MYOCARDIAL REVASCULARIZATION

Cardiorespiratory fitness and the incidence of coronary surgery and postoperative mortality: the HUNT study

Benedikte Therese Smenes [a,*], **Bjarne Martens Nes** [a], **Jon Magne Letnes** [a,c,d],
Katrine Hordnes Slagsvold [a,b], **Ulrik Wisløff** [a,e], and **Alexander Wahba** [a,b]

[a] Department of Circulation and Medical Imaging, Norwegian University of Science and Technology, NTNU, Trondheim, Norway
[b] Clinic of Cardiothoracic Surgery, St. Olavs Hospital, Trondheim University Hospital, Norway
[c] Clinic of Cardiology, St. Olavs Hospital, Trondheim University Hospital, Norway
[d] Department of Internal Medicine, Levanger Hospital, Nord-Trøndelag Health Trust, Norway
[e] School of Human Movement and Nutrition Science, University of Queensland, Queensland, Australia

* Corresponding author. Benedikte Therese Smenes. NTNU, Faculty of Medicine and Health Sciences, Department of Circulation and Medical Imaging, Postbox 8905, 7491 Trondheim, Norway. Tel: (+47) 92666428; e-mail: btsmenes@gmail.com.

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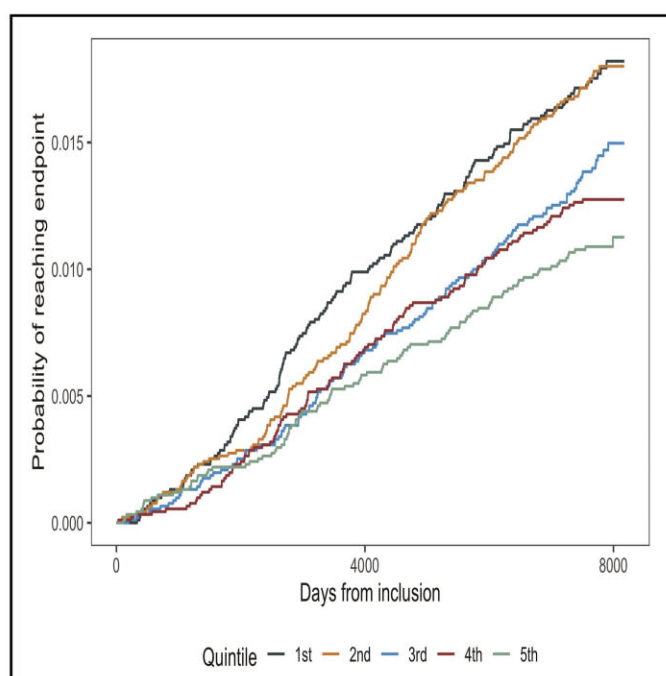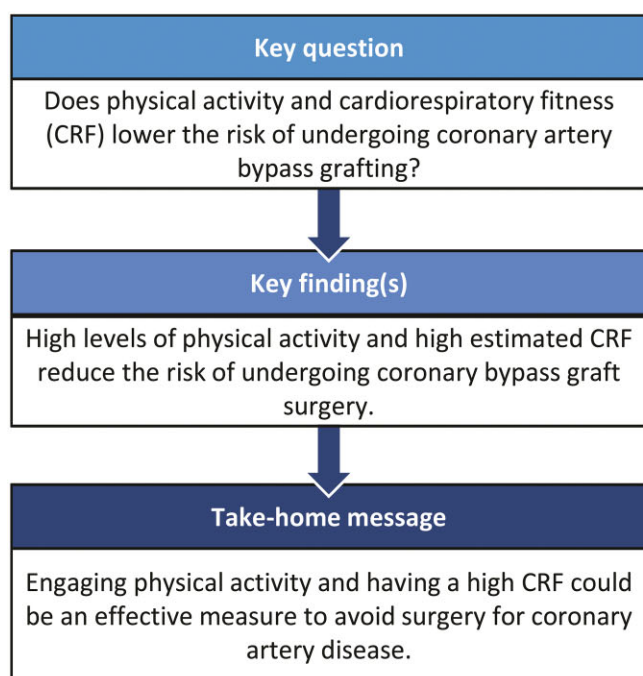
Abstract

OBJECTIVES: Low physical activity and cardiorespiratory fitness are known risk factors for coronary artery disease, but how they affect the risk of undergoing coronary artery bypass graft surgery is not established. We explored how physical activity and estimated cardiorespiratory fitness affect the risk of coronary surgery and postoperative outcome.

METHODS: Participants with no history of coronary disease from the second wave of the Trøndelag Health Study (HUNT2) were cross-linked with the local heart surgery register and the Norwegian Cause of Death Registry. Cardiorespiratory fitness was estimated by a previously developed algorithm using clinical and self-reported information. Fine-Gray competing risk analyses were used to calculate the risk

of undergoing isolated coronary surgery across physical activity groups and estimated cardiorespiratory fitness (mL/kg/min) as quintiles and per 1 metabolic equivalent of task (MET) (3.5 mL/kg/min).

RESULTS: We included 45,491 participants. The mean population age was 46.0 [standard deviation (SD) 15.8] years, and the mean estimated fitness was 41.3 (SD 8.9) mL/kg/min. A total of 672 (1.5%) participants underwent coronary surgery during the follow-up period. The risk of undergoing isolated coronary surgery was 26% [95% confidence interval (CI) 3–44] lower for those classified as highly active compared to those classified as least active. Further, an 11% (95% CI 6–15) lower risk per 1-MET (3.5 mL/kg/min) of higher fitness. Finally, we observed a 15% (95% CI 5–23) lower mortality risk after surgery per 1-MET of higher fitness among those undergoing surgery.

CONCLUSIONS: High levels of physical activity and high estimated fitness levels were inversely associated with the risk of developing coronary disease requiring surgery and overall mortality after surgery.

Keywords: Coronary heart disease • Coronary heart surgery • Cardiorespiratory fitness • Primary prevention

ABBREVIATIONS

CABG	coronary artery bypass graft surgery
CAD	coronary artery disease
CI	confidence interval
CoDR	Norwegian Cause of Death Registry
CRF	cardiorespiratory fitness
CVD	cardiovascular disease
eCRF	estimated cardiorespiratory fitness
HUNT	The Trøndelag Health Study
MET	metabolic equivalent of task
MI	myocardial infarction
PA	physical activity
SD	standard deviation

INTRODUCTION

Coronary artery disease (CAD) is an important manifestation of cardiovascular disease (CVD), causing about one-third of all deaths in individuals older than 35 years [1]. Physical activity (PA) is a known modifiable risk factor to reduce risk of CVD and CAD. Therefore, health authorities worldwide promote PA to reduce morbidity and mortality. Cardiorespiratory fitness (CRF) has been shown to be strongly associated with future CVD including coronary heart disease [2] and a stronger predictor for CVD compared to several other traditionally acknowledged risk factors [3]. However, literature regarding the relationship between PA, CRF and coronary artery bypass grafting surgery (CABG) is scarce. CABG is one of the most common cardiac surgical procedures and remains one of the pillars of revascularization treatment, with indications based on clinical characteristics, severity of the coronary lesions and anatomical aspects. Although CABG is a well-established surgical procedure with overall satisfying results and outcomes, the procedure involves an extensive intervention in a patient group that is becoming increasingly older and more complex [4, 5]. Further, it is not known whether high levels of exercise postpone symptoms of CAD or expedite the process of being referred for CABG by provoking symptoms at an earlier stage. The goal of the present study was to determine how leisure-time PA and CRF influenced the incidence of and mortality after CABG in a cohort that was healthy at baseline. We hypothesized that increasing levels of PA and estimated CRF (eCRF) protect against CABG, with greater risk reduction in those who perform the largest amounts of PA and those with the highest eCRF. Further, we hypothesized that among patients undergoing CABG, those with high CRF and high levels of PA experienced lower mortality rates.

PATIENTS AND METHODS

Ethical statement

Study design and population

The HUNT Study is a large population-based cohort study for medical and health-related research with 4 surveys undertaken the last 4 decades. The second wave (HUNT2) was carried out in 1995 to 1997, and the entire adult population in Nord-Trøndelag county in Mid-Norway was invited with 65,237 (69.5%) participating. All participants filled out questionnaires regarding their health and lifestyle and attended a clinical examination. Detailed information about the HUNT cohort can be found elsewhere [6]. Our study included men and women from HUNT2 with available data on leisure-time PA and the covariates needed for our analyses. HUNT2 was selected due to the high participation rates and the long follow-up time. We excluded participants who had a history of angina pectoris or myocardial infarction (MI) and those with missing variables for the main analyses. For participants who underwent more than 1 open-heart operation during follow-up period, the first procedure was used.

Questionnaire-based and clinical variables

Self-reported data from the HUNT questionnaires were processed and categorized. Alcohol consumption was categorized as abstainer (0 drinks), 1 to 4 drinks, or ≥5 drinks, over the last 2 weeks. Cigarette smoking was indicated as "yes" if participants had reported to be current or occasional smokers and "no" if they were non- or ex-smokers. Occupational status was classified into 6 groups: higher-grade professionals, lower-grade professionals, routine non-manual workers, manual workers, non-workers and retired. Family history of CVD was defined as having first degree relatives with an MI before the age of 60. Clinical variables included waist circumference and resting heart rate. All measurements were conducted in a standardized manner and performed by trained nurses. Blood pressure and resting heart rate were measured 3 times at 1-min intervals with the use of a Dinamap 845XT (Critikon, Tampa, FL, USA), using the mean of the second and third systolic and diastolic blood pressures and the lowest value of the 3 heart-rate measurements. Blood samples were

analysed for non-fasting levels of total cholesterol, high-density lipoprotein cholesterol and triglycerides. Waist circumference was measured to the nearest 1 cm at the level of the umbilicus [7].

Assessment of physical activity

The questionnaire included 2 questions regarding leisure time PA that were previously validated and found to have reasonable repeatability with respect to questions regarding hard PA [8]. Participants were asked to report the hours of light- and high-intensity PA per week with the alternatives "None", "Less than 30 min", "1–2 hours" and "3 or more hours" for both categories. Based on these responses, participants were classified into least active (<1 h hard and <3 h light PA per week), moderately active (1–3 h hard or >3 h light activity per week) or highly active (>3 h hard activity per week), which is a classification previously used [9]. We estimated CRF (peak oxygen uptake, VO_{2peak}) based on previously developed non-exercise prediction models [10]. The models were sex-specific and included age, waist circumference, PA and resting heart rate. PA was dichotomized to PA = 1 if they met the recommended volume of a minimum 75 min vigorous PA or 150 min moderate PA or a combination of these per week and PA = 0 if they did not. Participants were further classified into sex-specific eCRF quintiles within each 10-year age group (<40, 40–49, 50–59, 60–69, ≥70), before combining them to form quintiles for the whole cohort, as previously recommended [11]. eCRF was expressed as a metabolic equivalent task (MET), a common measure of energy expenditure, where 1 metabolic equivalent of task (MET) equals the oxygen consumption at rest (3.5 mL/kg/min).

Ascertainment of outcomes

The primary outcomes of this study were incidence of isolated CABG and mortality after CABG surgery. HUNT data were cross-linked with the local heart surgery database of St. Olavs University Hospital, Trondheim, Norway to gain information regarding surgery. This surgical database is a comprehensive registry with anamnestic and clinical variables on all open-heart operations performed at the hospital since 1992. St. Olavs hospital, Trondheim University Hospital is the district hospital for all inhabitants of Nord-Trøndelag County. Therefore, cross-linking the HUNT data with this database would identify almost all relevant procedures and give detailed information regarding surgical variables and incidence. We included only those who underwent isolated CABG operations without concomitant procedures such as valvular replacement or aortic root surgery. Ablation for atrial fibrillation was not regarded as a concomitant procedure. Data were also cross-linked with the Norwegian Cause of Death Registry (CoDR).

Statistical analyses

All descriptive data are presented as means and standard deviations (SD) for continuous variables and numbers and percentages (%) for categorical variables. The cumulative incidence of CABG, other cardiac operations and death is presented graphically by PA levels and quintiles of eCRF. We defined all-cause mortality and cardiac surgery other than isolated CABG as competing risks, the latter because it might affect the primary indication for

CABG. To account for competing risks for undergoing CABG, we used an extension of the Fine-Gray competing risk regression method for stratified data [12], allowing the baseline hazard function to differ across different strata of 10-year age groups. Results are presented based on separate models for the predictors of interest (measures of eCRF and PA) and presented as hazard ratios with 95% confidence intervals (CIs). End of follow-up was December 2017. Two models were constructed to adjust for confounders in the relationship between eCRF/PA and the outcome. Model 1 was adjusted for age and sex, and model 2 was further adjusted for family history of cardiac disease, smoking, alcohol intake and occupational status. For postoperative mortality data, we used a Cox proportional hazards model where follow-up was defined as time from surgery to death or to the end of follow-up in March 2020. When analysing the risk of death after surgery, we adjusted for age at the time of surgery. All other covariates were collected from the HUNT2 baseline examination. We did not adjust for BMI because waist circumference was included in the eCRF algorithm and could potentially lead to collinearity. Hazard ratios with 95% CIs for the outcomes are reported according to PA categories, per MET of eCRF and by quintiles of eCRF. The proportional hazards assumption was assessed by testing Schoenfeld residuals. All analyses were performed using SPSS for Macintosh version 26.0 (IBM-SPSS Inc., Armonk, NY, USA) and R 4.05 (www.r-project.org, *Survival* [version 3.2–10], *cmprsk* [version 2.2–10] and *crrSC* [version 1.1] packages) (R Foundation for Statistical Computing, Institute for Statistics and Mathematics, Vienna, Austria).

Data availability statement

The data underlying this article were provided by the CoDR, the local heart surgery registry of St. Olavs hospital and the HUNT Study under license. Data can be shared on request to the corresponding author after permission from the CoDR and the local heart surgery registry of St. Olavs hospital. Data from the HUNT study cannot be shared publicly due to the privacy of the participants in the study, but the data can be shared on reasonable request to the HUNT Research Centre.

RESULTS

Baseline characteristics

A total of 45,491 participants from HUNT2 were included. Patients who had a history of angina pectoris and/or myocardial infarction and those with missing data for the main analyses were excluded (*n* = 19,746). Baseline characteristics of the participants are outlined in Table 1 and the number of participants and incidence of CABG per age groups are outlined in Table 2 HUNT inclusion took place between 1995 and 1997. Mean age for the population was 46.0 (SD 15.8) years, and gender distribution was balanced with 51% women. The mean eCRF of the total population was 46.2 (SD 7.9) mL/kg/min and 36.5 (SD 7.1) mL/kg/min among men and women, respectively. For participants undergoing CABG, the mean age at the time of surgery was 64.9 (SD 9.6) and 66.0 (SD 9.4) years, and eCRF was 42.3 (SD 5.9) and 31.8 (SD 5.0) for men and women, respectively. For reference, objectively measured VO_{2peak} reference values from a different wave of HUNT (HUNT3) were found to be 44.3 ml/kg/min for men and

Table 1: Baseline characteristics of study population and stratified by sex

	All n = 45491	Men n = 22194	Women n = 23297
Age, years (mean SD)	46.0 (15.8)	46.1 (15.5)	45.9 (16.0)
eCRF (ml/min/kg, mean SD)	41.3 (8.9)	46.2 (7.9)	36.5 (7.1)
Current smoker, %	29.0	27.7	30.2
Family history of CVD, %	13.5	12.3	14.6
Alcohol units last 2 weeks (mean SD)	3.5 (5.0)	4.8 (6.1)	2.2 (3.3)
Waist circumference (cm, mean SD)	85.6 (11.6)	91.2 (9.2)	80.2 (11.1)
Systolic BP (mmHg, mean SD)	135.2 (20.2)	138.5 (17.8)	132.0 (21.7)
Diastolic BP (mmHg, mean SD)	79.3 (11.8)	81.2 (11.6)	77.4 (11.6)
Resting heart rate (beats/min, mean SD)	69.9 (12.4)	67.7 (12.3)	71.9 (12.1)
Total cholesterol (mmol/l, mean SD)	5.7 (1.2)	5.74 (1.15)	5.76 (1.29)
HDL cholesterol (mmol/l, mean SD)	1.4 (0.4)	1.25 (0.33)	1.51 (0.39)
Triglycerides (mmol/l, mean SD)	1.7 (1.1)	1.94 (1.27)	1.45 (0.88)
Isolated CABG, %	1.5	2.5	0.5

CABG: coronary artery bypass grafting surgery; BP: blood pressure; CVD: cardiovascular disease; eCRF: estimated cardiorespiratory fitness; HDL, high-density lipo-protein; SD: standard deviation.

Table 2: Number of participants and incidence of coronary artery bypass graft per age groups

Age group (years)	Participants	Undergoing CABG
<40	17805	65
40–50	10799	157
50–60	7699	235
60–70	4981	185
>70	4207	30

CABG: coronary artery bypass grafting surgery.

35.9 mL/kg/min for women [13]. The mean time from HUNT inclusion to CABG was 11.0 years (SD 5.7). Operative mortality (within 30 days from surgery) was 0.9% (n = 6) and the mean number of bypasses was 3.5 (SD 1.0).

Physical activity levels, estimated cardiorespiratory fitness and risk of undergoing coronary artery bypass grafting

A total of 672 (1.5%) of the participants [551 men (82%)]) underwent CABG during a total follow-up time of 887,828 person-years (mean 19.5 years, SD 4.6), giving an incidence rate of 0.76 events per 1000 person-years.

Our first main finding was that being classified as highly active was associated with a lower risk of undergoing CABG compared to the least active (Fig.1). The highly active group had a 26% [95% confidence interval (CI) 3–44] lower risk of undergoing CABG compared to the least active group when adjusting for sex, age, alcohol consumption, smoking, family history of MI and occupational status (Model 2, Table 3). In analyses separated by sex, the strongest relationship was found for women (Supplementary Material, Table 1).

We found similar results with an 11% (95% CI 6–15) lower risk of having CABG per 1 MET higher eCRF (Model 2). Results are presented by quintiles in Table 3. As was the case for the PA

groups, the strongest relationship was found for women (Supplementary Material, Table 1). Fig. 2 demonstrates the lower risk of the event in quintiles of individuals with higher eCRF.

Physical activity levels, estimated cardiorespiratory fitness and overall mortality after coronary artery bypass grafting

We observed a trend towards a lower risk of death among those with higher levels of PA, but the results were not statistically significant. However, individuals in the highest eCRF quintile had 53% (95% CI 25–61) lower risk of death compared to those in the lowest quintile (Fig. 3). Moreover, we observed a 15% (95% CI 5–23) lower mortality risk after CABG per 1-MET higher eCRF among those who had undergone isolated CABG (model 2). Detailed results are outlined in Table 4.

DISCUSSION

The main results of this study indicate that both high levels of PA and high eCRF are associated with a lower risk of undergoing isolated CABG. Our data, therefore, imply that engaging in PA can prevent CAD, and more specifically surgery-demanding CAD. Interestingly, each 1-MET improvement of eCRF was associated with a substantial reduction of risk associated with surgery.

Although PA and exercise have long been known to yield beneficial effects on cardiovascular health, this is to our knowledge the first study to explore in depth the association between PA, eCRF and CABG. In a recent study involving cardiopulmonary exercise testing of 4527 individuals from the third wave of HUNT (HUNT3), we found a 17% lower risk of pooled coronary revascularization per 1-MET higher CRF [2]. However, most of these individuals had percutaneous coronary intervention (PCI), and the associations with CABG were not fully explored due to the low incidence of CABG. CAD treated with CABG is in most cases more comprehensive and complex compared to CAD treated with PCI. Although our results are based on estimated and not on directly measured CRF, they indicate a comparable risk
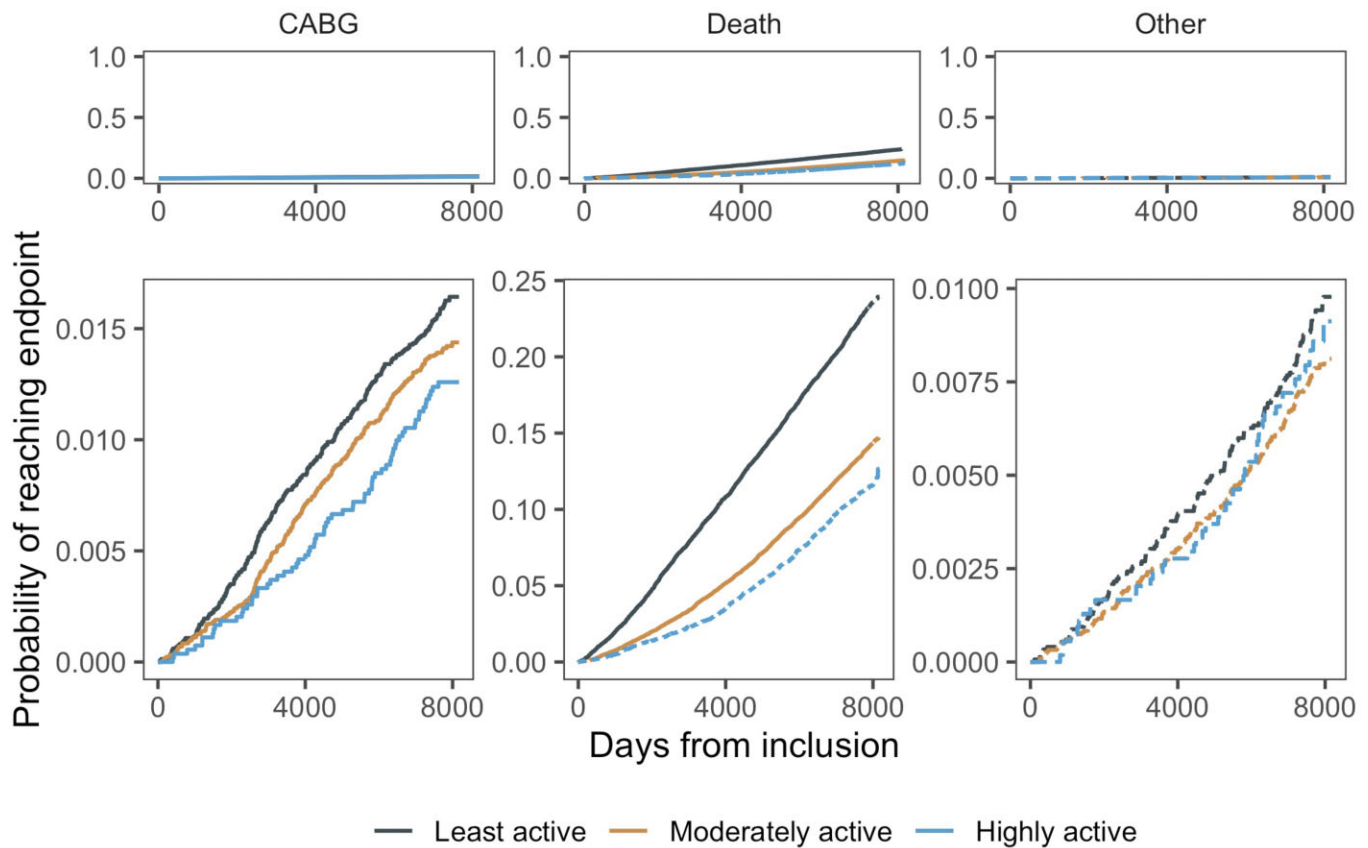
Figure 1: Cumulative incidence of events by physical activity group. Other: Other cardiac surgical procedures. CABG: coronary artery bypass graft surgery.

Table 3: Hazard ratios for primary end point of coronary artery bypass graft surgery per physical activity group, per 1 metabolic equivalent of task, higher estimated cardiorespiratory fitness and by quintiles of estimated cardiorespiratory fitness

		n	Events (n)	Model 1 HR	Model 1 95% CI	Model 2 HR	Model 2 95% CI
Physical activity	Less active	14846	239	1	–	1	–
	Moderately active	21569	305	0.87	0.74-1.03	0.9	0.76-1.07
	Highly active	5412	68	0.71	0.54-0.93	0.74	0.56-0.97
eCRF	Per 1 MET	45491	672	0.89	0.84-0.93	0.89	0.85-0.94
	Q1	9097	162	1	–	1	–
	Q2	9099	162	1.01	0.81-1.25	1.02	0.82-1.27
	Q3	9102	132	0.83	0.66-1.05	0.85	0.67-1.07
	Q4	9098	116	0.75	0.59-0.95	0.77	0.61-0.98
	Q5	9095	100	0.67	0.52-0.86	0.70	0.54-0.9

Model 1: Adjusted for sex and age.
Model 2: Model 1 + alcohol use, smoking status, family history of myocardial infarction and occupational status.
Less active: <1 h hard and <3 h light PA per week; moderately active: 1 to 3 h hard or >3 h light activity per week; highly active: >3 h hard activity per week.
CI: confidence interval; eCRF: estimated cardiorespiratory fitness; HR: hazard ratio; MET: metabolic equivalent of task.

reduction of undergoing CABG and revascularization. Altogether, these findings support the idea that fitness could be included in clinical risk stratification tools for CAD.

Our results also indicate that those in the highest quintile of eCRF had the lowest risk of both having to undergo CABG as well as lower overall mortality risk after surgery. Many studies have suggested that the greatest risk reduction of CVD is between sedentary and the next least fit groups, with a smaller risk reduction per increased activity at higher doses [14]. We found that the incidence of CABG was progressively lower with higher eCRF across quintiles, whereas for postoperative death, it seems that the main benefit for risk reduction was keeping out of the least fit quintile.

Although PA is generally promoted for health benefits, the relationship is not unequivocal, and studies have shown an association between long-term endurance exercise and heart disease
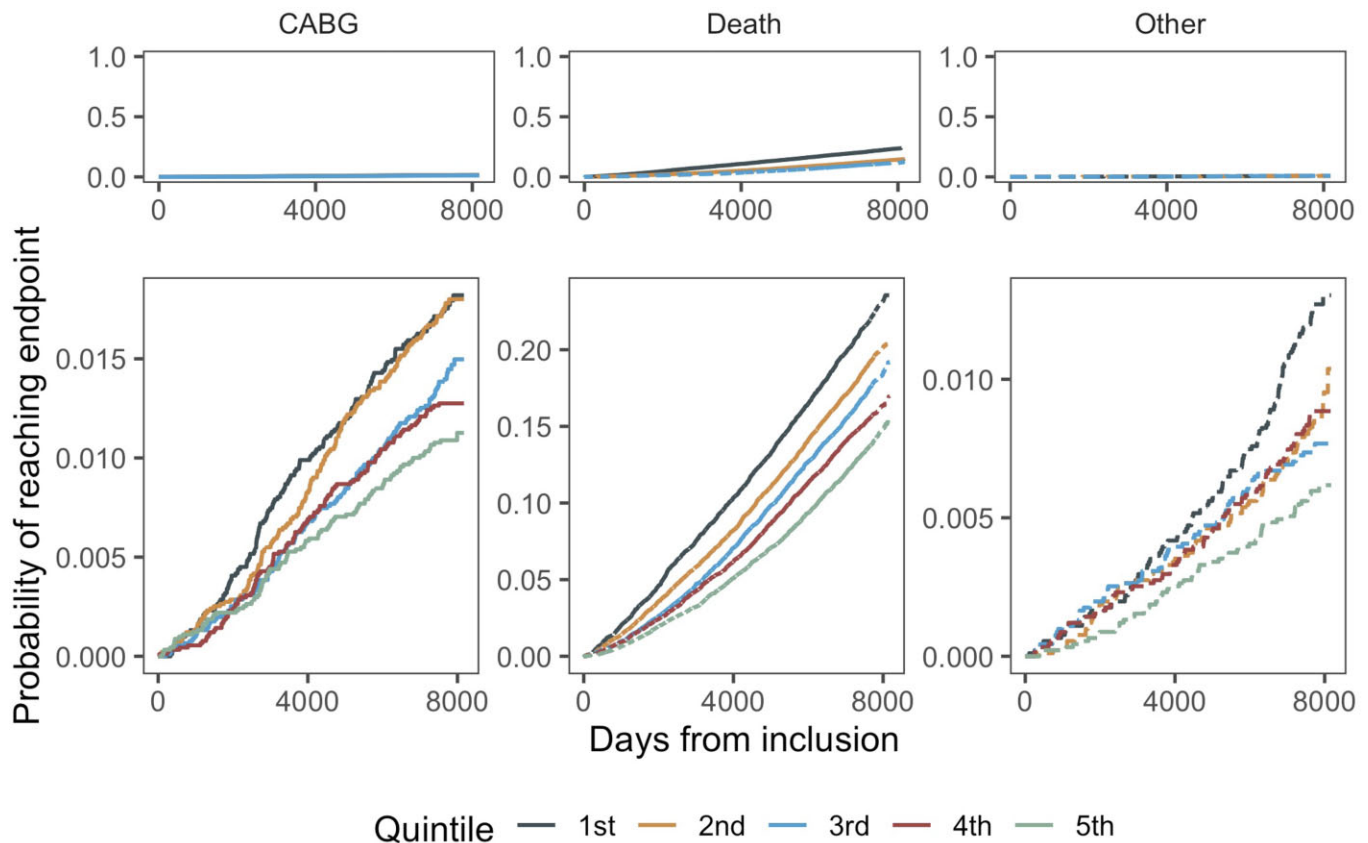
Figure 2: Cumulative incidence of events by quintiles of estimated cardiorespiratory fitness. CABG: coronary artery bypass graft surgery.
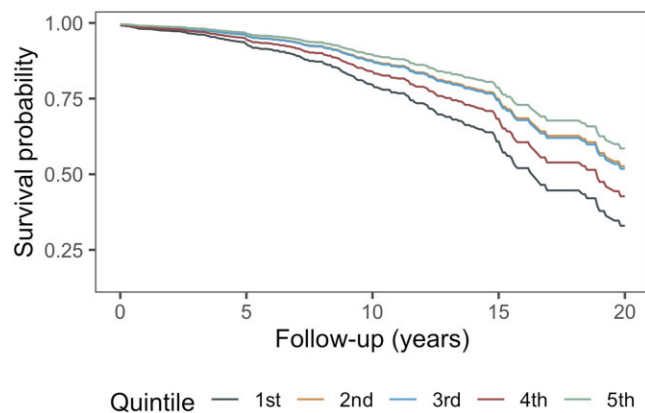

Figure 3: Adjusted survival curves for overall mortality after coronary artery bypass graft surgery by quintiles of cardiorespiratory fitness. Other: Other cardiac surgical procedures.

such as atrial fibrillation [15]. Some also argue that high levels of exercise, particularly strenuous exercise, increase the incidence of CAD by accelerating coronary artery calcification [16, 17]. However, some evidence also suggests that coronary stenosis in athletes is more calcified and stable in nature [17], but how this affects the risk of CABG is not known. Further, one may argue that strenuous PA increases the probability of detecting angina by producing symptoms from less severe lesions, leading to earlier referral for cardiac examination and subsequently heart surgery. We did not find an increased risk among the most active,

although our PA questionnaire was not well-suited to uncover such relationships. Our findings indicate that being among the most active group of the population, or in the highest eCRF quintile, may reduce the risk of undergoing isolated CABG.

Furthermore, our results indicate that high levels of PA and higher eCRF are associated with improved survival after CABG. CRF is postulated to be one of the strongest predictors in individuals with CAD; it has previously been shown that reduced preoperative CRF in participants with known or suspected CAD is associated with higher operative and 30-day mortality after CABG, as well as increased mortality after various other surgical procedures [18]. Our analyses show that this association also is relevant to participants without known CAD at baseline and to the subsequent risk of mortality when developing CAD and undergoing CABG. While results from preoperative treadmill testing and the complexity of the surgery itself may be affected by the severity of the established CAD, our results indicate that fitness even prior to developing the disease, or early in its development, may have the potential to identify individuals at higher risk of worse postoperative outcomes.

We found that both higher PA volumes and eCRF reduced the risk of undergoing CABG in a similar fashion. Some have argued that PA and CRF modify cardiovascular risk through different mechanisms and that the relationship between the 2 factors is only weak to moderate [19, 20]. Whereas PA denotes a behaviour, CRF measures a physical attribute affected by PA, sex, age, genotype and other factors [21,22]. Evidence suggests that PA and CRF reduce the risk of cardiovascular morbidity and

Table 4: Hazard ratios for postoperative survival after coronary artery bypass graft surgery per 1 metabolic equivalent of task of higher estimated cardiorespiratory fitness and by quintiles of estimated cardiorespiratory fitness

		n	Events (n)	Model 1		Model 2	
				HR	95% CI	HR	95% CI
Physical activity	Less active	239	73	1	–	1	–
	Moderate active	305	85	0.89	0.65-1.21	0.92	0.67-1.27
	Highly active	68	17	0.77	0.45-1.33	0.83	0.48-1.43
eCRF	Per 1 MET	672	195	0.84	0.76-0.93	0.85	0.77-0.95
	Q1	162	56	1	–	1	–
	Q2	162	37	0.54	0.35-0.82	0.57	0.38-0.88
	Q3	132	34	0.58	0.38-0.90	0.57	0.36-0.88
	Q4	116	40	0.72	0.47-1.09	0.76	0.50-1.15
	Q5	100	28	0.47	0.30-0.75	0.47	0.29-0.75

Model 1: Adjusted for sex and age at surgery.
Model 2: Model 1 + alcohol use, smoking status, family history of MI, occupational status upon HUNT inclusion.
Event: Postoperative mortality.
CI: confidence interval; eCRF: estimated cardiorespiratory fitness; HR: hazard ratio; MET: metabolic equivalent of task

mortality beyond improvement of the traditional risk factors [3]. Although various factors interact, increasing PA is the main way to improve CRF. Increasing eCRF by 1 MET requires a relatively minor effort and is likely achievable for most individuals. We can, however, not establish the full interrelationship between PA, eCRF and CABG based on our results.

Strengths and limitations

The prospective design and the long follow-up period of this large population database are some of the main strengths of this study, including high participation rates [6]. Since data on surgical outcomes were based on a local surgical register, individuals who underwent surgery elsewhere are not included in our analyses. St. Olavs University Hospital is, however, the dedicated cardiac surgical centre for patients living in the region covered by HUNT, and we know from national databases that fewer than 1% of operations are performed in other units. Emigration rates are known to be very low among participants in the HUNT Study [6], so these numbers are expected to be negligible. Misclassification is expected to be non-differential, which would most likely give an underestimation of effect estimates. Because the CoDR is a national database and contains information on all individuals who die in Norway or who live in Norway and die abroad, classification of deaths during follow-up is considered complete.

The observational study design prohibits establishing a causal relationship between PA/eCRF and CABG. Although we have performed several adjustments for important covariates, the possibility of residual confounding by unmeasured factors such as, for instance, diet or unmeasured comorbidities cannot be excluded. Furthermore, PA was self-reported and CRF was estimated, which may have led to exposure misclassification. Moreover, changes in PA during the follow-up period may also lead to misclassification. However, due to the design, this type of misclassification is expected to be non-differential. Self-reported assessment of PA is often selected in large epidemiological studies due to the practical advantages, although there are limitations such as misreporting and cognitive limitations related to comprehension or recall. A validity study of the self-reported PA in HUNT2 has been conducted and concluded that the question regarding "hard activity" has acceptable repeatability and is considered a valid measure of vigorous activity, whereas the utility of the "light activity" question needs to be established [8]. Self-reported PA has also been shown to be less valid in older age groups [23], which could have affected our results.

CONCLUSIONS

We found that high levels of PA and higher eCRF were associated with a lower risk of undergoing CABG. High PA and eCRF were also associated with lower postoperative mortality after CABG.

Conflict of interest: The algorithm used to estimate fitness in the article is also integrated and freely available in a publicly accessible online tool (www.worldfitnesslevel.org). Professors U.W. and B.M.N. hold IP rights for this tool, which is available for commercial actors upon license agreements.

Authors' contributions

BTS contributed to the design of the study, performed data preparation and analyses, interpreted the results and drafted the manuscript. JML contributed to the study design and performed data analyses and result interpretations. BMN

contributed to the study design and interpretation of the results. KHS contributed to interpretation of the results. UW contributed to the study design and the interpretation of the results. AW contributed to the conception, design of the study and interpretation of the results. All authors have contributed to the drafting, critically revised the manuscript and agreed to be accountable for all aspects of the work ensuring integrity and accuracy.

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