH CANCER AT BASELINE (n = 131)								WOMEN WITH CVD AT BASELINE (n = 79)								WOMEN WITHOUT CANCER AND CVD AT BASELINE (n = 489)							
	n	†	Cancer, n		CVD, n		Other, n		n	†	Cancer, n		CVD, n		Other, n		n	†	Cancer, n		CVD, n		Other, n		n	†	Cancer, n		CVD, n		Other, n	
Danger (<85 % to <85 % of avg. VO_{2peak})	86	5	1	1.2 %	1	1.2 %	3	3.5 %	15	0	0	0.0 %	0	0.0 %	0	0.0 %	24	2	2	8.3 %	0	0.0 %	0	0.0 %	61	5	1	1.6 %	1	1.6 %	3	4.9 %
Unsafe, decrease (≥85 % to <85 %)	22	1	1	4.5 %	0	0.0 %	0	0.0 %	1	0	0	0.0 %	0	0.0 %	0	0.0 %	23	1	1	4.3 %	0	0.0 %	0	0.0 %	19	1	1	5.3 %	0	0.0 %	0	0.0 %
Unsafe increase (<85 % to ≥85 %)	76	8	8	10.5 %	0	0.0 %	0	0.0 %	17	6	6	35.3 %	0	0.0 %	0	0.0 %	18	0	0	0.0 %	0	0.0 %	0	0.0 %	51	1	1	2.0 %	0	0.0 %	0	0.0 %
Safe (≥85 % to ≥85 %)	604	15	13	2.2 %	1	0.2 %	1	0.2 %	98	5	5	5.1 %	0	0.0 %	0	0.0 %	14	0	0	0.0 %	0	0.0 %	0	0.0 %	462	9	7	1.5 %	1	0.2 %	1	0.2 %

Fig. 3. The Grim Reaper overseeing older men and women during their weekly outdoor exercise, on the lookout for potential victims.

mortality risk. In contrast, although men maintaining a $VO_{2peak} \geq 85$ % of average had a 71 % lower risk of Death than men in the danger zone, there was no association between change in VO_{2peak} and all-cause mortality *within* the safe zone, which supports the notion of them being in less danger. Our observation that a 1-mL/kg/min increase in VO_{2peak} over 1-year decrease the risk of Death is in line with similar observations by Kokkinos et al.,[21] and collectively, these findings suggest that mortality risk can be modified by small improvements in VO_{2peak} over time. Taken together, it appears that reasonable and achievable improvements in VO_{2peak} in men may lead to substantial health benefits, even in those aged ≥70 years.

In contrast to Kokkinos et al.,[21] we observed no association between the 1-year change in VO_{2peak} and all-cause mortality in women. One reason for this discrepancy may be a longer period between the two VO_{2peak} assessments; mean 5.8 years versus 1.0 year in our study. Another reason could be that our study had a shorter follow-up time, ranging from 1.4 to 5.0 years versus 1.0 to 20.5 years, with both fewer participants and lower event rate than that of Kokkinos and colleagues.[21] Nevertheless, our findings suggest that improving VO_{2peak} over one year was not enough to modify the 5-year risk of Death in women within this age category. Therefore, women in the safe zone should focus on staying in the safe zone to avoid facing Death. Another factor to consider is that women develop lifestyle diseases later in life than men.[26] It seems reasonable to speculate that with an expected higher mortality prevalence in this study population in the years to come, similar findings will also be seen in women. Indeed, we observed a large drop in survival probability during the last year of follow-up in both men and women categorised as unfit at baseline (Fig. 1). More studies are needed to elaborate on this topic.

In accordance with the findings by Imboden et al.,[27] our findings suggest that men who maintained a $VO_{2peak} \geq 85$ % of the sex-specific average over 1-year intervention showed a reduced all-cause mortality, with a similar trend in women. Imboden et al. studied the impact of a short-term exercise intervention on VO_{2peak} in 683 healthy adults (mean age 42.7 years, 41 % women).[27] After 3–8 months of individually prescribed exercise (based upon CPET results), VO_{2peak} improved by approximately 5 mL/kg/min, corresponding to a 15 % increase. In addition, maintaining a VO_{2peak} > 25th percentile was found to lower mortality risk, whereas participants who maintained a VO_{2peak} below this threshold showed an approximate 2-fold increase in mortality risk. Compared to our study, the study by Imboden et al. had a notably longer mortality follow-up (29.8 years versus 4.9 years) and a 2–3-fold larger relative increase in VO_{2peak} pre- to post-exercise.

Compared to other populations, the VO_{2peak} levels in our study are in line with that previously reported in Norwegian older adults aged ≥70 years.[28] This indicates that our findings are generalizable to healthy older adults in Norway. However, one of the largest reference materials for VO_{2peak} levels in different age groups (*FRIEND*), suggests that our 70–77-year-old men and women have the same average VO_{2peak} as 50–60-year-old men and 40–50-year-old women in the US, respectively.[29] This calls for larger studies assessing whether different optimal thresholds for VO_{2peak} can serve as guidance for future exercise programs for broader populations.

Survival of the fittest?

Contrary to our hypothesis, we found that even lower VO_{2peak} levels than the population average is enough to get a head start in the race with the Grim Reaper. Our findings align with observations by Laukkanen et al. from the *Kuopio Ischemic Heart Disease Risk Factor Study* including 1294 healthy men (mean age 52.1 years).[30] Their main findings were that VO_{2peak} showed a strong, graded, and independent association with overall-, CVD-, and non-CVD-related mortality and that the highest risk of all-cause mortality was found among men with a VO_{2peak} <27.6 mL/kg/min, not far from the <26.5 mL/kg/min in men categorised as unfit in our study. Compared to the participants in the study by Laukkanen et al., Generation 100 study participants were about 20 years older, but the men had similar average VO_{2peak} levels at baseline (32.7 mL/kg/min in their study versus 31.2 mL/kg/min in ours). Our findings contribute to the existing body of research by demonstrating the relevance of defining age- and sex-specific VO_{2peak} as targets for prevention of premature death.[31] Our data underscore the potential benefits of higher CRF levels in promoting health and longevity in later life and suggests that efforts to improve, and most importantly maintain, a sufficiently high CRF should not be neglected in older adults. This supports what Kokkinos et al.[32] observed among 70-year-old individuals referred for exercise tolerance testing, that a high age- and sex-relative CRF was associated with reduced all-cause mortality in both men and women. Of interest, a more recent study by Kokkinos et al. showed that changes in CRF reflect reciprocal changes in all-cause mortality.[21] Collectively, these findings reinforce the idea that staying ≥85 % of the average VO_{2peak} for one's sex and age is associated with lower all-cause mortality. Our data suggest that the Grim Reaper tends to target older men and women with a VO_{2peak} <26.5 mL/kg/min and <22.2 mL/kg/min, respectively. We acknowledge that the Grim Reaper's choice of target levels of VO_{2peak} may differ in other countries, as notably, the Grim Reapers target VO_{2peak} levels in Norwegian men and women is shown to correspond to the 80th and 90th percentile for American men and women aged 70–79 years old, respectively.[29] Of interest, using the FRIEND equation for VO_{2peak} to predict walking speed,[33] knowing that the treadmill inclination was 12.4 % and 11.8 % for men and women during VO_{2peak}-testing in our population,[34] we estimated that a walking speed of 6.2 km/h (men) and 5.8 km/h (women) were needed to obtain the required VO_{2peak} levels of ≥85 % of the sex-specific average in order to outrun the Grim Reaper. No data exist for women at this age, but the observed walking speed, for both men and women, was not far from the

5 km/h needed for men aged 70+ living in Australia to avoid contact with Death.[1]

Strength and limitations

Several limitations should be considered for this study. The Grim Reaper was not a participant in the Generation 100 Study, which only invited residents in Trondheim, Norway, aged 70–77 years. Also, considering his dangerous presence, we were unable to measure the Grim Reaper's VO_{2peak} directly. However, we do not consider this to be a significant limitation. Rather, we estimate the Grim Reaper's VO_{2peak} on the assumption that there is a VO_{2peak} threshold for reducing all-cause mortality, defined as the CRF level needed to outrun Death. Although the Generation 100 Study is one of the most comprehensive studies assessing the effect of directly measured VO_{2peak} on mortality in older adults, the participants may represent a healthier proportion of the general older-aged population. The observed mortality rate of 4.6 % is about half that of the expected mortality rate in this population over 5 years.[17] Thus, the generalizability of the findings to less healthy populations must be done with caution. The low mortality rate limits statistical power, which increases the risk of type II errors and false negative results (i.e., not detecting a difference where there is one). We acknowledge that we have used data from a randomized controlled trial but re-categorised the participants based on VO_{2peak} at baseline and 1-year follow-up. Instead, we classified our work as a prospective cohort study, and thus we do not draw any firm conclusions about cause and effect. Our rationale for re-categorizing the participants was a more direct analysis of the association between *differences and changes* in VO_{2peak} and all-cause mortality, and the fact that participants in the control group had a high level of activity throughout the study (Hawthorn effect), and most of them exercised using high intensity training (that is known to increase VO_{2peak} more than low-to-moderate intensity training). Further studies of the Grim Reapers working preferences in different regions/countries are needed.

The main strengths of the study include objectively measured VO_{2peak} in both men and women via CPET at two timepoints. This contrasts most previous studies that rely on VO_{2peak} estimates from one single occasion. Thus, our findings underscore the importance of *achieving and maintaining* an adequate VO_{2peak} level later in life for both sexes, and that small short-term changes in VO_{2peak} modify all-cause mortality in older men. Furthermore, we had a complete follow-up of all participants in the Norwegian Population Registry and Norwegian Cause of Death Registry. Despite the lower-than-expected mortality rate, our study was able to demonstrate sex-specific results, which should be considered a strength. The risk of type I errors and false positive results (i.e., detecting a difference where there is none), was held constant using the standard significance level of 5 %.

Conclusions and clinical implications

Our findings are a valuable addition to the understanding of CRF and all-cause mortality, with several unique contributions. We have shown that for older individuals, a $VO_{2peak} \geq 85$ % of the observed age- and sex-specific average is associated with a considerable reduction in all-cause mortality, and that small improvements in VO_{2peak} for men at baseline high risk provide substantial risk-reductions.

These findings highlight the importance of maintaining or improving CRF in later life, offering clear targets for clinicians when evaluating patient fitness levels, and for public health officials in designing age-appropriate PA recommendations. The evidence presented here reinforces the predictive value of VO_{2peak} and should encourage more personalized, proactive approaches to CRF and health in the aging population. In essence, this paper offers new insights into the predictive power of VO_{2peak} and its practical application in devising PA programs tailored to the aging demographic, marking a significant contribution to the field of preventive medicine and public health policies. In cases when direct measurements of VO_{2peak} are not feasible, we recommend older adults to estimate their CRF using our fitness calculator based on 20 years of research at The Norwegian University of Science and Technology.[35] Indeed, as suggested by the findings of this paper, CRF is directly associated with the risk of being outpaced by the Grim Reaper in the proximate future. Therefore, knowing one's CRF can aid in implementing targeted training programs to mitigate this risk and allow individuals to remain a step or more ahead of Death in the race of life. Effective training programs are free and available for all on our webpage.[36]

Author contributions

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Daniel E. Brissach – literature search, data analysis and interpretation, drafting manuscript.

Emma M.L. Ingeström – literature search, data analysis and interpretation, critical review of manuscript.

Tristan Tyrell – literature search, data analysis and interpretation, critical review of manuscript.

Carl Foster – literature search, supervision, critical review of manuscript.

Kimberley Radtke – literature search, supervision, critical review of manuscript.

John P. Porcari – literature search, supervision, critical review of manuscript.

Stian Lydersen – conceptualization, supervision, literature search, data analysis and interpretation, critical review of manuscript.

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Jeff Coombes – supervision, literature search, interpretation, critical review of manuscript.

Dorthe Stensvold – conceptualization, supervision, literature search, data analysis and interpretation, critical review of manuscript.

Ulrik Wisløff – conceptualization, supervision, literature search, data analysis and interpretation, drafting of manuscript.

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Data sharing

We are not permitted to share individual data from the current trial, but we are open to collaborative research with researchers worldwide, who can have access to analysed data from our university. We have also established a biobank of blood and genetic material that we plan to share with researchers worldwide, but individual data must be analysed within our university only.

Declaration of competing interest

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: Support from the Research Council of Norway; Norwegian University of Science and Technology (NTNU); Central Norway Regional Health Authority; St Olavs hospital, Trondheim, Norway; and the National Association for Public Health, Norway; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

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