Master's thesis

NTNU
Norwegian University of Science and Technology
Faculty of Medicine and Health Sciences
Department of Neuromedicine and Movement Science

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Non-Exercise Estimated Cardiorespiratory Fitness in Relation to Urinary Tract, Bladder and Kidney Cancer Incidence

The HUNT Study

Master's thesis in Physical Activity and Health
Supervisor: Xiao-Mei Mai
Co-supervisor: Yi-Qian Sun

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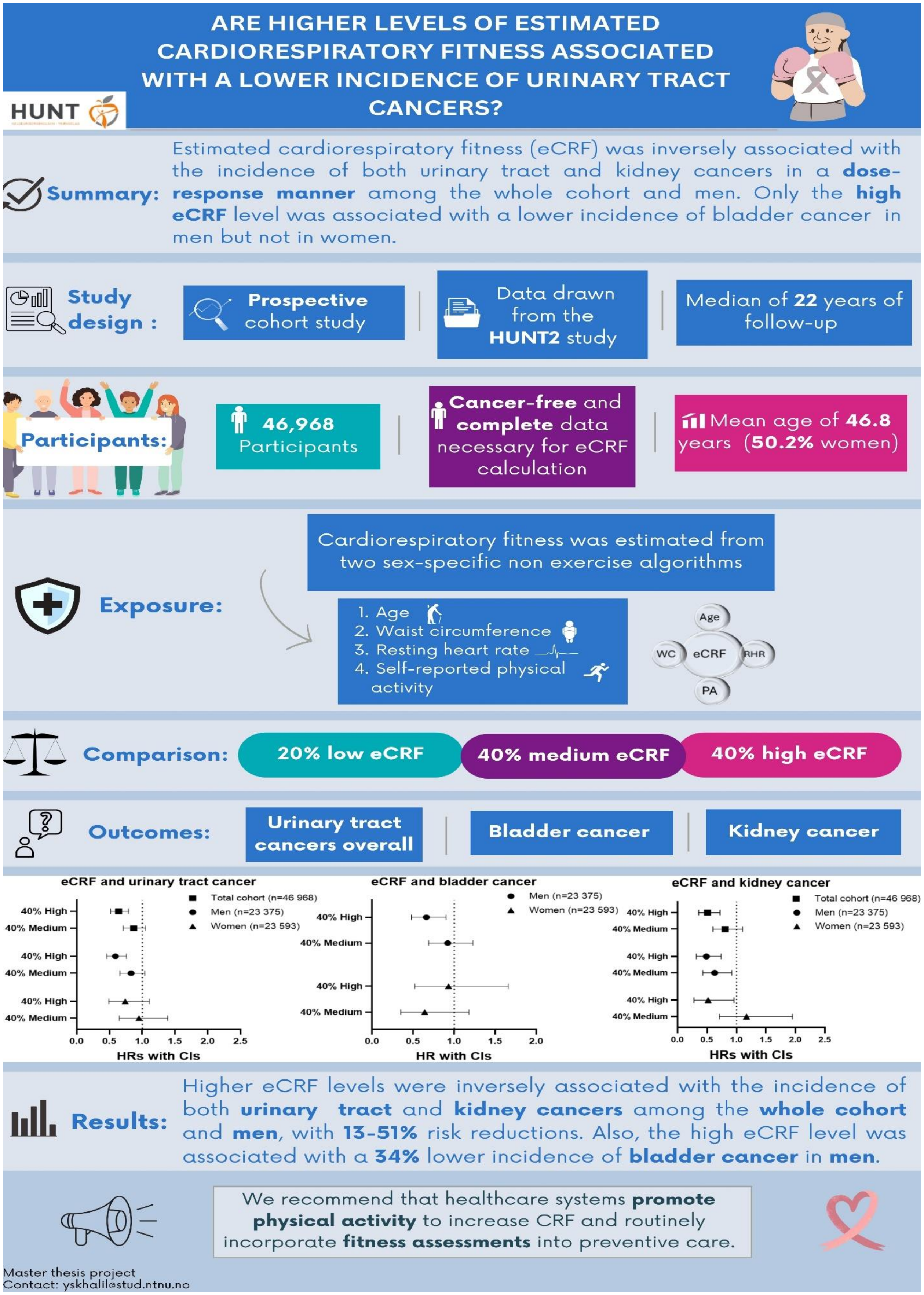
List of Abbreviations

Abbreviation	Full Form
ACSM	American College of Sports Medicine
BMI	Body Mass Index
CI	Confidence Interval
CRF	Cardiorespiratory Fitness
DAG	Directed Acyclic Graph
DM	Diabetes Mellitus
eCRF	Estimated Cardiorespiratory Fitness
EGP	Erikson Goldthorpe Portocarero
HUNT	The Nord-Trøndelag Health Study
HR	Hazard Ratio
ICD–10	International Classification of Diseases, Tenth Revision
IRR	Incidence Rate Ratio
LRT	Likelihood Ratio Test
LOWESS	Locally Weighted Scatterplot Smoothing
PA	Physical Activity
PH	Proportional Hazard
pyrs	Person-Years
RHR	Resting Heart Rate
VO2max	Maximum Oxygen Uptake
VO2peak	Peak Oxygen Uptake
WC	Waist Circumference
WHO	World Health Organization

Infographic



Abstract

Objective: To investigate the associations between non-exercise estimated cardiorespiratory fitness (eCRF) and the incidence of urinary tract cancer overall, along with the site-specific incidence of bladder and kidney cancers within a large prospective cohort of Norwegian adults.

Methods: This prospective cohort study used the second survey of the Nord-Trøndelag Health Study (HUNT2), conducted between 1995 and 1997. 46 968 cancer-free adults who had complete data on eCRF at baseline were included. eCRF was determined using two sex-specific prediction models based on age, waist circumference, resting heart rate, and self-reported physical activity. eCRF was further classified into age-specific quintiles (based on a 10-year interval) within each sex group and merged into 3 categories: 20% low, 40% medium, and 40% high. Information about cancer diagnosis was obtained from the Cancer Registry of Norway. We used the Cox proportional hazards models to estimate hazard ratios (HR) and 95% confidence intervals (CI) after adjusting for important confounders.

Results: Over a median follow-up of 22.2 years, there were 652, 381, and 255 incidents of urinary tract, bladder, and kidney cancers, respectively. Medium and high levels of eCRF were associated with lower incidence of urinary tract cancer in the total cohort (HR = 0.64, 95% CI: 0.51–0.79 and HR = 0.87, 95% CI: 0.71–1.05, P-value for trend <0.001), and especially among men (HR = 0.83, 95% CI: 0.66–1.04 and HR = 0.59, 95% CI: 0.46–0.76, P-value for trend <0.001). Only the high eCRF level was associated with a lower incidence of bladder cancer in men (HR = 0.66, 95% CI: 0.48–0.90), but no association was found in women (HR = 0.93, 95% CI: 0.52–1.66). The P-value of the Likelihood Ratio Test for effect modification by sex = 0.027. There was a clear and inverse dose-response association between eCRF and kidney cancer in the total cohort (P-value for trend <0.001) and specifically in men (P-value for trend <0.001). The high eCRF level was also associated with a reduced incidence of kidney cancer among women (HR = 0.52, 95% CI: 0.28–0.96).

Conclusion: Higher levels of eCRF were associated with a lower incidence of both urinary tract and kidney cancers in the total cohort and especially among men. Also, only the high eCRF level was associated with a lower incidence of bladder cancer in men. Future studies with larger sample sizes are needed to explore the potential roles of eCRF in preventing these cancers among women.

1. Introduction

1.1 Epidemiology and burdens of urinary tract cancers

Cancer is a term defining a set of diseases characterized by uncontrolled and abnormal growth of cells, which can occur at different body sites, leading to severe health conditions (1). According to the World Health Organization (WHO), cancer is the second most common cause of death (1), and its burdens are the highest around the world (2). In 2022, an estimated 20 million new cancer cases were reported, and approximately 9.7 million deaths occurred across the globe (3). New cancer cases are expected to rise by 76%, with a 90% higher mortality rate in 2050 (4). Surprisingly, 22.5% of the world's cancer cases occurred in Europe, despite having only 10% of the world's population (3), leading to significant healthcare strain and an economic cost equal to €97 billion in 2018 (5).

Notably, Europe experienced a significant burden of urinary tract cancers, including bladder and kidney cancers. These cancers accounted for a total of 370 498 new cases in 2022, and an alarming increase of an additional 110 657 cases is predicted to occur in 2050 (3, 4). Within urinary tract cancer subgroups, bladder and kidney cancers together are the fifth most diagnosed cancer, as well as the fifth leading cause of cancer-related mortality across all genders in Europe (3). Separately, bladder cancer ranks fourth, while kidney cancer is the fifth most prevalent cancer among European males (3, 5).

According to a recent report from the Cancer Registry of Norway, urinary tract cancers accounted for 7.5% of the total 182 531 reported cancer cases between 2018 and 2022 (6). The report further indicated variations in the incidence rates of urinary tract cancers based on, among others, sex and age groups. For instance, the age-adjusted incidence rate was 3.3 times higher in men than in women and was highest among individuals over 70 years old, aligning with the overall trends previously observed in Europe (6).

1.2 Risk factors of urinary tract cancers

The development of urinary tract cancers is influenced by the complex interplay of multiple risk factors, which can be classified into three categories: lifestyle, genetic, and environmental factors (7). Lifestyle choices, in particular, play a critical role in increasing the incidence of these cancers. Several well-established risk factors for bladder and kidney cancers were previously documented, including obesity, physical inactivity, smoking, alcohol consumption, family history of cancer, hypertension, diabetes mellitus (DM), and occupational hazards (8, 9).

Previous literature suggested that making positive changes in behaviors related to lifestyle could potentially prevent 33–50% of cancers (7). Specifically, a wide range of studies showed that higher levels of PA were associated with a reduced risk of developing bladder and kidney cancers (10, 11). For instance, a systematic review and meta-analysis of 15 observational studies concluded that individuals with higher levels of PA experienced a 15% decrease in bladder cancer risk when compared to those with lower activity levels (10). Similarly, higher levels of PA were associated with a 12% lower risk of kidney cancer in another systematic review (11).

Despite these benefits, using PA as an exposure metric in epidemiological research may present challenges due to potential misclassification and recall biases associated with self-reporting methods (12). Additionally, accurately capturing the different components of PA, such as frequency, intensity, and duration, might introduce additional biases, underling the need for more objective measurements (11, 12).

1.3 Exercise-measured cardiorespiratory fitness

Cardiorespiratory fitness (CRF) is a critical parameter reflecting the ability of the individual's cardiovascular and respiratory systems to supply sufficient oxygen to muscles during exercise (13, 14). It gives information about the individual's overall health condition (14). A higher level of CRF indicates a higher aerobic capacity that sustains more extended periods of exercise and, thus, a better health condition (14). The optimal approach for measuring CRF requires quantifying the individual's maximal oxygen uptake (VO_{2max}) through a progressive increase in exercise intensity until exhaustion is reached. Typically, these measurements are obtained on a treadmill or stationary bike in a laboratory setting (13).

While factors such as age, sex, and genetics significantly impact CRF, persistent engagement in moderate-vigorous PA presents a key strategy for its improvement (15). Therefore, CRF provides a more objective way to assess the PA level, overcoming the challenges associated with self-reported PA (15). Such measurements are central and have been previously studied to understand their impacts on different health outcomes.

Strong evidence from a wide range of epidemiological studies found an association between higher CRF and decreased all-cause mortality, as well as cardiovascular disease and cancer-specific mortality (13, 16, 17). Furthermore, increased CRF has also been linked to a reduced incidence of cancer (18-22). From the limited evidence available, a Swedish cohort study assessed the association between CRF and the risk of 18 site-specific cancers among 1 078 000 young males aged 16–25 years at baseline, who were followed up for a mean duration of 33 years (22). After adjusting for various confounders, the study reported that high versus low CRF levels were significantly associated with a 20% decrease in kidney cancer incidence. Besides, participants with higher levels of CRF appeared to have a lower risk of bladder cancer (HR = 0.90, 95% CI: 0.81–1.00) (22).

Another epidemiological study explored the association between CRF, divided into tertiles, and site-specific cancer incidence among 1997 healthy Norwegian men (21). Over a mean follow-up period of 26 years, 898 cancer cases were reported (21). The results from this study showed that the upper CRF tertile was significantly associated with a lower risk of bladder, pancreatic, and lung cancer (21). Contrary to the Swedish study, no significant association was found between higher levels of CRF and a lower risk of kidney cancer (21). Most of the previous studies examined the association between CRF and overall cancer incidence (18-20), and fewer studies focused on site-specific cancer incidence (21, 22). Also, the results from these studies were inconsistent (21, 22), focused only on men (21, 22), included fewer participants (21), or did not adequately adjust for potential confounders, such as socioeconomic factors and alcohol intake (21, 22).

However, CRF measurements have some limitations, specifically when used in large population-based cohorts. Accurate measurements require special laboratory settings with strict protocols and experts in the field; therefore, the process is time-consuming and requires higher costs (23-25). Furthermore, it is not a reliable method for older populations and individuals with functional and physical disabilities (25, 26).

1.4 Estimated cardiorespiratory fitness

Alternative innovative methods have evolved to overcome the challenges of measuring $VO2_{max}$, one of which includes the use of estimated cardiorespiratory fitness (eCRF). In this study, we refer to eCRF as a method for predicting the peak oxygen uptake (VO_{2peak}) from non-exercise algorithms (26, 27). In contrast with the exercise-measured CRF, eCRF relied on easily obtained variables, reducing time and expenses (24). The variables for healthy individuals were primarily comprised of clinical measurements, such as age, sex, waist circumference (WC), resting heart rate (RHR), and self-reported PA (24, 26, 27). This method of estimating CRF has recently been approved by the American Heart Association as an alternative method when CRF measurements are not available (28, 29).

Similar to the objectively measured CRF, two recent studies demonstrated an inverse relationship between eCRF and overall cancer incidence in different populations (26, 29). While these studies suggested a decrease in overall cancer incidence with the increase in eCRF, the results were inconsistent between men and women (26, 29), and the studies were conducted in a considerably older population (29).

To the best of our knowledge, only these two studies additionally evaluated the relationship between eCRF and site-specific cancer incidence (26, 29). One study observed an inverse association between eCRF and prostate cancer incidence in men and no association with breast cancer incidence in women (26). The other study found a tendency of reduced incidence of colorectal cancer only in men and breast cancer in women (29). However, no study has yet investigated the associations between eCRF and overall urinary tract cancer incidence or bladder and kidney cancer incidence specifically.

1.5 Research objective

Therefore, our study aims were to examine the prospective relationships between CRF, estimated from non-exercise prediction models, and: 1) the incidence of urinary tract cancer overall, as well as 2) the site-specific incidence of bladder and kidney cancers in a large population-based survey.

2. Methods

2.1 Study setting

In this prospective cohort study, we used data from the Nord-Trøndelag Health Study (HUNT). HUNT is Norway's largest population-based, longitudinal study, providing extensive health information (30). All residents aged 20 years or more in the northern region of Trøndelag county were invited by regular mail or email to participate in 4 consecutive phases: HUNT1 started from 1984 to 1986, followed by HUNT2 from 1995 to 1997, then HUNT3 from 2006 to 2008, and lastly HUNT4 from 2017 to 2019. The data in the HUNT study was collected through self-reported questionnaires, clinical examinations, and laboratory tests (30, 31). Additionally, participation was optional and informed consent regarding the use of the data was obtained from each participant.

In this study, information about participants was de-identified. For reporting, we adhered to the guidelines outlined in the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) (32). This Master thesis is part of a large project approved by the Regional Committee for Medical Research (REK 2019/337).

2.2 Study design and population

This study utilized data from the HUNT2 study, in which 93 898 eligible subjects were initially invited. Out of these, a total of 65 226 (69.5%) individuals participated. Non-participation in HUNT2 was mainly due to lack of time or immigration out of the county (30). Exclusions were made for 1454 participants because of a pre-existing cancer diagnosis prior to the start of HUNT2. Additionally, 16 804 participants were excluded due to the lack of data essential for calculating eCRF from the non-exercise algorithms. This included information related to WC and RHR (n = 1075), as well as PA (n = 15 729). Consequently, the final analysis comprised 46 968 cancer-free participants, including 23 375 men and 23 593 women, as shown in Figure 1.

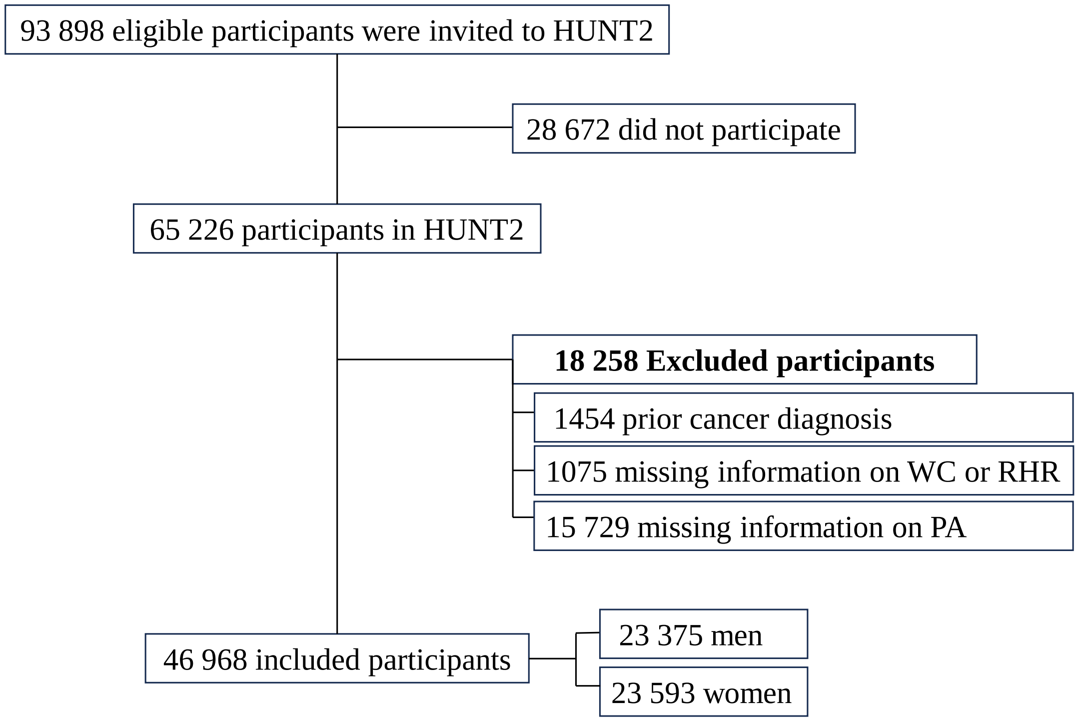


Figure 1. The flowchart illustrates the exclusion criteria for participants in this study. Participants were excluded mainly due to prior cancer diagnosis at baseline and lacking data on waist circumference (WC), resting heart rate (RHR), or physical activity (PA).

2.3 Clinical measurements and self-reported questionnaires

Specialized healthcare professionals were responsible for obtaining the clinical measurements in HUNT2, which included WC, RHR, blood pressure, weight, and height (33). Participants were also asked to complete two questionnaires, which covered subjective topics related to their health status, socioeconomic variables, lifestyle factors, and family medical history (33).

To measure WC, a metal tape was used at the participants' umbilicus level while standing with the arms flattened and registered to the nearest centimeter. RHR and blood pressure were measured three times after sitting for 2 minutes using Dinamap 845XT (Critikon), a device designed to calculate the mean systolic and diastolic pressure, as well as the mean pulse rate (33). Weight and height were taken while participants were dressed in lightweight clothes without footwear. Weight was recorded to the nearest half kilogram and height to the nearest centimeter. Consequently, body mass index (BMI) was obtained by dividing weight in kilograms by square height in meters (kg/m^2). In our study, we categorized BMI into three groups following the cut-offs of the WHO: underweight/normal weight (< 25 kg/m^2), overweight (25–29.9 kg/m^2), and obese (≥30 kg/m^2) (34).

Data on PA was obtained from the questionnaires. Participants answered questions about their intensity levels and duration of leisure-time PA during the past year. Intensity was divided into: light, defined as "not sweating/being out of breath," and vigorous, defined as "sweating/out of breath." The duration of each intensity level was reported as an average of hours per week (0, <1 h, 1–2 h, or ≥3 h). We initially classified participants' levels of PA into four categories: inactive (no activity, or ≤2 h light activity only), low (≥3 h light activity only, or ≤2 h light activity and <1 h vigorous activity), moderate (≥3 h light activity and <1 h vigorous activity, or 1–2 h vigorous activity regardless of light activity), and high (≥3 h vigorous activity regardless of light activity) (35). This classification was widely used in studies utilizing HUNT2 and showed a dose-response association of PA levels with overall cancer incidence and mortality (26, 35).

To calculate eCRF, we further classified PA into two categories (PA_{ACSM}): a value of "1" was given to those who had moderate or high PA levels. They were regarded as meeting the American College of Sports Medicine (ACSM) recommendations, i.e., at least 75 minutes (min) per week of vigorous-intensity exercise or at least 150 min per week of moderate-intensity exercise; and a value of "0" was given to those who were inactive or had low PA level. They were regarded as not meeting the ACSM recommendations (28).

2.4 Assessment of estimated cardiorespiratory fitness

Estimated cardiorespiratory fitness is determined as the exposure variable and was calculated from non-exercise prediction models. The models aimed at predicting eCRF in VO_{2peak} and were derived from a sample of healthy middle-aged adults from the HUNT3 population (36) and further adjusted for use in HUNT2 (28).

The models were composed of variables that are highly correlated to the exercise-measured CRF, such as age, WC, RHR, and self-reported PA. They also showed reasonably good precision, considered gender-related differences, and their effectiveness was closely similar to other non-exercise prediction models (36-38). The models and the self-administrated PA questionnaires were previously validated, and further details on procedures are described elsewhere (28, 36, 39).

The prediction models used for estimating CRF as a VO_{2peak} in (ml/kg/min) were as follows (28):

For men (Goodness of fit statistic = 0.58, Standard error of estimate = 5.88):

$105.91 - (0.334 \times Age) - (0.402 \times WC) - (0.144 \times RHR) + (3.102 \times PA_{ACSM})$

For women (Goodness of fit statistic = 0.52, Standard error of estimate = 5.37):

$78.00 - (0.297 \times Age) - (0.270 \times WC) - (0.110 \times RHR) + (2.674 \times PA_{ACSM})$

The models' parameters were obtained as previously described. eCRF was further classified into age-specific quintiles (based on a 10-year interval) within each sex group. Then, we merged the quintiles into 3 groups; the first quintile into 20% low eCRF; the second and third quintiles into the 40% medium eCRF; and the fourth and fifth quintiles into the 40% high eCRF group. In our study, we will refer to those categories as low, medium, and high, respectively. This classification was derived from the Aerobics Center Longitudinal Study (40) and was based on previous recommendations (26). We have also classified eCRF into sex and age-specific tertiles to be consistent with other previous literature (21, 26).

2.5 Covariates

Based on existing literature, we identified age, sex, sitting time, smoking status, alcohol consumption, educational level, occupational class, hypertension, and DM in a priori as potential confounding variables. They were obtained at baseline and retrieved from the HUNT questionnaires or the clinical examinations. Missing values were classified into an "unknown" category for each covariate. We have also used the Directed Acyclic Graph (DAG) to map out and visualize the impact of each confounder on the association between the exposure and the outcome. A variable was considered a confounder if associated with eCRF and with the incidence of urinary tract, bladder, or kidney cancer. Also, it was a condition that the confounder should not be a consequence of eCRF or any of the cancers. A detailed DAG illustrating the previous procedure is shown in Figure 2.

In our study, we adopted established classifications from previous HUNT studies to categorize each of the covariates (26, 27). For sitting time, we constructed a categorical variable as the following: 0–4, 5–7, and ≥8 hrs/day (35). Smoking status was categorized into never smoked, former smoker <10 pack-years (pyrs), former smoker 10–20, former smoker >20, current smoker <10, current smoker 10–20, or current smoker >20 pyrs. Alcohol consumption was classified according to the frequency of intake per month into abstainer, 1–4, or ≥5 times/month. We classified participants' educational levels into those with <10 years, 10–12 years, or ≥13 years of education. The occupational class was divided into 7 categories following the Erikson Goldthorpe Portocarero (EGP) classification. This classification reflects the socio-economic status of participants, ranking them from the highest class (class I) to the lowest class (class VII) (41).

Family history of cancer, based on self-reporting of whether any of the relatives (parents, siblings, or children) have or have had cancer, was treated as a binary variable (yes/no). It was included in our analysis because it is closely associated with our outcomes. Hypertension status was identified by either reporting the use of antihypertensive medications or the measured systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg. DM was classified according to participants' answers to the following question: "Have you had, or do you have DM?" to yes or no. A study verified that 96.4% of the self-reported diabetes cases matched their DM diagnoses in medical records (42).

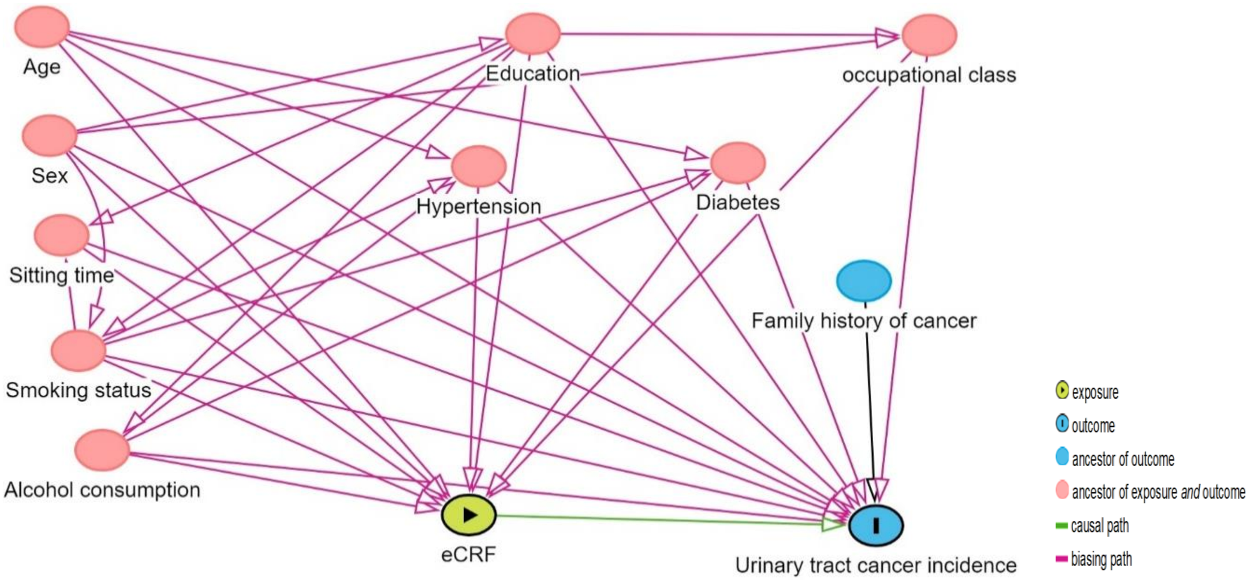


Figure 2. Directed acyclic graph (DAG) showing the casual association between estimated cardiorespiratory fitness (eCRF) and urinary tract cancer incidence, accounting for potential confounders.

2.6 Follow-up and the assessment of the outcome

The follow-up period for participants started from the date of data collection at baseline until one of the following: the first diagnosis of urinary tract, bladder, or kidney cancer; death; immigration from Norway; or the year-end of 2018. This was achieved by linking HUNT2 data with the Cancer Registry of Norway and the National Population Register using the personal identification number (Fødselsnummer). We identified the types of cancer from the Cancer Registry of Norway using the International Statistical Classification of Disease and Related Health Problems (ICD–10) (43).

Urinary tract, bladder, and kidney cancers were coded as (C64–C68), (C67), and (C64), respectively. It is important to note that urinary tract cancers were defined in this classification as malignant neoplasms of the bladder, kidney, renal pelvis (C65), ureter (C66), and other unspecified urinary organs such as the urethra (C68) (43). Subjects who did not experience any of the outcomes or were lost to follow-up before the end of the study due to death or immigration were right censored (Figure 3).

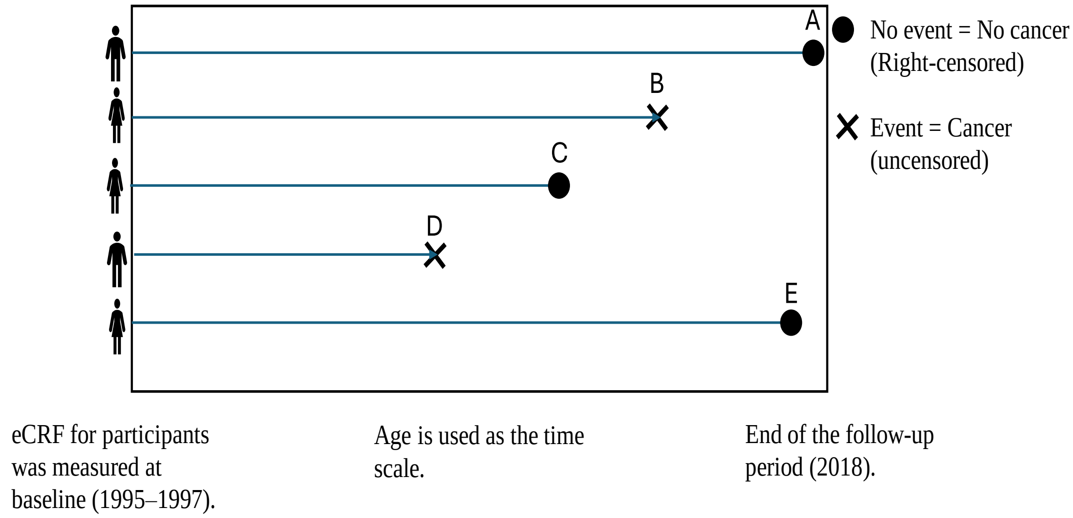


Figure 3. This diagram shows the process of censoring for participants who did not experience a cancer diagnosis by the end of the follow-up period (A) or were lost to follow-up due to death (C) or immigration (E). Uncensored participants are those who experienced the event of cancer diagnosis (B and D).

2.7 Statistical analysis

The baseline characteristics are presented across the three age-specific eCRF categories in men and women separately, using descriptive statistics: means (standard deviations) for continuous variables, while counts (percentages) for categorical variables. For each of these continuous and categorical variables, we used the one-way analysis of the variance (ANOVA) and the Chi-Square test to compare the parameters across the eCRF categories, respectively. Due to the large sample size, the data is assumed to follow a normal distribution for continuous variables.

The Cox Proportional Hazards (PH) models were used to study the associations between eCRF and the incidence of urinary tract, bladder, or kidney cancer. Age (set the date of birth as the date of origin) was used as the time scale (in years) to adjust for age, and participants were followed from the date they entered the study until any of the cancers occurred, death, immigration, or by the end of 2018. Crude and adjusted hazard ratios (HR), as well as 95% confidence intervals (CI), were estimated to quantify the relative risk and the random error, respectively. We adjusted covariates in two models differently; Model 1 adjusted for sex (for the total study cohort only), sitting time, smoking, alcohol consumption, education, occupational class, family history of cancer, hypertension, and DM; and Model 2 was further adjusted for BMI and PA levels as a part of the sensitivity analysis to avoid over-adjustment in Model 1 and because WC and PA were already accounted for in the equations for estimating CRF (27). Model 1 was considered the main model, and HRs from Model 1 were presented as the main results.

The association was examined for the total cohort, as well as for men and women separately. We used the low eCRF as the reference group, and we included the unknown categories for all the covariates to minimize possible selection bias.

We have tested the PH assumption using the overall global test for Schoenfeld residuals and visually examined the plots of scaled Schoenfeld residuals, as well as the locally weighted scatterplot smoothing (LOWESS) curves for each covariate separately. Besides, to test the potential effect modification by sex in the associations between eCRF and the incidence of urinary tract, bladder, or kidney cancer, we compared the Cox PH models with and without including an interaction term between eCRF and sex (eCRF*sex) using the Likelihood Ratio Test (LRT). An effect modification is identified when the P-value of the LRT is < 0.05, meaning that the effect of the eCRF on cancer incidence differs between men and women.

Two sensitivity analyses were performed. Initially, we excluded participants who experienced urinary tract cancer diagnosis during the 3 first years of follow-up in order to account for reverse causality; undiagnosed cancer before the start of the follow-up might have been associated with a reduced level of eCRF. However, this was not performed for bladder and kidney cancers due to the low number of cases in these associations. Additionally, we analyzed the associations between eCRF tertiles and the incidence of urinary tract, bladder, or kidney cancer separately. This was to explore any differences between the two different classifications of eCRF and to test the robustness of our results. All analyses were conducted using Stata 18.0 (StataCorp LLC, College Station, TX, USA).

3. Results

3.1 Baseline characteristics

The baseline characteristics for the eCRF categories in men and women are presented in Table 1. Out of the 46 968 included participants in this study, 49.8% were men and 50.2% were women. The mean age (SD) was 47.3 years (16) for men and 46.4 years (16.4) for women (range 19.1 to 99.3). Men and women in the higher eCRF categories were younger and had a higher proportion of individuals with a normal BMI (Table 1). Participants with higher levels of eCRF tended to be more physically active, had less tendency to smoke, generally had a higher education level, and were employed in a higher occupational class. For sitting time and family history of cancer, no clear variations between levels of eCRF were observed among both sexes. Additionally, hypertension and DM were less prevalent with the increase in the levels of eCRF.

Table 1. The baseline characteristics of 46 968 participants in the HUNT Study, stratified by eCRF categories in men and women.

	eCRF categories in men (*n* = 23 375)				**eCRF categories in women (*n* = 23 593)**			
	20% low	**40% medium**	**40% high**	**P-value**	**20% low**	**40% medium**	**40% high**	**P-value**
N	4676	9351	9348		4721	9437	9435	
Age at baseline (years)	48.4 (16.3)	47.6 (15.9)	46.4 (15.9)	<0.001	47.6 (16.8)	46.8 (16.5)	45.3 (16.2)	<0.001
WC (cm)	102.5 (8.7)	92.5 (6.1)	84.9 (6.0)	<0.001	94.3 (10.6)	80.9 (8.0)	72.9 (6.4)	<0.001
RHR (bmp)	79.4 (13.3)	71.2 (10.9)	63.6 (9.8)	<0.001	81.6 (13.6)	75.5 (11.4)	69.0 (10.0)	<0.001
eCRF (mL/kg/min)	37.9 (7.3)	44.2 (6.6)	49.7 (6.6)	<0.001	30.0 (6.6)	35.1 (6.2)	39.4 (5.9)	<0.001
BMI				<0.001				<0.001
Normal/Underweight	320 (6.8%)	2509 (26.8%)	5563 (59.5%)		477 (10.1%)	3908 (41.4%)	6885 (73.0%)	
Overweight	2226 (47.6%)	5805 (62.1%)	3677 (39.3%)		1728 (36.6%)	4306 (45.6%)	2391 (25.3%)	
Obesity	2109 (45.1%)	1028 (11.0%)	102 (1.1%)		2454 (52.0%)	1193 (12.6%)	152 (1.6%)	
Unknown	21 (0.4%)	9 (0.1%)	6 (0.1%)		62 (1.3%)	30 (0.3%)	7 (0.1%)	
PA				<0.001				<0.001
Do not meet PA recommendation	3509 (75.0%)	4554 (48.7%)	1600 (17.1%)		3635 (77.0%)	5373 (56.9%)	1841 (19.5%)	
Meet PA recommendation	1167 (25.0%)	4797 (51.3%)	7748 (82.9%)		1086 (23.0%)	4064 (43.1%)	7594 (80.5%)	
PA level				<0.001				<0.001
Inactive	2250 (48.1%)	2647 (28.3%)	870 (9.3%)		2618 (55.5%)	3710 (39.3%)	1240 (13.1%)	
Low	1407 (30.1%)	2512 (26.9%)	1392 (14.9%)		1239 (26.2%)	2373 (25.1%)	1719 (18.2%)	
Moderate	634 (13.6%)	2475 (26.5%)	3805 (40.7%)		564 (11.9%)	2084 (22.1%)	3983 (42.2%)	
High	211 (4.5%)	1067 (11.4%)	2485 (26.6%)		99 (2.1%)	483 (5.1%)	1180 (12.5%)	
Unknown	174 (3.7%)	650 (7.0%)	796 (8.5%)		201 (4.3%)	787 (8.3%)	1313 (13.9%)	
Sitting time (hours/day)				<0.001				<0.001
≤4 h	840 (18.0%)	1979 (21.2%)	2230 (23.9%)		1170 (24.8%)	2506 (26.6%)	2504 (26.5%)	
5–7 h	1059 (22.6%)	2240 (24.0%)	2347 (25.1%)		1216 (25.8%)	2440 (25.9%)	2532 (26.8%)	
≥8 h	1637 (35.0%)	3131 (33.5%)	3023 (32.3%)		1292 (27.4%)	2591 (27.5%)	2636 (27.9%)	
Unknown	1140 (24.4%)	2001 (21.4%)	1748 (18.7%)		1043 (22.1%)	1900 (20.1%)	1763 (18.7%)	

Smoking (pack-years)				<0.001				<0.001
Never smoked	1607 (34.4%)	3536 (37.8%)	4242 (45.4%)		2098 (44.4%)	4316 (45.7%)	4667 (49.5%)	
Former smoker <10	579 (12.4%)	1317 (14.1%)	1310 (14.0%)		649 (13.7%)	1387 (14.7%)	1375 (14.6%)	
Former smoker 10–20	417 (8.9%)	765 (8.2%)	554 (5.9%)		171 (3.6%)	322 (3.4%)	271 (2.9%)	
Former smoker >20	361 (7.7%)	546 (5.8%)	346 (3.7%)		61 (1.3%)	92 (1.0%)	79 (0.8%)	
Current smoker <10	401 (8.6%)	821 (8.8%)	766 (8.2%)		696 (14.7%)	1358 (14.4%)	1312 (13.9%)	
Current smoker 10–20	425 (9.1%)	811 (8.7%)	735 (7.9%)		536 (11.4%)	1015 (10.8%)	845 (9.0%)	
Current smoker >20	474 (10.1%)	823 (8.8%)	735 (7.9%)		247 (5.2%)	461 (4.9%)	375 (4.0%)	
Unknown	412 (8.8%)	732 (7.8%)	660 (7.1%)		263 (5.6%)	486 (5.1%)	511 (5.4%)	
Alcohol consumption (times/month)				<0.001				<0.001
Never	1203 (25.7%)	2090 (22.4%)	2029 (21.7%)		2313 (49.0%)	3705 (39.3%)	3201 (33.9%)	
1–4	2472 (52.9%)	4964 (53.1%)	5078 (54.3%)		1842 (39.0%)	4384 (46.5%)	4615 (48.9%)	
≥5	738 (15.8%)	1758 (18.8%)	1755 (18.8%)		225 (4.8%)	686 (7.3%)	998 (10.6%)	
unknown	263 (5.6%)	539 (5.8%)	486 (5.2%)		341 (7.2%)	662 (7.0%)	621 (6.6%)	
Education (years)				<0.001				<0.001
<10	1551 (33.2%)	2663 (28.5%)	2134 (22.8%)		1937 (41.0%)	3221 (34.1%)	2583 (27.4%)	
10–12	1866 (39.9%)	3795 (40.6%)	3712 (39.7%)		1459 (30.9%)	2869 (30.4%)	2681 (28.4%)	
≥13	1117 (23.9%)	2710 (29.0%)	3310 (35.4%)		1207 (25.6%)	3140 (33.3%)	3994 (42.3%)	
Unknown	142 (3.0%)	183 (2.0%)	192 (2.1%)		118 (2.5%)	207 (2.2%)	177 (1.9%)	
Occupational class				<0.001				<0.001
EGP class I	456 (9.8%)	998 (10.7%)	1089 (11.6%)		122 (2.6%)	278 (2.9%)	386 (4.1%)	
EGP class II	316 (6.8%)	816 (8.7%)	935 (10.0%)		620 (13.1%)	1515 (16.1%)	1745 (18.5%)	
EGP class III	252 (5.4%)	494 (5.3%)	572 (6.1%)		938 (19.9%)	2206 (23.4%)	2141 (22.7%)	
EGP class IV	811 (17.3%)	1525 (16.3%)	1441 (15.4%)		391 (8.3%)	663 (7.0%)	592 (6.3%)	
EGP class V+VI	609 (13.0%)	1396 (14.9%)	1435 (15.4%)		119 (2.5%)	256 (2.7%)	258 (2.7%)	
EGP class VII	657 (14.1%)	1167 (12.5%)	1039 (11.1%)		675 (14.3%)	1136 (12.0%)	976 (10.3%)	
Unknown	1575 (33.7%)	2955 (31.6%)	2837 (30.3%)		1856 (39.3%)	3383 (35.8%)	3337 (35.4%)	
Family history of cancer				0.12				0.15
No	3638 (77.8%)	7151 (76.5%)	7133 (76.3%)		3470 (73.5%)	6995 (74.1%)	7071 (74.9%)	
Yes	1038 (22.2%)	2200 (23.5%)	2215 (23.7%)		1251 (26.5%)	2442 (25.9%)	2364 (25.1%)	

Hypertension				<0.001				<0.001
No	1780 (38.1%)	4676 (50.0%)	5824 (62.3%)		2386 (50.5%)	6095 (64.6%)	7014 (74.3%)	
Yes	2886 (61.7%)	4665 (49.9%)	3505 (37.5%)		2331 (49.4%)	3334 (35.3%)	2410 (25.5%)	
Unknown	10 (0.2%)	10 (0.1%)	19 (0.2%)		4 (0.1%)	8 (0.1%)	11 (0.1%)	
DM				<0.001				<0.001
No	4413 (94.4%)	9050 (96.8%)	9130 (97.7%)		4470 (94.7%)	9226 (97.8%)	9311 (98.7%)	
Yes	246 (5.3%)	274 (2.9%)	174 (1.9%)		233 (4.9%)	181 (1.9%)	97 (1.0%)	
Unknown	17 (0.4%)	27 (0.3%)	44 (0.5%)		18 (0.4%)	30 (0.3%)	27 (0.3%)	

Abbreviation: BMI (body mass index); bpm (beats per minute); DM (diabetes mellitus); eCRF (estimated cardiorespiratory fitness); EGP (Erikson Goldthorpe Portocarero); PA (physical activity); RHR (resting heart rate); WC (waist circumference).

Data: as means (standard deviation) for continuous variables and participant counts (percentages) for categorical variables. ANOVA and Chi-square tests were used to calculate the P-values for continuous and categorical variables, respectively.

eCRF is stratified by sex and age-specific categories: 20% in the low category, 40% in the medium category, and 40% in the high category.

Note: Due to rounding, percentages may not precisely sum to 100%.

3.2 Results of the tests of PH assumptions

The global test showed no evidence of any potential violations of the PH assumption in Model 1 for urinary tract (P-value = 0.14), bladder (P-value = 0.26), and kidney cancers (P-value = 0.13). Furthermore, the scaled Schoenfeld residuals plots showed that the LOWESS curves were almost horizontal for all the covariates, assuming no deviation from the PH assumption (Figure 4).

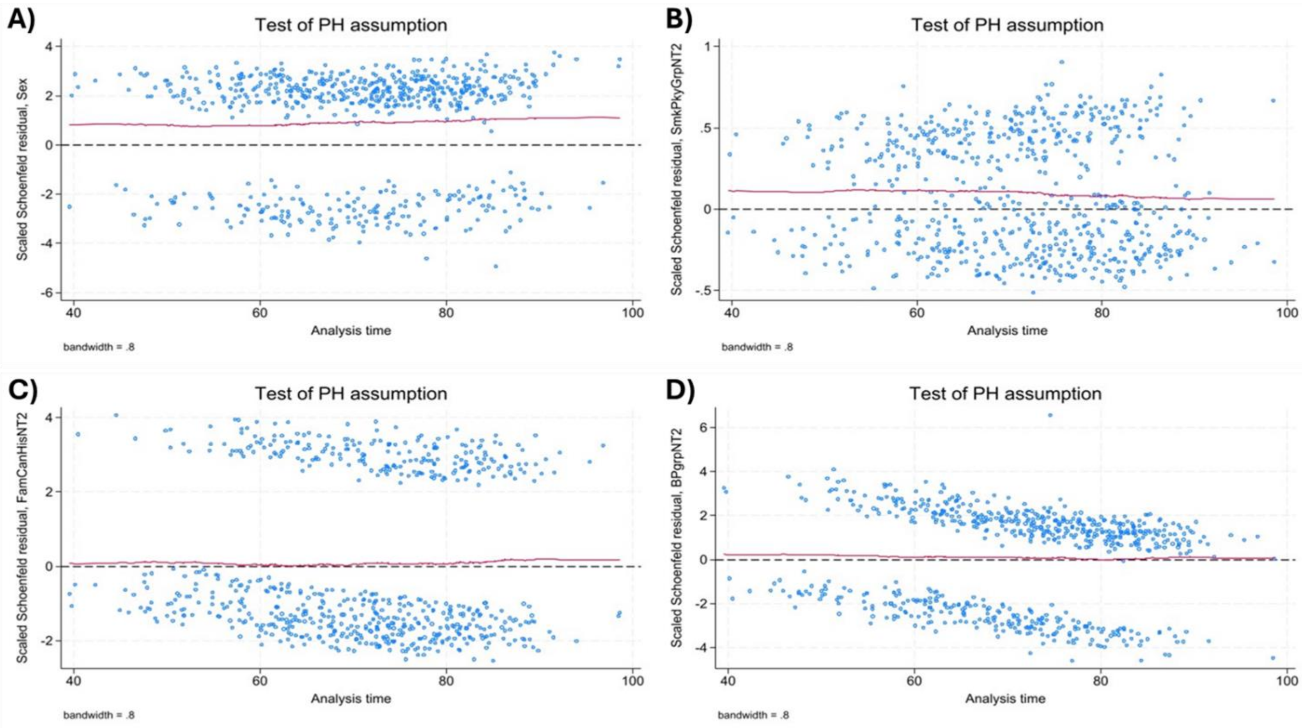


Figure 4. The scaled Schoenfeld residual plots with the fitted LOWESS curves (marked in red) in Model 1 for the incidence of urinary tract cancers in the total sample. The plots are shown as examples and each plot represents a confounder; A) sex, B) smoking, C) family history of cancer and D) Hypertension.

3.3 Association between eCRF and urinary tract cancer incidence

During a median follow-up period of 22.2 years (948 398 person-time), 652 urinary tract cancer cases were observed in the total cohort, with 468 cases in men and 184 in women (the incidence rate ratio (IRR) between men and women is 2.67). Table 2 presents HRs with 95% CIs for the association between eCRF categories and the incidence of urinary tract cancer. Among the entire study population, the high eCRF category was significantly associated with a lower incidence of urinary tract cancer (HR = 0.64, 95% CI: 0.51–0.79). Participants in the medium eCRF group also seemed to have a reduced incidence of urinary tract cancer (HR = 0.87, 95% CI: 0.71–1.05) and P-value for trend <0.001.

Men in the medium and high eCRF category had a respectively 17% and 41% reduced hazard of developing urinary tract cancer (HR = 0.83, 95% CI: 0.66–1.04 and HR = 0.59, 95% CI: 0.46–0.76, P-value for trend <0.001). Among women, the association between the eCRF categories and the risk of urinary tract cancer incidence appeared weaker (P-value for trend = 0.12). Nevertheless, the LRT indicated that the effect of eCRF on the incidence of urinary tract cancer did not statistically vary by sex (P-value = 0.48) (Supplementary table 5).

Table 2. The association between eCRF categories and urinary tract cancer incidence in the HUNT study.

eCRF categories	Cases	IR (per 1000 person-years)	Crude model			Model 1			Model 2		
			HR (95% CI)		P-value for trend	HR (95% CI)		P-value for trend	HR (95% CI)		P-value for trend
Total (*n* = 46 968)											
20% low	161	0.88	1.00	[Reference]		1.00	[Reference]		1.00	[Reference]	
40% medium	287	0.76	0.85	(0.70–1.03)	< 0.001	0.87	(0.71–1.05)	< 0.001	0.83	(0.70–1.03)	< 0.001
40% high	204	0.53	0.60	(0.48–0.73)		0.64	(0.51–0.79)		0.61	(0.46–0.80)	
Men (*n* = 23 375)											
20% low	120	1.35	1.00	[Reference]		1.00	[Reference]		1.00	[Reference]	
40% medium	206	1.12	0.80	(0.64–1.00)	< 0.001	0.83	(0.66–1.04)	< 0.001	0.78	(0.61–1.01)	< 0.001
40% high	142	0.75	0.54	(0.42–0.69)		0.59	(0.46–0.76)		0.55	(0.40–0.76)	
Women (*n* = 23 593)											
20% low	41	0.43	1.00	[Reference]		1.00	[Reference]		1.00	[Reference]	
40% medium	81	0.42	0.96	(0.66–1.40)	0.11	0.95	(0.65–1.39)	0.12	0.99	(0.65–1.52)	0.41
40% high	62	0.31	0.74	(0.50–1.10)		0.74	(0.49–1.11)		0.82	(0.48–1.39)	

Abbreviations: BMI (body mass index); CI (confidence interval); eCRF (estimated cardiorespiratory fitness); HR (hazard ratio); IR (incidence rate); PA (physical activity).

eCRF is stratified by sex and 10-year age-specific categories: 20% in the low category, 40% in the medium category, and 40% in the high category.

Crude model: Age is used as the time scale.

Model 1: Age is used as the time scale and adjusted for sex (only in total), sitting time, smoking, alcohol consumption, education, occupational class, family history of cancer, hypertension, and diabetes.

Model 2: Adjusted for BMI and PA in addition to variables in Model 1.

3.4 Association between eCRF and bladder cancer incidence

381 bladder cancer cases were identified during the same follow-up period; 299 cases in men and 82 in women (IRR between men and women = 3.82). Because of the observed effect modification by sex for bladder cancer (P-value = 0.027), we presented the results separately for men and women and not in the total population. The high eCRF category was associated with a 34% reduced incidence of bladder cancer among men (HR = 0.66, 95% CI: 0.48–0.90). Among women, no association was found between eCRF categories and the incidence of bladder cancer (Table 3).

Table 3. The association between eCRF categories and bladder cancer incidence in the HUNT study.

eCRF categories	**Cases**	**IR (per 1000 person-years)**	**Crude model**		**Model 1**		**Model 2**	
			HR (95% CI)	**P-value for trend**	**HR (95% CI)**	**P-value for trend**	**HR (95% CI)**	**P-value for trend**
Men (*n* = 23 375)								
20% low	71	0.80	1.00 [Reference]		1.00 [Reference]		1.00 [Reference]	
40% medium	135	0.73	0.88 (0.66–1.17)	< 0.001	0.92 (0.69–1.23)	0.006	0.92 (0.67–1.27)	0.09
40% high	93	0.49	0.59 (0.43–0.80)		0.66 (0.48–0.90)		0.72 (0.48–1.07)	
Women (*n* = 23 593)								
20% low	18	0.19	1.00 [Reference]		1.00 [Reference]		1.00 [Reference]	
40% medium	26	0.13	0.70 (0.39–1.28)	0.63	0.64 (0.35–1.18)	0.87	0.51 (0.26–1.00)	0.64
40% high	38	0.19	1.03 (0.59–1.81)		0.93 (0.52–1.66)		0.70 (0.33–1.50)	

Abbreviations: BMI (body mass index); CI (confidence interval); eCRF (estimated cardiorespiratory fitness); HR (hazard ratio); IR (incidence rate); PA (physical activity).
eCRF is stratified by sex and 10-year age-specific categories: 20% in the low category, 40% in the medium category, and 40% in the high category.
Crude model: Age is used as the time scale.
Model 1: Age is used as the time scale and adjusted for sex (only in total), sitting time, smoking, alcohol consumption, education, occupational class, family history of cancer, hypertension, and diabetes.
Model 2: Adjusted for BMI and PA in addition to variables in Model 1.

3.5 Association between eCRF and kidney cancer incidence

Table 4 demonstrates the association between eCRF categories and the incidence of kidney cancer in the total cohort and stratified by sex. In men, 160 kidney cancer cases were reported, compared to 95 cases in women, leading to a total of 255 cases. The incidence rate of kidney cancer was 1.76 times higher in men than in women. Compared to all participants within the low eCRF category, those with medium and high levels of eCRF demonstrated HRs of 0.81 (95% CI: 0.60–1.10) and 0.51 (95% CI: 0.36–0.72) (P-value for trend <0.001), respectively. In men, both medium and high eCRF categories were associated with reduced incidence of kidney cancer, showing a dose-response association (Table 4). Among women, only the high eCRF category was inversely associated with kidney cancer incidence in Model 1 (HR = 0.52, 95% CI: 0.28–0.96). The LRT revealed that the impact of eCRF on kidney cancer incidence showed no statistically significant differences between sexes (P-value = 0.08) (Supplementary table 5).

Table 4. The association between eCRF categories and kidney cancer incidence in the HUNT study.

eCRF categories	Cases	IR (per 1000 person-years)	Crude model		Model 1		Model 2	
			HR (95% CI)	P-value for trend	HR (95% CI)	P-value for trend	HR (95% CI)	P-value for trend
Total (*n* = 46 968)								
20% low	71	0.39	1.00 [Reference]		1.00 [Reference]		1.00 [Reference]	
40% medium	115	0.30	0.78 (0.58–1.05)	< 0.001	0.81 (0.60–1.10)	< 0.001	0.80 (0.57–1.13)	0.001
40% high	69	0.18	0.47 (0.33–0.65)		0.51 (0.36–0.72)		0.46 (0.30–0.72)	
Men (*n* = 23 375)								
20% low	49	0.55	1.00 [Reference]		1.00 [Reference]		1.00 [Reference]	
40% medium	64	0.35	0.63 (0.43–0.91)	< 0.001	0.63 (0.43–0.92)	0.001	0.53 (0.35–0.82)	< 0.001
40% high	47	0.25	0.45 (0.30–0.68)		0.49 (0.32–0.74)		0.32 (0.19–0.56)	
Women (*n* = 23 593)								
20% low	22	0.23	1.00 [Reference]		1.00 [Reference]		1.00 [Reference]	
40% medium	51	0.26	1.13 (0.68–1.86)	0.008	1.17 (0.71–1.95)	0.02	1.48 (0.84–2.62)	0.50
40% high	22	0.11	0.49 (0.27–0.88)		0.52 (0.28–0.96)		0.79 (0.36–1.71)	

Abbreviations: BMI (body mass index); CI (confidence interval); eCRF (estimated cardiorespiratory fitness); HR (hazard ratio); IR (incidence rate); PA (physical activity).
eCRF is stratified by sex and 10-year age-specific categories: 20% in the low category, 40% in the medium category, and 40% in the high category.
Crude model: Age is used as the time scale.
Model 1: Age is used as the time scale and adjusted for sex (only in total), sitting time, smoking, alcohol consumption, education, occupational class, family history of cancer, hypertension, and diabetes.
Model 2: Adjusted for BMI and PA in addition to variables in Model 1.

3.6 Sensitivity Analysis

After excluding the first 3 years of the follow-up period in the sensitivity analysis, the association between eCRF categories and urinary tract cancer incidence is presented in Supplementary table 1. The findings from this analysis were closely consistent with the main analysis among the entire study population, as well as in men and women separately (Supplementary table 1).

In the sensitivity analysis concerning eCRF tertiles and urinary tract cancer incidence, the relationship between the high eCRF tertile and urinary tract cancer incidence slightly changed among women, showing a significantly reduced HR in the crude and adjusted Model 1 (Supplementary table 2). Compared with eCRF categories and bladder cancer, a non-statistically significant effect modification was identified between eCRF tertiles and bladder cancer incidence (P-value = 0.12), despite having similar findings (Supplementary table 3). The results for eCRF tertiles and kidney cancer were quite similar to those for the eCRF categories and kidney cancer. There was a dose-response association in the total population and in men. In women, only the high eCRF tertile was associated with a >60% reduced incidence of kidney cancer (Supplementary table 4).

After further adjustment for BMI and PA in Model 2, the association between eCRF categories and the incidence of urinary tract cancer was consistent with both the crude model and Model 1 for the total cohort, as well as in men and women specifically (Table 2). Also, these adjustments had a minimal effect on the inverse association between the high eCRF category and bladder cancer incidence in men (Table 3). However, the association between the high eCRF category and kidney cancer incidence was substantially weakened among women after these adjustments in Model 2 (Table 4).

4. Discussion

4.1 Main Findings

Our study provides compelling evidence on the associations between eCRF and the incidence of urinary tract cancer overall, as well as bladder and kidney cancers specifically, in a large population-based cohort of both sexes. We found that eCRF was inversely associated with the incidence of urinary tract and kidney cancers in a dose-response manner in the whole cohort and particularly among men. Also, our analysis revealed that only the high eCRF level was associated with a lower incidence of bladder cancer in men but not in women, suggesting the association was modified by sex. Furthermore, the high level of eCRF was inversely associated with kidney cancer incidence among women.

4.2 Comparison with previous literature

We did not identify any studies that assessed the association between CRF, whether exercise-measured or estimated, and the incidence of urinary tract cancer. Previous studies looked at the relationship between eCRF and the overall cancer incidence, urinary tract cancer included, across different populations (26, 29). Our investigations into the incidence of urinary tract cancer are consistent with these studies. Wang et al. (26) revealed a clear dose-response relationship between higher eCRF and reduced overall cancer incidence in both the total cohort and among men. As is the case with our study, they did not observe an effect modification by sex in their study. Similarly, the NIH-AARP Diet and Health Study found an inverse graded relationship between eCRF and overall cancer incidence for both sexes after following 402 548 adults with a mean age of 62 years for approximately 13.7 years (29). While the latter study supported our results, both our study and Wang et al. (26) reported a weaker association among women compared to the more uniform inverse association between men and women in the NIH-AARP Study. This could be due to the older population in the NIH-AARP Study, which might allow for more cancer events to occur within the study period, potentially increasing statistical power, especially among women. Thus, more studies, preferably including a larger sample size of women, are needed to further explore the association between CRF and urinary tract cancer incidence in men and women specifically.

4.2.1 The association between eCRF and bladder cancer incidence

In our study, we observed that the high level of eCRF was associated with a 34% reduced incidence of bladder cancer in men, and there was no association in women, even though the LRT of the effect modification by sex did not reach statistical significance using the eCRF tertiles (P-value = 0.12). Given that previous research often overlooked women, these observations highlight the critical need for larger studies, including both sexes, to explore the gender-specific impacts of eCRF on bladder cancer incidence.

Previous studies investigated the association between exercise-measured CRF and the incidence of bladder cancer only among men (21, 22). Consistent with our findings, the study by Onerup et al. (22) observed a linear inverse association between CRF and bladder cancer incidence in a large Swedish population-based cohort. They reported a 7% and 10% reduction in the risk of bladder cancer incidence for men with medium and high levels of CRF compared to those with lower levels, respectively. Similarly, a smaller Norwegian study conducted by Robsahm et al. (21) showed that the high CRF tertile was associated with a 60% lower incidence of bladder cancer in men.

The variation in the magnitude of the observed risk reductions may be attributed to the demographic differences across these studies; specifically, the study by Onerup et al. (22) included young and healthy men (aged 16–25 years), who generally might have had a lower risk of developing bladder cancer due to their overall healthier status compared to our middle-aged (mean age 46 years) study population. Robsahm et al. (21) selected only healthy participants free from diseases and without the use of medications. Besides, this study was relatively very small, which could result in imprecise estimates and increase the potential for a chance finding. Furthermore, the different classifications of CRF used across these studies could lead to varied detection of associations. However, the use of two distinct classifications in our analysis revealed no major differences in the effect measures. Unlike the previous studies (21, 22), which did not account for confounders like smoking, alcohol consumption, and socioeconomic status, our rigorous adjustment for these factors might provide more accurate estimates between eCRF and bladder cancer incidence.

4.2.2 The association between eCRF and kidney cancer incidence

The link between both exercise-measured and estimated CRF and kidney cancer incidence received minimal attention, especially regarding its impact on women. Our study addresses this gap by reporting a 48% reduction in kidney cancer incidence among women within the high eCRF category. Additionally, we observed an inverse dose-response relationship where medium and high levels of eCRF were associated with a 19% and 49% reduction in kidney cancer incidence across the total cohort, and 37% and 51% reductions specifically among men, respectively. This was in line with the study by Onerup et al. (22), who documented reduced hazards of 8% for medium and 20% for high levels of exercise-measured CRF in relation to kidney cancer incidence in men.

The differences in the magnitude of the risk reduction in kidney cancer incidence between our study and the study by Onerup et al. (22) may be due to the baseline age differences, as previously discussed. However, contrasting with our findings and those of Onerup et al. (22), Robsahm et al. (21) could not find a significant association between higher CRF tertiles and a lower incidence of kidney cancer. This might be explained by the very small sample size in the latter study, which requires further investigations using both exercise-measured and estimated CRF to validate these findings across larger and more diverse populations.

4.3 Biological mechanisms

The biological mechanisms behind the role of CRF in decreasing urinary tract cancers remain unclear. One possible explanation for this could be the roles of CRF in inhibiting factors known to contribute to cancer development. For instance, individuals with optimal CRF have decreased systemic inflammation and increased immune response, which could help in the elimination and early detection of emergent cancer cells (44). Moreover, optimal CRF is believed to safeguard against cancer by preventing DNA mutations, enhancing DNA repair processes, and reducing oxidative stress (10).

As PA is the only practical means to increase CRF, regular PA serves as a preventive measure against cancer incidence and should be promoted. PA’s own effects include lowering obesity and blood pressure, improving insulin regulation and sensitivity, as well as reducing the tendency to smoke and biomarkers related to cancer, in addition to improving CRF (12). However, further biological research exploring the potential mechanisms by which CRF itself contributes to the prevention of site-specific cancer is warranted.

4.4 Strengths and limitations

To our knowledge, this study is the first to examine the associations between eCRF and the incidence of urinary tract cancer, along with site-specific cancers of the bladder and kidney, in a large population-based study. Since previous studies were conducted mainly in men, the novelty of this research lies in examining the mentioned associations in the total cohort, as well as in men and women separately. Our study has several other strengths: the long follow-up period with a median of 22.2 years, the large case numbers for total urinary tract cancers, and a study population drawn from a region with low immigration and predominantly native inhabitants. Additionally, our algorithms for calculating eCRF are derived from the same source of population, allowing for better estimations (27). We have also adjusted for various potential confounders, such as lifestyle, socioeconomic, and medical factors, enhancing our study's internal validity. Cancer diagnoses are obtained from the Cancer Registry of

Norway and the ICD–10 classification, ensuring the accuracy of our cancer outcomes. Furthermore, we have performed several sensitivity analyses to test the robustness of our findings.

Nonetheless, the present study has some limitations. First, we could not completely eliminate selection bias by excluding participants who had missing information on WC, RHR, or PA. Wang et al. (26), using the same study population, showed previously that those who were excluded were generally older, being women, and less educated. Hence, the results should be interpreted with caution. Second, the use of CRF predictive models in our study might introduce a non-differential misclassification bias because PA was self-reported. In addition, the equations would generally overestimate CRF for those who are least active and underestimate CRF for those who are most active (36). Despite this, Nes et al. (36) showed that 90% of the participants were correctly classified within the nearest quartile of their actual VO_{2peak} measurements, which enables the models to identify those at increased risk. Moreover, we have used two widely used eCRF classifications to address potential misclassification of CRF in our study, and the results were quite similar. Third, eCRF was measured only one time at baseline, which may not allow for capturing the changes in eCRF throughout the study period. Fourth, we cannot eliminate the possibility of residual confounding, as we did not have information about diet and occupational exposure. However, the HUNT population is derived from a region that might have limited employment in occupations with high exposure to carcinogenic agents. Additionally, while we adjusted for key confounders across two models, including BMI and PA in the adjusted Model 2 may have led to biased estimates, especially for the association between eCRF and kidney cancer incidence in women. Thus, in line with recommendations by Garnvik et al. (27), we suggest that future studies investigating the effects of CRF estimated by similar equations may consider not adjusting for these variables in the main models since the two variables are already included in the equations for estimating CRF, as their inclusion may result in over-adjustment. Fifth, our study is limited by a small sample size for some of the associations, especially in women. Despite this, previous literature supported our results, and further research with larger sample sizes is warranted to confirm these observations. Sixth, although our study population is derived from an area fairly representing the Norwegian population, extrapolating our results to other European populations and populations with other ethnicities should be careful (31). Lastly, as is the case of other observational studies, our findings cannot prove causality despite the thorough adjustment for confounding and the robustness of the results.

5. Conclusion

In this large population-based cohort, we observed inverse dose-response relationships between higher levels of non-exercise eCRF and the incidence of urinary tract and kidney cancers in the total cohort and especially in men. Only the high level of eCRF was associated with a lower incidence of bladder cancer in men. Our findings suggest the importance of using eCRF in routine clinical examinations as it can give an indication of the overall health status of those who are at higher risk. However, further research with a larger sample size is needed to explore the potential role of eCRF in preventing these cancers among women.

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Supplementary tables:

Supplementary table 1. The association between eCRF and urinary tract cancer incidence after excluding the first three years of follow-up in the HUNT study.

eCRF categories	Cases	IR (per 1000 person-years)	Crude model HR (95% CI)	Crude model P-value for trend	Model 1 HR (95% CI)	Model 1 P-value for trend	Model 2 HR (95% CI)	Model 2 P-value for trend
Total (*n* = 46 176)								
20% low	148	0.95	1.00 [Reference]		1.00 [Reference]		1.00 [Reference]	
40% medium	266	0.83	0.85 (0.69–1.04)	< 0.001	0.87 (0.71–1.07)	< 0.001	0.86 (0.69–1.08)	0.002
40% high	191	0.58	0.60 (0.48–0.74)		0.65 (0.52–0.81)		0.65 (0.49–0.86)	
Men (*n* = 22 886)								
20% low	112	1.49	1.00 [Reference]		1.00 [Reference]		1.00 [Reference]	
40% medium	190	1.21	0.78 (0.62–0.99)	< 0.001	0.81 (0.64–1.03)	< 0.001	0.78 (0.60–1.02)	0.001
40% high	132	0.82	0.53 (0.41–0.68)		0.59 (0.45–0.76)		0.56 (0.40–0.79)	
Women (*n* = 23 290)								
20% low	36	0.45	1.00 [Reference]		1.00 [Reference]		1.00 [Reference]	
40% medium	76	0.46	1.02 (0.68–1.51)	0.18	1.02 (0.68–1.52)	0.26	1.13 (0.72–1.77)	0.86
40% high	59	0.35	0.79 (0.52–1.19)		0.81 (0.53–1.24)		0.98 (0.56–1.73)	

Abbreviations: BMI (body mass index); CI (confidence interval); eCRF (estimated cardiorespiratory fitness); HR (hazard ratio); IR (incidence rate); PA (physical activity).
eCRF is stratified by sex and 10-year age-specific categories: 20% in the low category, 40% in the medium category, and 40% in the high category.
Crude model: Age is used as the time scale.
Model 1: Age is used as the time scale and adjusted for sex (only in total), sitting time, smoking, alcohol consumption, education, occupational class, family history of cancer, hypertension, and diabetes.
Model 2: Adjusted for BMI and PA in addition to variables in Model 1.

Supplementary table 2. The association between eCRF tertiles and urinary tract cancer incidence in the HUNT study.

eCRF tertiles	Cases	IR (per 1000 person-years)	Crude model		Model 1		Model 2	
			HR (95% CI)	P-value for trend	HR (95% CI)	P-value for trend	HR (95% CI)	P-value for trend
Total (*n* = 46 968)								
Low	260	0.84	1.00 [Reference]		1.00 [Reference]		1.00 [Reference]	
Medium	228	0.72	0.85 (0.71–1.01)	< 0.001	0.87 (0.73–1.04)	< 0.001	0.85 (0.70–1.04)	0.001
High	164	0.51	0.60 (0.50–0.73)		0.65 (0.53–0.79)		0.64 (0.50–0.82)	
Men (*n* = 23 375)								
Low	187	1.25	1.00 [Reference]		1.00 [Reference]		1.00 [Reference]	
Medium	165	1.07	0.84 (0.68–1.04)	< 0.001	0.88 (0.71–1.08)	< 0.001	0.87 (0.69–1.10)	0.004
High	116	0.73	0.58 (0.46–0.73)		0.64 (0.51–0.81)		0.64 (0.47–0.86)	
Women (*n* = 23 593)								
Low	73	0.46	1.00 [Reference]		1.00 [Reference]		1.00 [Reference]	
Medium	63	0.39	0.84 (0.60–1.18)	0.02	0.84 (0.60–1.19)	0.02	0.84 (0.58–1.23)	0.09
High	48	0.29	0.65 (0.45–0.93)		0.65 (0.45–0.95)		0.66 (0.41–1.06)	

Abbreviations: BMI (body mass index); CI (confidence interval); eCRF (estimated cardiorespiratory fitness); HR (hazard ratio); IR (incidence rate); PA (physical activity).
eCRF is stratified by sex and 10-year age-specific tertiles.
Crude model: Age is used as the time scale.
Model 1: Age is used as the time scale and adjusted for sex (only in total), sitting time, smoking, alcohol consumption, education, occupational class, family history of cancer, hypertension, and diabetes.
Model 2: Adjusted for BMI and PA in addition to variables in Model 1.

Supplementary table 3. The association between eCRF tertiles and bladder cancer incidence in the HUNT study.

eCRF tertiles	Cases	IR (per 1000 person-years)	Crude model		Model 1		Model 2	
			HR (95% CI)	P-value for trend	HR (95% CI)	P-value for trend	HR (95% CI)	P-value for trend
Total (*n* = 46 968)								
low	137	0.44	1.00 [Reference]		1.00 [Reference]		1.00 [Reference]	
medium	136	0.43	0.95 (0.75–1.21)	0.026	0.98 (0.77–1.24)	0.09	0.99 (0.76–1.29)	0.43
high	108	0.33	0.75 (0.58–0.96)		0.80 (0.62–1.03)		0.88 (0.63–1.21)	
Men (*n* = 23 375)								
low	112	0.80	1.00 [Reference]		1.00 [Reference]		1.00 [Reference]	
medium	110	0.73	0.93 (0.72–1.21)	0.002	0.98 (0.75–1.28)	0.031	1.05 (0.78–1.41)	0.43
high	77	0.49	0.63 (0.47–0.85)		0.71 (0.53–0.96)		0.85 (0.59–1.23)	
Women (*n* = 23 593)								
low	25	0.16	1.00 [Reference]		1.00 [Reference]		1.00 [Reference]	
medium	26	0.16	1.02 (0.59–1.77)	0.44	0.99 (0.57–1.72)	0.59	0.88 (0.48–1.61)	0.93
high	31	0.19	1.23 (0.73–2.08)		1.15 (0.67–1.99)		1.02 (0.51–2.05)	

Abbreviations: BMI (body mass index); CI (confidence interval); eCRF (estimated cardiorespiratory fitness); HR (hazard ratio); IR (incidence rate); PA (physical activity).
eCRF is stratified by sex and 10-year age-specific tertiles.
Crude model: Age is used as the time scale.
Model 1: Age is used as the time scale and adjusted for sex (only in total), sitting time, smoking, alcohol consumption, education, occupational class, family history of cancer, hypertension, and diabetes.
Model 2: Adjusted for BMI and PA in addition to variables in Model 1.

Supplementary table 4. The association between eCRF tertiles and kidney cancer incidence in the HUNT study.

eCRF tertiles	Cases	IR (per 1000 person-years)	Crude model			Model 1			Model 2		
			HR (95% CI)		P-value for trend	HR (95% CI)		P-value for trend	HR (95% CI)		P-value for trend
Total (*n* = 46 968)											
low	118	0.38	1.00	[Reference]		1.00	[Reference]		1.00	[Reference]	
medium	85	0.27	0.70	(0.53–0.93)	< 0.001	0.73	(0.55–0.97)	< 0.001	0.69	(0.50–0.94)	< 0.001
high	52	0.16	0.43	(0.31–0.59)		0.46	(0.33–0.65)		0.39	(0.26–0.59)	
Men (*n* = 23 375)											
low	73	0.49	1.00	[Reference]		1.00	[Reference]		1.00	[Reference]	
medium	50	0.32	0.67	(0.47–0.96)	< 0.001	0.69	(0.48–0.99)	0.002	0.58	(0.39–0.87)	< 0.001
high	37	0.23	0.49	(0.33–0.72)		0.53	(0.35–0.80)		0.36	(0.22–0.61)	
Women (*n* = 23 593)											
low	45	0.28	1.00	[Reference]		1.00	[Reference]		1.00	[Reference]	
medium	35	0.22	0.76	(0.49–1.18)	< 0.001	0.78	(0.49–1.22)	< 0.001	0.84	(0.51–1.40)	0.017
high	15	0.10	0.33	(0.18–0.59)		0.34	(0.19–0.62)		0.39	(0.18–0.81)	

Abbreviations: BMI (body mass index); CI (confidence interval); eCRF (estimated cardiorespiratory fitness); HR (hazard ratio); IR (incidence rate); PA (physical activity).
eCRF is stratified by sex and 10-year age-specific tertiles.
Crude model: Age is used as the time scale.
Model 1: Age is used as the time scale and adjusted for sex (only in total), sitting time, smoking, alcohol consumption, education, occupational class, family history of cancer, hypertension, and diabetes.
Model 2: Adjusted for BMI and PA in addition to variables in Model 1.

Supplementary table 5. The P-values of the likelihood ratio test for testing the interaction by sex across the associations between eCRF and urinary tract, bladder, and kidney cancers across Model 1 and Model 2.

Models/Association	eCRF & urinary tract cancer	eCRF & bladder cancer	eCRF & kidney
Model 1 (P-value)	0.48	0.027	0.08
Model 2 (P-value)	0.47	0.03	0.23

Abbreviations: eCRF (estimated cardiorespiratory fitness).
P-values obtained from the likelihood ratio test.

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