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

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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

PATIENTS AND METHODS

Ethical statement

All participants gave informed, written consent before participation in the Trøndelag Health Study (HUNT). The regional committee for medical and health research ethics approved the current study (REK 2018/986).

Study design and population

The HUNT Study is a large population-based cohort study for medical and health-related research with 4 surveys undertaken in 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, Survial [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
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). Fig. 2 demonstrates the lower risk of the event in quintiles of individuals with higher eCRF.

### 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...
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.

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 | Model 2 |
|-----|------------|---------|---------|
|     |            | HR 95% CI | HR 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.
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...
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.

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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

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

| Physical activity | Less active | 239 | 73 | Model 1 | Model 2 |
|-------------------|-------------|-----|----|---------|---------|
|                   | 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      | 1.0     |
| 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.
REFERENCES

[1] Sanchis-Gomar F, Perez-Quilis C, Leischik R, Lucia A. Epidemiology of coronary heart disease and acute coronary syndrome. Ann Transl Med 2016;4:256.

[2] Letnes JM, Dalen H, Vesterbøkkmo EK, Wisloff U, Nes BM. Peak oxygen uptake and incident coronary heart disease in a healthy population: the HUNT Fitness Study. Eur Heart J 2019;40:1633-9.

[3] Ross R, Blair SN, Arena R, Church TS, Despres JP, Franklin BA, Stroke Council et al. Importance of Assessing Cardiorespiratory Fitness in Clinical Practice: a Case for Fitness as a Clinical Vital Sign: a Scientific Statement From the American Heart Association. Circulation 2016;134:e53-e99.

[4] Cornwell LD, Omer S, Rosengart T, Holman WL, Bakaeen FG. Changes over time in risk profiles of patients who undergo coronary artery bypass graft surgery: the Veterans Affairs Surgical Quality Improvement Program (VASQIP). JAMA Surg 2015;150:308-15.

[5] Biancari F, Kangasniemi OP, Aliasim Mahar M, Rasinaho E, Satomaa A, Tiozzo V et al. Changing risk of patients undergoing coronary artery bypass surgery. Interact CardioVasc Thorac Surg 2008;8:40-4.

[6] Krokstad S, Langhammer A, Hveem K, Holmen TL, Midtbjell K, Stene TR et al. Cohort Profile: the HUNT Study, Norway. Int J Epidemiol 2013;42:968-77.

[7] Holmen J, Midtbjell K, Kruger Ø, Langhammer A, Holmen TL, Bratberg G et al. The Nord-Trøndelag Health Study 1995-97 (HUNT 2): objectives, contents, methods and participation. Nor Epidemiol 2003;13:19-32.

[8] Kurtze N, Rangul V, Hustvedt BE, Flanders WD. Reliability and validity of self-reported physical activity in the Nord-Trøndelag Health Study (HUNT 2). Eur J Epidemiol 2007;22:379-87.

[9] Morkedal B, Vatten LJ, Romundstad PR, Laugsand LE, Jensky I. Risk of myocardial infarction and heart failure among metabolically healthy but obese individuals: HUNT (Nord-Trøndelag Health Study), Norway. J Am Coll Cardiol 2014;63:1071-8.

[10] Nauman J, Nes BM, Lavie CJ, Jackson AS, Sui X, Coombes JS et al. Prediction of Cardiovascular Mortality by Estimated Cardiorespiratory Fitness Independent of Traditional Risk Factors: the HUNT Study. Mayo Clin Proc 2017;92:218-27.

[11] Kokkinos P, Myers J, Franklin B, Narayan P, Lavie CJ, Faselis C. Cardiorespiratory Fitness and Health Outcomes: a Call to Standardize Fitness Categories. Mayo Clin Proc 2018;93:333-6.

[12] Zhou B, Latouche A, Rocha V, Fine J. Competing risks regression for stratified data. Biometrics 2011;67:661-70.

[13] Aspenes ST, Nilsen TI, Skaug EA, Bertheussen GF, Ellingsen O, Vatten L et al. Peak oxygen uptake and cardiovascular risk factors in 4631 healthy women and men. Med Sci Sports Exerc 2011;43:1465-73.

[14] Epsvogels TM, Thompson PD. Exercise Is Medicine: at Any Dose? Jama 2015;314:1915-6.

[15] Myrstad M, Lochen ML, Graff-Iversen S, Gulsvik AK, Thelle DS, Stigum H et al. Increased risk of atrial fibrillation among elderly Norwegian men with a history of long-term endurance sport practice. Scand J Med Sci Sports 2014;24:e238-44-e244.

[16] Mohlenkamp S, Lehmann N, Breuckmann F, Brocker-Preuss M, Nassenstein K, Halle M, on behalf of the Marathon Study Investigators and the Heinz Niedorf Recall Study Investigators et al. Running: the risk of coronary events: prevalence and prognostic relevance of coronary atherosclerosis in marathon runners. Eur Heart J 2008;29:1903-10.

[17] Aengevaeren VL, Mosterd A, Braber TL, Prakken NHJ, Doevendans PA, Grobbbee DE et al. Relationship Between Lifelong Exercise Volume and Coronary Atherosclerosis in Athletes. Circulation 2017;136:138-48.

[18] Smith JL, Vernill TA, Boura JA, Sakwa MP, Shannon FL, Franklin BA. Effect of cardiorespiratory fitness on short-term morbidity and mortality after coronary artery bypass grafting. Am J Cardiol 2013;112:1104-9.

[19] Williams PT. Physical fitness and activity as separate heart disease risk factors: a meta-analysis. Med Sci Sports Exerc 2001;33:754-61.

[20] DeFina LF, Haskell WL, Willis BL, Barlow CE, Finley CE, Levine BD et al. Physical activity versus cardiorespiratory fitness: two (partly) distinct components of cardiovascular health? Prog Cardiovasc Dis 2015;57:324-9.

[21] Caspersen CJ, Powell KE, Christenson GM. Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research. Public Health Rep 1985;100:126-31.

[22] Zieger J, Ombrellaro KJ, Perumal N, Keil T, Mensink GBM, Finger JD. Correlates and Determinants of Cardiorespiratory Fitness in Adults: a Systematic Review. Sports Med Open 2019;5:39. 10. 1186/s40798-019-0211-2PMID: 31482208.

[23] Dyrstad SM, Hansen BH, Holme IM, Andersen SA. Comparison of self-reported versus accelerometer-measured physical activity. Med Sci Sports Exerc 2014;46:99-106.