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Age-related change in peak oxygen uptake and change of cardiovascular risk factors. The HUNT Study

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ABSTRACT

Background: Large longitudinal studies on change in directly measured peak oxygen uptake (VO_{2peak}) is lacking, and its significance for change of cardiovascular risk factors is uncertain. We aimed to assess ten-year change in VO_{2peak} and the influence of leisure-time physical activity (LTPA), and the association between change in VO_{2peak} and change in cardiovascular risk factors.
Methods and results: A healthy general population sample had their VO_{2peak} directly measured in two ($n = 1431$) surveys of the Nord-Trøndelag Health Study (HUNT3; 2006–2008 and HUNT4; 2017–19).
Average ten-year decline in VO_{2peak} was non-linear and progressed from 3% in the third to about 20% in the eight decade in life and was more pronounced in men. The fit linear mixed models including an additional 2,933 observations from subjects participating only in HUNT3 showed similar age-related decline. Self-reported adherence to LTPA recommendations was associated with better maintenance of VO_{2peak}, with intensity seemingly more important than minutes of LTPA with higher age. Adjusted linear regression analyses showed that one mL/kg/min better maintenance of VO_{2peak} was associated with favorable changes of individual cardiovascular risk factors (all $p \leq 0.002$). Using logistic regression one mL/kg/min better maintenance of VO_{2peak} was associated with lower adjusted odds ratio of hypertension (0.95 95% CI 0.92 to 0.98), dyslipidemia (0.92 95% CI 0.89 to 0.94), and metabolic syndrome (0.86 95% CI 0.83 to 0.90) at follow-up.
Conclusions: Although VO_{2peak} declines progressively with age, performing LTPA and especially high-intensity LTPA is associated with less decline. Maintaining VO_{2peak} is associated with an improved cardiovascular risk profile.

Cardiovascular disease (CVD) is a burden to societies and healthcare systems globally despite the reduction in CVD mortality over the last decades,[1,2] and strategies for population-level prevention of CVD should have high priority. Low cardiorespiratory fitness (CRF) is a strong predictor of morbidity and mortality from both CVD and other causes.[3,4] Furthermore, it is a predictor of dependence,[5] which is of interest given the aging populations in most countries. The growing knowledge of CRF as a powerful composite health measure in both clinical and apparently healthy populations was highlighted in the 2016 recommendations for cardiopulmonary exercise testing (CPET) by the European Association for Cardiovascular Prevention & Rehabilitation and the American Heart Association.[6] To exploit the potential of CRF in both preventive and clinical settings knowledge about reference values and normal age-related changes in CRF is needed.

In a sub-study of the third wave of the Nord-Trøndelag Health Study (HUNT3, 2006–2008) peak oxygen uptake (VO_{2peak}) was assessed by CPET in 4631 apparently healthy men and women, establishing a large reference material on VO_{2peak}.[7] Reference values from the Norwegian HUNT population and several other populations have shown that normal CRF values differ widely across various populations.[7–9]

Knowledge on the age-related decline in CRF is important for follow-up of patients in lifestyle interventions and for identification of

Abbreviations: ACLS, Aerobics Center Longitudinal Study; BMI, Body mass index; BP, Blood pressure; CARDIA, Coronary Artery Risk Development in Young Adults; CPET, Cardiopulmonary exercise testing; CRF, Cardiorespiratory fitness; CVD, Cardiovascular disease; HbA1c, Glycosylated hemoglobin; HDL, High-density lipoprotein cholesterol; HR, Heart rate; HUNT, Nord-Trøndelag Health Study [Helseundersøkelsen Nord-Trøndelag]; LTPA, Leisure-time physical activity; PA, Physical activity; VO_{2peak}, Peak oxygen uptake; WC, Waist circumference.

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abnormal trajectories in CRF for possible intervention. However, large studies have traditionally been confined to investigate this by cross-sectional designs which seem to underestimate the age-related decline observed when VO_{2peak} are investigated serially.[10,11] To our knowledge only two large individual-level longitudinal studies examining CRF in the whole adult population-span have been conducted.[11,12] Of these, only one measured CRF as VO_{2peak} by CPET.[11] The differences in cross-sectional and longitudinal findings, and lack of rigorous longitudinal studies emphasize the need for further studies.

Given the strong prognostic value of CRF for future health outcomes it is not unexpected that both CRF and change in CRF have been associated to favorable levels of CVD risk factors.[7,13] However, no studies have examined the association between change in directly measured VO_{2peak} and concurrent change in CVD risk factor levels in a large adult population.

Therefore, our aims were to use novel follow-up data from the HUNT study (HUNT4, 2017–2019) on VO_{2peak} to assess I) the age-related change in VO_{2peak} in an apparently healthy population sample after ten years, II) the influence of intensity and volume of leisure-time physical activity (LTPA) on change in VO_{2peak}, and III) the association between change in VO_{2peak} and change in CVD risk factors.

Methods

Study population

The study population includes 4404 participants from the HUNT3 Fitness Study, of whom 1471 also participated in the HUNT4 Fitness Study (Fig. 1). Exclusion criteria in the HUNT3 Fitness Study were presence of CVD, malignant, or pulmonary disease, or use of antihypertensive medication,[7] while exclusion criteria for the HUNT4 Fitness Study were disease or disability prohibiting exercise testing (see exhaustive list in Supplemental Methods).

Ethical approval for the current study and the HUNT4 Fitness Study itself was obtained from the Regional Committee for Medical Research Ethics (2019/7243, 2017/911).

CPET in HUNT4

The treadmill protocol used in HUNT4 was similar to HUNT3, which have been described previously.[7] In short, participants performed a 10-min warm-up followed by a stepwise protocol starting with two submaximal levels of 3 and 1.5 min, respectively, before inclination (1–2%) and/or speed (0.5–1 km/h) was increased every minute until voluntary exhaustion. Continuous gas analysis was done with the MetaLyzer II (Cortex Biophysik Gmbh, Leipzig, Germany) mixing chamber system with participants wearing an oro-nasal mask (Hans Rudolph V2, US) tested for leakage. VO_{2peak} was defined as the highest oxygen uptake averaged over 30 s (three 10 s measurements), and are presented as absolute (L/min) and relative (mL/kg/min) values. Observations were excluded from the analyses ($n = 227$, HUNT3; $n = 34$, HUNT4) if the respiratory exchange ratio was <1.0, indicating a submaximal effort, which is in line with previous studies.[9] Forty participants had a submaximal effort in HUNT3 but not in HUNT4. Peak heart rate (HR) was defined as the highest HR recorded during exercise. Further information regarding CPET, criteria for maximal oxygen uptake, calibration procedures, and reproducibility of measures are available in Supplemental Methods.

Clinical and biochemical measurements

Detailed information on collection of these measures have been described for HUNT3.[14] Briefly, weight was measured wearing light clothes without shoes, height standing relaxed, and waist circumference (WC) horizontally at umbilical level in a relaxed standing position with arms hanging. Body mass index (BMI) was calculated. Blood pressure (BP) was measured sitting using standardized methods to the nearest 2 mmHg by an oscillometry-based Dinamap Carescape V100 in HUNT4 and Critikon 845XT in HUNT3. The average of the last two of three measurements were used. Resting HR was measured during BP measurements and defined as the lowest of three measures. Non-fasting blood samples were analyzed for high-density lipoprotein (HDL) and total cholesterol, triglycerides, glucose (HUNT3 only), glycosylated hemoglobin (HbA1c; HUNT4 only), c-reactive protein, and creatinine. Total-cholesterol to HDL-cholesterol ratio was calculated.

Self-reported measures

Smoking status (never, former, regular, occasional, plus former occasional in HUNT4) was dichotomized to current occasional or regular smoker (yes/no), snuffing (never, former, regular, occasional) was dichotomized to current occasional or regular snuffer (yes/no), and alcohol intake ("About how often during the last 12 months did you drink alcohol?") was dichotomized to more than once per week (yes/no). Information on family history of CVD (stroke or myocardial infarction <60 years of age in first-degree relative), and information on previous cardiac, pulmonary, and malignant disease was also based on self-report questionnaires. Information on LTPA was gathered by validated questionnaires[15,16] in the baseline examinations of HUNT3 and HUNT4 with questions regarding frequency (never, less than once per week, once per week [1], 2–3 times [2.5] per week, or roughly every day [5]), duration of exercise each session (less than 15 min [7.5], 15–29 min [22.5], 30–60 min [45], or over 60 min [75]), and intensity as low ("I take it easy, I don't get out of breath or break a sweat"), moderate ("I push myself until I'm out of breath or break into a sweat"), or high ("I practically exhaust myself") intensity. Weekly minutes of LTPA was calculated based on values in brackets. Never or less than once per week of exercise was interpreted as inactive (no regular/weekly LTPA). Weighted weekly minutes of LTPA were calculated where low, moderate, and high intensity was weighted as 0.5, 1, and 2 multiplied by the weekly minutes of LTPA (with inactive as 0). Adherence to LTPA recommendations[17] was defined as ≥75 min high intensity LTPA or ≥150 min moderate intensity LTPA.

Statistical analyses

Time between participation in the HUNT3 and HUNT4 Fitness Studies was mean 10.2 years (range 9.5 to 11.0), and change in VO_{2peak} and CVD risk factors were therefore scaled to ten-year change ((value HUNT4 – value HUNT3) * (10/time in years)). Descriptive data on mean change in VO_{2peak} is presented by age group and sex for subjects participating at both examinations ($n = 1431$). Analyses on changes in VO_{2peak} with age were further performed by linear mixed-effects regression models using the lme4[18] package in R, and fitted by maximal likelihood to assess model performance by the Akaike information criterion. This design handles dependency of observations within participants[19] and allows imbalance between HUNT3 and HUNT4 participation, meaning that those only participating in HUNT3 ($n = 2{,}933$) or HUNT4 ($n = 40$) still could contribute with information to the model. We included age, sex, survey, weighted weekly minutes and intensity of LTPA, current smoking, alcohol use, and presence of CVD or pulmonary disease in the models. Time was modelled as participant age. We explored for interaction between model covariates and polynomials for age and weighted weekly minutes of LTPA. The final regression equations are available in Supplemental Methods. Presented figures were produced keeping continuous covariates at their mean (unless otherwise specified) and categorical covariates at representable proportions.

We performed linear regression analyses with change of traditional cardiovascular risk factors (HDL-cholesterol, total cholesterol, total cholesterol to HDL-cholesterol ratio, triglycerides, systolic and diastolic BP, resting HR, and WC) as the outcome and change of relative VO_{2peak} as

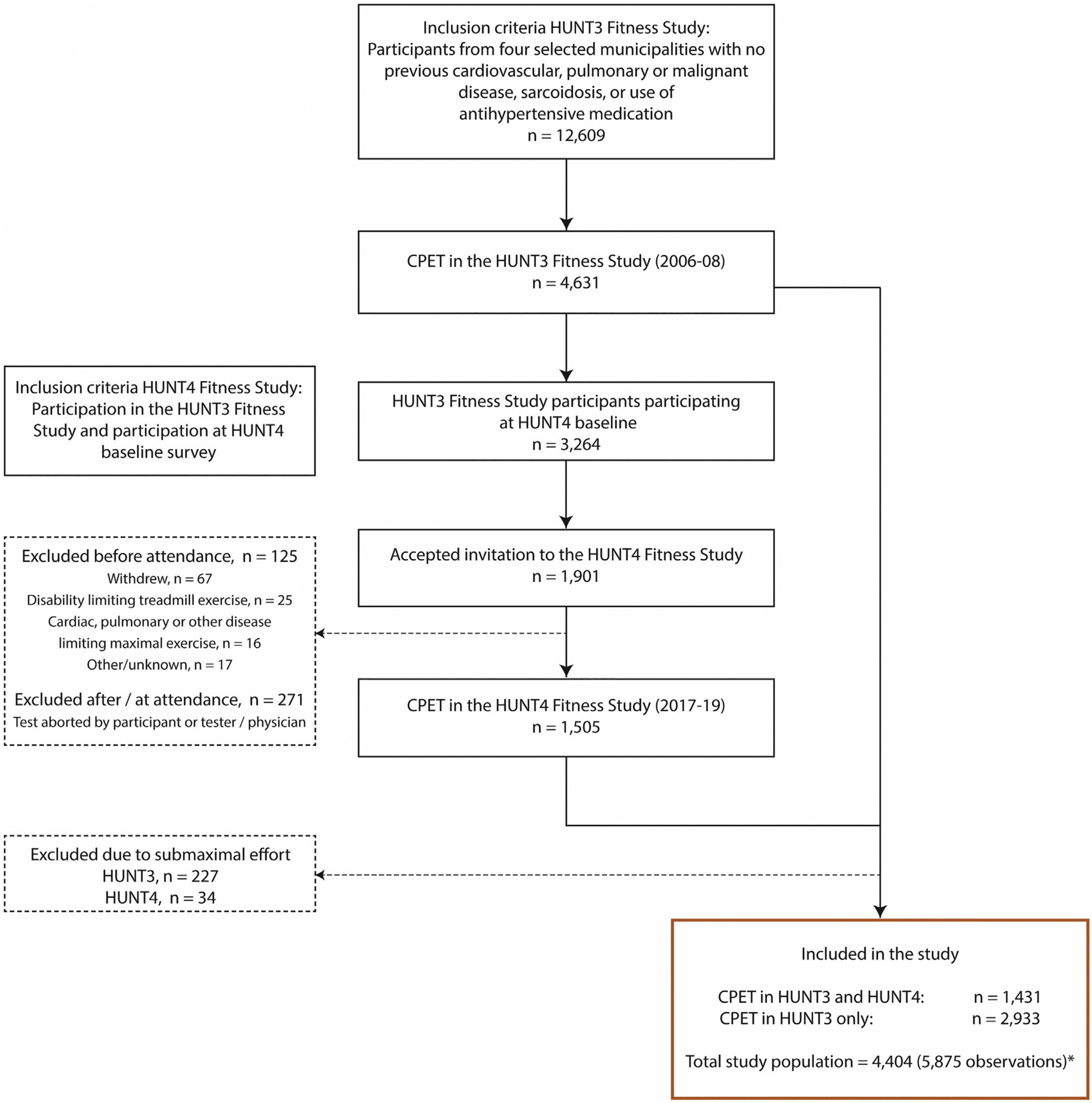

Fig. 1. Flow chart of the study population. *Forty participants had submaximal effort in HUNT3 but not in HUNT4.

predictor for the participants participating at both examinations. Analyses were adjusted for age and VO_{2peak} at baseline (HUNT3), sex, current smoking and regular alcohol intake at baseline and follow-up (HUNT4), family history of CVD, and incident CVD between baseline and follow-up in one model (model 1), plus weighted weekly minutes of LTPA at baseline and follow-up, and change and baseline value of weight in a second (model 2). Stratified analyses by sex, baseline VO_{2peak} (over/under age- and sex-specific averages), age (over/under 50 years), BMI (over/under 30 kg/m^2) were also performed. In analyses of systolic and diastolic BP and lipids we excluded participants with use of medication due to elevated BP or lipids, respectively. Assumptions regarding normality of residuals and heteroskedasticity were checked visually.

We also performed logistic regression analyses with presence of metabolic syndrome, dyslipidemia, and hypertension in HUNT4 as the outcome and change of relative VO_{2peak} as predictor for those participating at both examinations. Analyses were adjusted as for model 1 and model 2 plus adjustment for cholesterol and BP medication for dyslipidemia and hypertension, respectively, and adjustment for cholesterol medication for metabolic syndrome. Sensitivity analyses were performed by excluding those with medication use. Due to non-linear associations for age, age was included as a categorical covariate in the analyses for the metabolic syndrome. Definitions of metabolic syndrome, dyslipidemia and hypertension were based on established criteria (see Supplemental Methods). All statistical analyses were performed using R (www.r-project.org).

Results

Baseline characteristics, stratified by sex, from HUNT4 is shown in Table 1, and the age distribution among participants in HUNT3 and HUNT4 in Fig. 2A. Sex was balanced within age groups at both surveys. General characteristics from HUNT3 for all HUNT3 Fitness Study participants ($n = 4404$) and the participants repeating CPET in HUNT4 ($n = 1471$), as well as the repeated measures in HUNT4, are presented in Supplemental Table 1. Notably, adherence to physical activity (PA) recommendations was higher in HUNT4 (37%) than HUNT3 (28%), with the same trend of higher adherence for all age groups (except similar for age > 80 years). Active smoking declined from 13 to 3% from HUNT3 to HUNT4. VO_{2peak} data by deciles of age are shown in Supplemental Fig. 1.

Age-related change in VO_{2peak}

Average ten-year decline in VO_{2peak} was 3.7 mL/kg/min (10%) in women and 5.3 mL/kg/min (12%) in men, ranging from mean 3% decline in those between 20 and 30 years of age at baseline to about 20% in those between 70 and 80 years of age at baseline (sexes combined). Average ten-year change in VO_{2peak} by sex and deciles of age for both absolute (L/min) and relative (mL/kg/min) VO_{2peak} is shown in Fig. 2B–C, demonstrating an accelerated decline with advanced age for men compared to women. Percentage decline in absolute VO_{2peak} was similar for men and women at lower ages, while the same trend of accelerated decline in men was seen with higher age (Fig. 2D). Similar trends in decline in VO_{2peak} were seen when excluding participants with CVD between baseline and follow-up (Supplemental Fig. 2). The results from the linear mixed model showed the same non-linear pattern (Fig. 3). Both the descriptive data and model-predicted results indicate that the accelerated decline among men is most pronounced for absolute VO_{2peak}. In women the age-related decline in relative VO_{2peak} was more linear. Sensitivity analyses regarding the age-related decline in VO_{2peak} excluding participants not reaching true VO_{2max} did not make notable changes to the results.

LTPA and change in VO_{2peak}

Descriptive data for mean change of relative VO_{2peak} from HUNT3 to HUNT4 showed a clear trend towards lower decline in VO_{2peak} with adherence to PA recommendations and with higher intensity of LTPA (Supplemental Table 2). Specifically, adherence to LTPA recommendations in HUNT4 was associated with a 9.0% ten-year decline compared to a 15.9% decline in those being inactive. A higher number of weekly minutes of LTPA did not show the same clear pattern of higher VO_{2peak} in the descriptive data. Similar trends were seen when stratified by sex, although low numbers in some strata when stratifying by both LTPA and sex (data not shown). Results from the linear mixed model showed similar findings with a better maintenance of VO_{2peak} with better adherence to LTPA recommendations (Fig. 4A). Seventy-five minutes of high-intensity LTPA was associated with a similar age-related decline in VO_{2peak} as for 150 min of moderate intensity. However, age affected this relationship for men with high-intensity being associated with better maintenance of VO_{2peak} at higher age (Fig. 4B). With higher age the lines for predicted relative VO_{2peak} for 75 and 150 min of LTPA converge within intensity categories, indicating that the relative effect on VO_{2peak} of intensity increases with higher age compared to minutes of LTPA. In both HUNT3 and HUNT4 the percentage of participants performing high-intensity LTPA was lower with higher age.

Change in VO_{2peak} and change of CVD risk factor levels

Linear regression analyses showed significant associations between change in relative VO_{2peak} and favorable changes of HDL- and total cholesterol, total-cholesterol to HDL-cholesterol ratio, triglycerides, systolic and diastolic BP, resting HR, and WC (Table 2; Model 1). After further adjustment for weighted volume of LTPA, weight at baseline, and weight change (Model 2), significant associations to change in VO_{2peak} were seen for change of HDL, total-cholesterol to HDL-cholesterol ratio, resting HR and WC. Results were similar in analyses stratified by sex, age, baseline VO_{2peak}, and BMI (Supplemental Fig. 3), although effect estimates were generally higher for those with high BMI (>30 kg/m^2) for lipid and BP measures.

Odds ratios from logistic regression analyses for the association between per one unit (mL/kg/min) lower decline in VO_{2peak} and presence of the metabolic syndrome in HUNT4 was 0.86 (95% CI 0.83 to 0.90; Model 1) and 0.93 (95% CI 0.89 to 0.98, Model 2). For present dyslipidemia in HUNT4 the odds ratio was 0.92 (95% CI 0.89 to 0.94, Model 1) and 0.96 (95% CI 0.93 to 0.99, Model 2), and for present hypertension 0.95 (95% CI 0.92 to 0.98, Model 1) and 0.96 (95% CI 0.93 to 1.00, Model 2). Sensitivity analyses excluding those with medication use gave similar results.

Discussion

Our long-term follow-up data of VO_{2peak} in adults demonstrate a non-linear decline with higher age, and the progressive decline is more pronounced in men. Performing LTPA according to recommendations was associated with better maintenance of VO_{2peak}, and for both sexes high-intensity LTPA was associated with maintaining a higher VO_{2peak} with aging compared to moderate intensity. Better maintenance of VO_{2peak} was associated with a more favorable change in individual CVD risk factors and less CVD risk factor clustering at follow-up.

Table 1
General characteristics of the HUNT4 study population by sex.

	Women*	Men*
N (%)	743 (50.5%)	728 (49.5%)
Age (years)	59.1 (11.6)	60.5 (11.7)
Weight (kg)	69.7 (11.3)	84.8 (11.3)
Height (cm)	166 (5.7)	179 (6.3)
BMI (kg/m^2)	25.4 (3.9)	26.4 (3.1)
Waist circumference (cm)	90 (12)	96 (11)
Hip circumference (cm)	97 (6)	102 (5)
Resting heart rate (beats/min)	66 (11)	64 (11)
Systolic blood pressure (mmHg)	128 (19)	132 (17)
Diastolic blood pressure (mmHg)	73 (9)	78 (10)
HDL (mmol/L)	1.63 (0.37)	1.32 (0.30)
Cholesterol (mmol/L)	5.70 (1.1)	5.42 (1.1)
Cholesterol/HDL ratio	3.65 (1.0)	4.29 (1.2)
Triglycerides (mmol/L)	1.33 (0.7)	1.67 (1.0)
HbA1c (mmol/mol)	33.5 (3.8)	34.7 (5.0)
Creatinine (μmol/L)	67.1 (10.2)	81.8 (13.1)
C-reactive protein (mg/L)	1.92 (4.1)	1.63 (2.3)
VO_{2peak} (mL/kg/min)	33.8 (7.6)	40.5 (9.3)
VO_{2peak} (L/min)	2.34 (0.5)	3.41 (0.8)
Oxygen pulse (ml/beat)	13.6 (2.7)	19.9 (4.2)
Respiratory exchange ratio	1.11 (0.05)	1.11 (0.05)
Peak heart rate (beats/min)	172 (14)	171 (15)
Current smoker, n(%)	25 (3.4%)	19 (2.6%)
Regular alcohol intake, n(%)	200 (27%)	256 (35%)
Physically active, n(%)	264 (36%)	281 (39%)
Metabolic syndrome, n(%)	102 (14%)	129 (18%)
Cardiac disease, n(%)	30 (4%)	83 (11%)
Pulmonary disease, n(%)	19 (2.6%)	26 (3.6%)

Abbreviations: SD = standard deviation; BMI = body mass index; HDL-cholesterol = high-density lipoprotein cholesterol; HbA1c = glycosylated hemoglobin; VO_{2peak} = peak oxygen uptake; Physically active = adherence to physical activity recommendations.
* Values are mean (SD) or n (%).

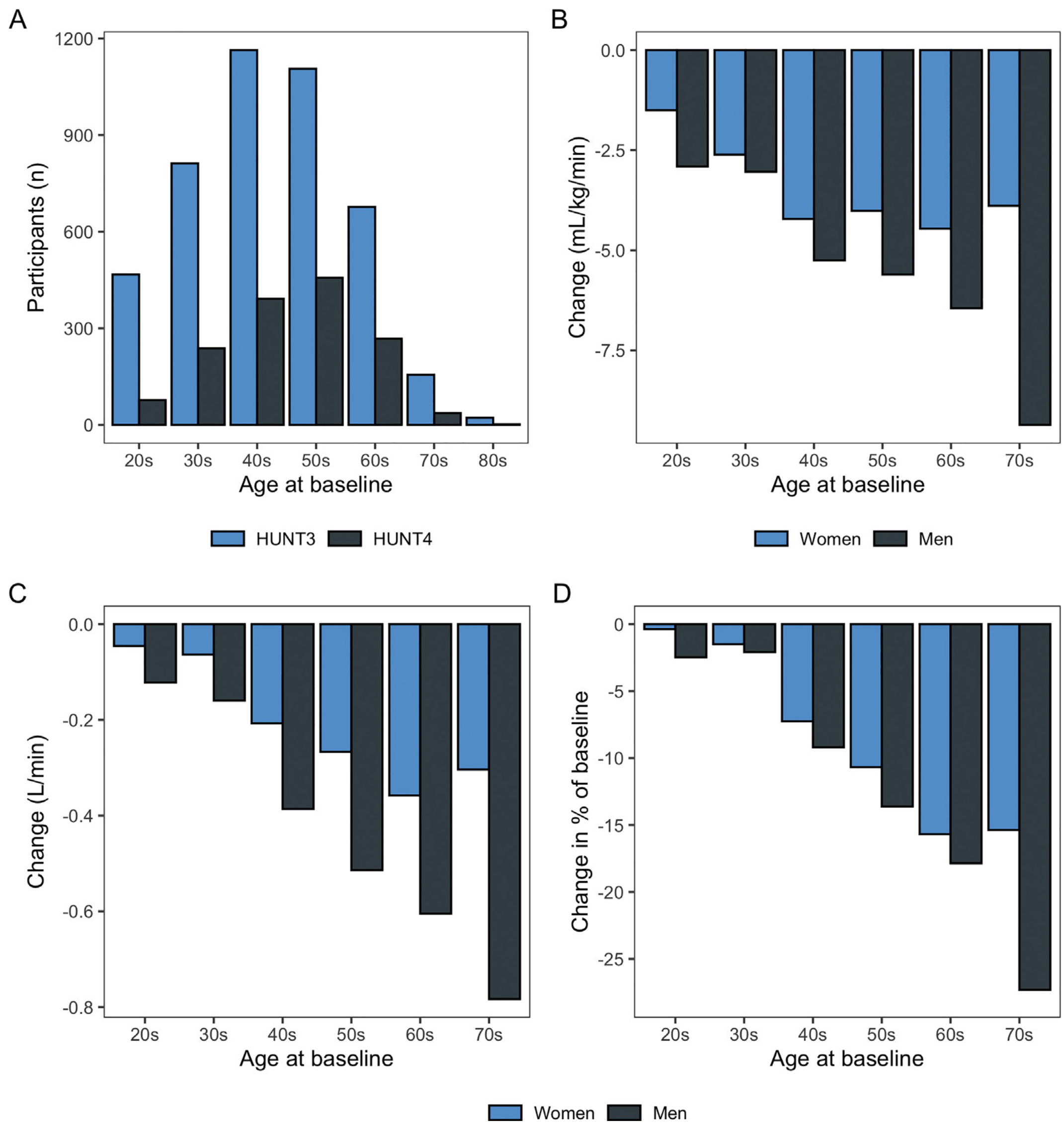

Fig. 2. Age distribution among participants in HUNT3 and HUNT4 (A), and decline in peak oxygen uptake as mL/kg/min (B), L/min (C) and percentage of baseline absolute peak oxygen uptake (D).

Age, LTPA, and change in VO_{2peak}

The progressive decline in VO_{2peak} with advanced age is in line with previous observations.[11,12] Fleg et al. assessed longitudinal changes in VO_{2peak} based on 2302 CPETs performed in 810 healthy volunteers (375 women) and reported an accelerated decline with higher age that was more pronounced in men.[11] The decline progressed from 5% per ten years in 30-year-old men to nearly 25% in 70-year-old men, comparable to our findings. The results for women were also similar, with a somewhat lower decline compared to men, and the percentage decline seemed to level off after the sixth decade. A study from the Aerobics Center Longitudinal Study (ACLS) using maximal treadmill exercise estimated CRF showed similar patterns.[12] Smaller longitudinal studies (~10 to 60 participants) with varied inclusion criteria have also shown relatively similar annual reductions in VO_{2peak}.[10] In our study the age-related peak in absolute VO_{2peak} occurs at about 25 to 30 years of age, similar to the findings by Fleg et al.[11] The decline in relative VO_{2peak} is evident from the early 20's. However, the study from the ACLS cohort showed a decline in relative CRF from about 35 years of age, but their models were conditioned for BMI providing a likely explanation for the different trends as weight change affects these interrelations, and weight increase at these ages is well established.[20] Longitudinal changes in VO_{2peak} scaled to fat-free mass support these interpretations.[11] Given weight being a decisive component in relative VO_{2peak} and the age-related changes in body weight/body composition, we decided not to condition for weight in models to predict age-related change in relative VO_{2peak}. Although our findings imply that the decline in VO_{2peak} in at least some sense seem to reflect inevitable physiological aging, performing LTPA, and especially high-intensity LTPA, may slow the decline. Both weekly minutes and intensity of LTPA was associated with higher VO_{2peak}, but notably high intensity was associated with a slower decline in VO_{2peak} by higher age compared to moderate intensity. The difference between the predicted lines of VO_{2peak} for 75 and 150 min of LTPA became smaller with higher age, while the difference between moderate and high-intensity LTPA was still large, especially in men. This may suggest that increasing intensity is more efficient than increasing minutes of LTPA, especially for older male individuals. Thus, these longitudinal observational data over a decade provide novel insights supporting findings from previous short-term randomized controlled trials showing superior effect of high-intensity compared to moderate intensity exercise on VO_{2peak}.[21] LTPA was also associated with higher CRF in previous longitudinal studies, however these studies did not report differential effects of LTPA intensity on the age-related decline.[11,12]

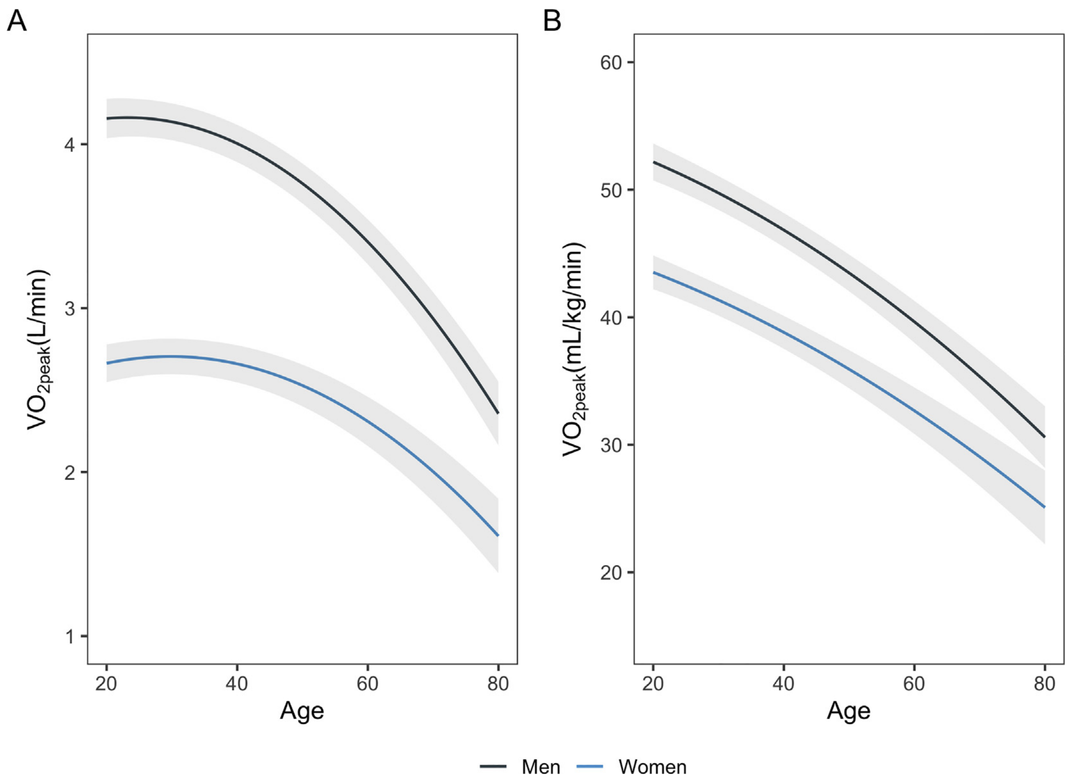

Fig. 3. Age-related change in absolute (A) and relative (B) peak oxygen uptake (VO_{2peak}) by sex with associated 95% confidence intervals.

Concurrent change in VO_{2peak} and CVD risk factors

Results from the CARDIA (Coronary Artery Risk Development in Young Adults) study showed a significant inverse association between change in CRF and development of the metabolic syndrome, but not with development of hypertension or hypercholesterolemia.[22] However, the 2478 participants were all relatively young (<30 years), and CRF was estimated by maximal treadmill time, which may explain some of the discrepancy to our study. Few other studies have examined the *concurrent change* of CRF and CVD risk factors, but another investigation from the CARDIA study showed how change in CRF was associated with change in HDL-, LDL- and total-cholesterol, and triglycerides, while only the association with HDL-cholesterol was significant after adjustment for weight change.[23] These findings are similar to ours. Similarly, a study from Belgium showed an association between change in VO_{2peak} over ~10 years and change in individual and clustered cardiovascular risk factors in 425 adults.[24] Further, they showed that the effect of moderate-to-vigorous PA on CVD risk factors was mediated by VO_{2peak}. A study from the ACLS cohort found significant associations between change in CRF and development of hypertension, dyslipidemia, and metabolic syndrome in 3148 participants, as well as significant correlations between change in CRF and change in the individual levels of blood lipids, BP, and WC.[25] In our models adjusted for LTPA, weight and weight change the associations were attenuated retaining only clear associations between VO_{2peak} and HDL-cholesterol, total-cholesterol to HDL-cholesterol ratio, resting HR, and WC. Clearly, PA and weight reduction are keys in CRF improvement and general CVD risk reduction, and attenuation of these associations is thus in line with what one would expect.

Strengths and limitations

The repeated measures of VO_{2peak} by gold standard CPET in a large, free-living, and at baseline apparently healthy population sample is the main strength of the study. As part of a large population study we had access to high-quality measurements of measured and self-reported covariates for analyses. As for all studies performing voluntary exercise testing, selection bias is an issue, and as previously reported the HUNT3 Fitness Study participants were slightly leaner, more physically active, and had a favorable CVD risk profile compared to non-participants.[7] Survivor bias (from death or diagnoses leading to study exclusion), in particular between HUNT3 and HUNT4, affects the population returning to testing in HUNT4. The differences at HUNT3 between those repeating testing in HUNT4 and the whole HUNT3-population were small, but with trends towards healthier returning participants and a higher baseline VO_{2peak}. Time of measurements (period effects) and birth cohort (cohort-effects) may influence studies on the normal aging-process of CRF such as ours due to e.g. societal changes. This may also explain some of the reported discrepancy between cross-sectional and longitudinal decline in CRF.[10,11] Self-reported LTPA at baseline and follow-up as the sole information on LTPA for a decade follow-up of change in VO_{2peak} is another limitation, and self-reported measures of PA has previously been shown to be less accurate in individuals >65 years compared to younger individuals,[26] which may affect the observed relationships between LTPA and VO_{2peak}. Also, levels of LTPA was not matched on energy expenditure in the comparisons in this study. The observational data also precludes firm conclusions regarding cause and effect, especially noteworthy for the analyses on change in VO_{2peak} and change in CVD risk factors adjusted for weight and LTPA, as these factors and VO_{2peak} are closely related entities without a straightforward causal relation. That mentioned, these longitudinal observational data over ten years support randomized trials indicating a relation between CRF response and lowering of CVD risk factors.

Clinical implications

Given that many of the health-benefits from PA seem to be mediated through CRF as shown in several studies, PA recommendations should

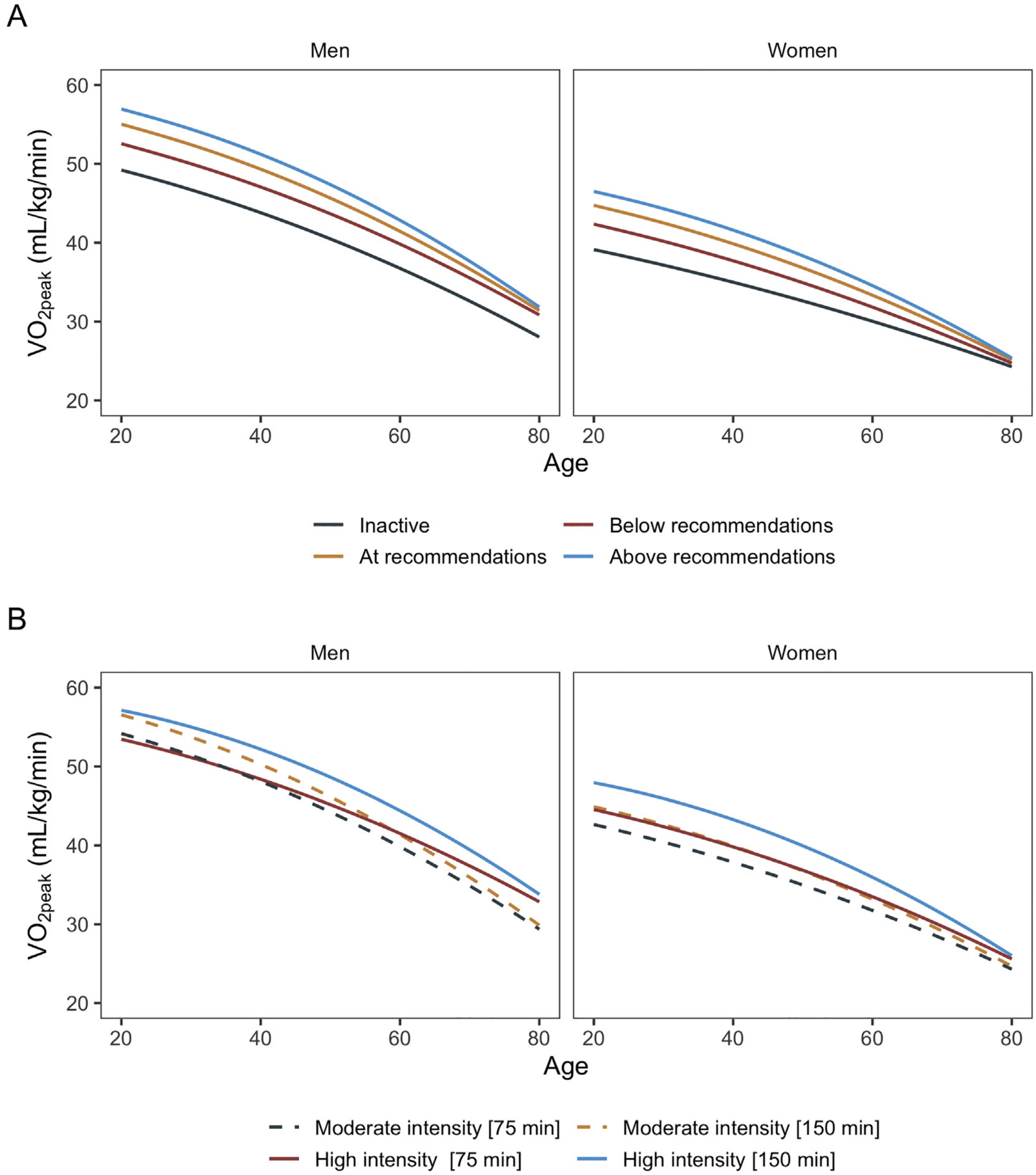

Fig. 4. Age-related change in relative peak oxygen uptake (VO_{2peak}) by measures of leisure-time physical activity (LTPA) for women and men by A) adherence to physical activity recommendations (inactive = 0, below recommendations = 75, at recommendations = 150, and above recommendations = 225 weighted weekly minutes of LTPA), and B) 150 and 75 weekly minutes of LTPA of moderate and high intensity.

Table 2
The associations of one mL/kg/min lower decline of peak oxygen uptake (VO_{2peak}) with change in different cardiovascular risk factors.

	Model 1†			Model 2‡		
Risk factor (dependent)*	Beta	95% CI	p	Beta	95% CI	p
HDL-cholesterol	0.010	0.008, 0.013	<0.001	0.005	0.001, 0.008	0.004
Cholesterol	−0.015	−0.024, −0.006	<0.001	−0.001	−0.011, 0.009	0.9
Cholesterol/HDL-cholesterol ratio	−0.040	−0.048, −0.031	<0.001	−0.014	−0.02, −0.005	0.003
Triglycerides	−0.028	−0.037, −0.018	<0.001	−0.004	−0.015, 0.006	0.4
Systolic blood pressure	−0.27	−0.44, −0.1	0.002	−0.088	−0.28, 0.11	0.4
Diastolic blood pressure	−0.16	−0.26, −0.0634	0.001	−0.095	−0.21, 0.02	0.10
Resting heart rate	−0.29	−0.40, −0.18	<0.001	−0.21	−0.34, −0.10	<0.001
Waist circumference	−0.70	−0.78, −0.61	<0.001	−0.13	−0.21, −0.06	<0.001

Abbreviations: CI = confidence interval; VO_{2peak} = peak oxygen uptake; HDL = high-density lipoprotein.
* Change in relative VO_{2peak} was used as independent variable in the models.
† Model 1: adjusted for age at baseline, sex, VO_{2peak} at baseline, current smoking and regular alcohol intake at baseline and follow up, family history of CVD, and incident CVD between baseline and follow-up.
‡ Model 2: adjusted as for model 1 plus weighted volume of physical activity at baseline and follow-up, and weight at baseline and change in weight between baseline and follow-up.

emphasize the importance of performing PA known to increase or maintain CRF. Results from this study suggest that, especially with higher age, performing high-intensity LTPA may be more beneficial on VO_{2peak} than increasing the weekly minutes of LTPA. Although this study presents observational data, the value of maintaining a high VO_{2peak} is supported by the association between maintaining VO_{2peak} and a more favorable CVD risk profile.

The provided longitudinal data on age-related decline in VO_{2peak} may assist clinicians in interpreting trajectories of CPET data to identify abnormalities, although caution should be taken when comparing different populations.

Conclusions

Our study shows that VO_{2peak} declines progressively with age, but performing LTPA, and especially high-intensity LTPA, may slow the decline. Maintaining a higher VO_{2peak} is also associated with favorable changes of CVD risk factors. These findings may have implications for future PA recommendations, and should ease and further encourage regular assessment of LTPA and CRF by clinicians involved in preventive medicine.

Authors contributions

Conceptualization: JL, HD, UW, and BN. Data curation: JL, HD, SA, UW, and BN. Formal analysis: JL, ØS and BN. Funding and acquisition: BN and UW. Investigation: All authors. Methodology: JL, ØS and BN. Project administration, recources and supervision: HD, UW and BN. Resources: UW and BN. Visualization: JL. Writing original draft: JL. Writing, review & editing: all authors. co All authors gave final approval of the manuscript, and agrees to be accountable for all aspects of work ensuring integrity and accuracy.

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There are no relations to industry associated with this work.

Declaration of Competing Interest

The Authors declare that there is no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pcad.2020.09.002.

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