UiT The Arctic University of Norway

Faculty of health sciences

Mediating effect of cardiorespiratory fitness in the association between physical activity and myocardial infarction

A cohort study

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Preface

I always had a passion for sports and physical activity, and after attending medical school for years, a curiosity of the positive effects it leads to. Therefor I contacted head of the research group UiT Physical activity and public health, Bente Morseth, if any of her PhD fellows had any ongoing project suitable for a master thesis. I was set in contact with Edvard Hamnvik Sagelv, which was looking to investigate the association between PA and MI and the modifying effect of CRF. This was of high interest and therefor I accepted the proposed task. The purpose of this thesis is to find if, and to which extend the association between physical activity and myocardial infarction is mediated trough cardiorespiratory fitness.

I would like to thank Edvard H. Sagelv for his immense help, and steady guidance during the process of writing this thesis. His interest and hunger for knowledge in his field is highly contagious, and he will without a doubt be a great resource for the UiT the Arctic University of Norway in years to come. Thank you!

Ørjan Hofsøy Johannessen, Mai 2022

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2 Abstract

Background: Cardiovascular disease (CVD) is one the global leading cause of mortality and myocardial infarctions (MI) make up a significant proportion of this. It has been previously found that the relationship between physical activity (PA) and all-cause mortality is largely mediated trough cardiorespiratory fitness (CRF), and in this context I hypothesised that CRF also mediates the association between PA and MI as well.

Method: This thesis is a longitudinal cohort study, using data form the fifth wave of Tromsø Study in 2001. PA was measured using the Saltin-Grimby Physical Activity Level Scale (SGPALS) grouped in three levels of PA: inactive, moderately active, and highly active. CRF was calculated using a non-exercise formula (estimated CRF). MI was derived from hospital records through 2014. Cox regression was used to assess the association between inactive (reference), moderate and high levels of PA and MI, adjusted for age, sex, education, smoking and waist circumference. The same analysis was performed with eCRF included from the abovementioned formula. Thereafter, Vanderwheele´s four-way decomposition analysis was applied in the Cox regression where I assessed the mediation effect of CRF on the association between PA and MI.

Results: In total, of the 5175 participants, 296 suffered an MI during the median 13.26 (interquartile range: 0.49) years of follow up. Comparing inactive as reference, moderately and highly active displayed 35% (HR: 0.65, 95%CI: 0.49-0.85) and 33% (HR: 0.66, 95%CI: 0.45-0.97) lower risk of MI, respectively. When including eCRF in the analysis, the associations were attenuated, where moderately active showed 28% (HR: 0.72, 95%CI: 0.55-0.94) lower risk of MI compared to inactive, while highly active versus inactive showed CIs crossing unity (HR: 0.83, 95%CI: 0.57-1.22). In the 4-way decomposition in both estimates (inactive versus moderately-, and versus highly active), the pure direct effects were insignificant (both p>0.50). The proportion explained by reference interaction were 60% (95%CI: 19, 102) and 76% (95%CI: -14, 166), and mediated interaction were -34% (95%CI: -55, -14) and -97% (95%CI: -211,18), and pure indirect effects explained 52% (19, 85) and 84% (95%CI: -5, 177%) of proportion in the association of lower MI risk.

Conclusion: Higher PA was associated with lower risk of MI. When assessing the mediating effect of eCRF in the association between PA and MI, eCRF appeared to fully mediate the association between PA and lower risk of MI.

3 Background

3.1 Cardiovascular disease

Although number of total deaths are declining globally, deaths from cardiovascular disease (CVD), defined as "any disease of the heart and its associated blood" (1), are rising, accounting for 17.8 million deaths annually (2). This makes CVD one of the leading causes of global mortality and the leading cause for disease burden worldwide (3). Burden of disease from CVD has been rising continuously for decades (3). Similar patterns are observed for Years of Life Lost (YLL) due to CVD (2), which represents the average time a person would have lived, if not to premature death (4). For example, ischemic heart disease was the number one leading cause of years of life lost (YLL) in 2017 (2). As CVD is the leading contributor of disease burden worldwide, the consequence of CVD is both serious for the society as a whole and on an individual level. Consequently, there is a need for both public health strategies and clinically effective strategies to lower the burden of the CVD epidemic (3).

3.2 Physical Activity

Physical activity (PA) can be defined as *"any bodily movement produced by skeletal muscles that result in energy expenditure"*(5). PA can be divided into frequency, duration and intensity (5). Frequency refers to how often the activity is performed, and duration refers to how long time is spent doing it. Intensity can represent either the absolute intensity of the PA or the relative intensity to maximal aerobic power (6). Together these factors sum up total physical activity volume. PA can be performed in different context such as leisure time PA, occupational activity, active travel, domestic activity and sedentary behaviours and it can be carried out in different modes, such as walking, running, cycling, skiing, rowing *etc.*

3.3 Prevention of CVD by PA

The updated guidelines for CVD prevention by the European Heart Journal (EHJ) from 2021 states that individuals should undertake moderate intensity PA for 150-300 min·week^{-1} or 75-150 min·week^{-1} of vigorous PA as "Class IA" evidence for reducing risk of CVD mortality

(7). Class IA evidence is based on multiple RCT´s and/or meta-analysis by the EHJ. It is also suggested by the same guidelines that engaging in light activity during the day will likely reduce risk of CVD mortality (7). Further, those who are medically restricted from following the guidelines are recommended to be "as active as possible" (7). The guidelines describe that those with the lowest physical activity level will have the largest effect in reducing CVD morbidity and mortality (7). These guidelines also conform the recent PA guidelines for the total population by the World Health Organization (WHO) (8).

3.4 Myocardial Infarction

Myocardial infarction (MI), which a recent definition defined as acute clinically evidence of myocardial ischemia with the rise and fall of troponin values above set value with a subset of positive diagnostic findings (9), are one of the CVDs that are likely preventable by intervening on lifestyle behaviours, such as PA. Studies examining the association between PA and MI shows in general an inverse association between higher PA and MI (10-12). For example, one study found an inverse association in women, but not in men (10), while another study reported similar lower risk of MI in women and men who reported to participate in leisure time sports activities of moderate and high intensity (11). The association also appears to be dose-response dependent, where higher volume of higher intensity shows an even further lower risk of MI compared with lower volumes (12), but this seems to be in a J-shaped curve. For example, one study reported that individuals who reported low (600-3999 metabolic equivalent of task (MET) min·week^{-1}), moderate (4000-7999 MET min·week^{-1}), and high (>8000 MET min·week^{-1}) volumes of PA had 16%, 23%, and 25% lower risk of ischemic heart disease, respectively, compared with those who were determined insufficient active individuals (<600 met-min/per week) (13).

3.5 Cardiorespiratory Fitness (CRF)

Cardiorespiratory fitness (CRF) was first defined in 1932 by Hill and Luton *"as the maximum amount of oxygen that can be taken in, transported and utilized by the working tissue during dynamically strenuous exercise involving large muscle mass"*(14). Since then, CRF is becoming an increasingly important parameter for health assessment. For example, CRF is a better predictor for all-cause mortality than some of the traditional markers in both healthy individuals and those with any form of cardiovascular disease (CVD), such as pack-years of smoking, hypertension, and diabetes (15), and it has been shown that a single measurement of CRF will improve categorization of both short and long term risk of CVD mortality when also

considering traditional risk factors (16). Consequently, the American Heart Association suggests using CRF as a clinical vital sign in routine assessment (17).

Measuring and/or calculating CRF can be done in several ways. One way to measure CRF is direct measurements by indirect calorimetry. This is usually measured during incremental test to exhaustion with two or more efforts where the test subjects push themselves to exhaustion, and this is defined as maximal oxygen uptake (VO_{2max}) (18). Another way of measuring CRF is peak oxygen uptake (VO_{2peak}), where all criteria for VO_{2max} is not met in tests to exhaustion (18). In epidemiology, although tests to exhaustion is feasible, they are influenced by selection bias (for example, ~50% usually refuse to perform an exercise test) (19). Therefore, the usual measure of CRF is submaximal exercise tests, where either VO_{2max} is estimated (20) or CRF is expressed as exercise capacity (e.g. metabolic equivalent of tasks (MET)) (15), which both potentially does not impose high selection bias (*e.g.* of those unable or unwilling to push themselves to their maximum).

Another way of assessing CRF is by estimation formula from non-exercise prediction models. One non-exercise formula developed in 2014 uses variables that can easily be measured, such as waist circumference, resting heart rate, and Personal Activity calculated from a physical activity questionnaires (PAQ). By plotting these measurements into a formula, eCRF can be calculated to a tolerably accurate degree; for example, ~50-60% of variance in a maximal test are found to be explained by these variables in the regression formula (21, 22). This allows other researchers to use an accessible and easy way of estimating CRF for adaptation in population based studies or in clinical settings (22).

CRF changes with age, and men usually have higher CRF than women (23). However CRF is also adaptable through participation in regular PA (24), where up to 70% of CRF can be attributed to recent PA patterns (25). For example, one study found that the association between PA at baseline was a strong predictor of CRF over two decades later (26), and one can expect PA to increase CRF regardless of sex, age or initial fitness levels although these factors attenuate the magnitude in the effect. The intensity of PA patterns also plays a role in determining the individual level of CRF, where higher intensity produces higher increases in CRF than lower intensity (27). A meta-analysis found that aerobic exercise improves CRF in previously healthy young adults between the age of 18-45 years old; both interval training and/or interval training combined with continuous training resulted in improved CRF (27). In contrast, no PA (*i.e.,* bedrest) will dramatically decrease CRF (28). This is illustrated by the

seminal Dallas Bedrest study showing that three weeks of bedrest is similar to 40 years of aging (29). Although not fully understood, it seems the ageing process plays a significant role in CRF declines, which then further accelerates in old age (29-31). This may have implications for the independency and quality of life for the aging population (30).

3.6 Mediator

A mediator is defined as a variable that may explain the relationship between an independent and dependent variable, i.e. the effect of the independent variables on the outcome act through the mediator (32). This presumes a model presented in Figure 1. For the variable to function as a mediator there are some criteria needed to be fulfilled; 1) changes in the independent variable will lead to significant change in the assumed mediator (path a), 2) change in the mediating variable will significantly change the dependent variable (path b) and 3) when controlling for path a and b, path c will change significantly (32).

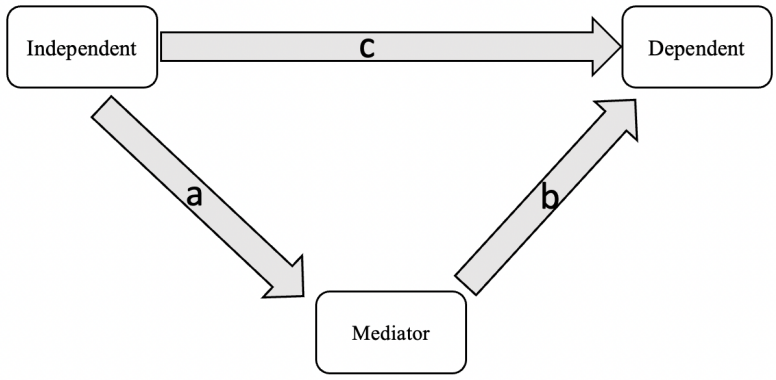

Figure 1 presents a flow chart of the three main pathways between an independent and dependent variable mediated trough a mediator.

In short, when including a potential mediator in a regression analysis, the association between the exposure and the outcome, will either be weaker or disappear, depending on 1) whether the hypothesized mediator is in reality a mediator and 2) whether the hypothesized mediator partly or fully mediates the association between the exposure and the outcome, respectively.

3.7 CRF mediation of lower risk of myocardial infarction from high levels of physical activity

As mentioned above, PA lowers the risk of CVD (10-13) and as CRF is improved by higher levels of PA, a likely causal association reported by numerous studies (27, 33-40), this may be the reason why observing lower risk of MI form higher levels of PA: Higher PA improves/maintain CRF which then explains why one can observe lower risk of MI from PA.

Moreover, this is expected to be comparable to the findings of Wolfson *et al*, that reported that CRF mediated the association between PA and all-cause mortality (41).

3.8 Purpose

The purpose of this thesis was to assess whether the association between PA and MI is mediated by CRF. I hypothesized that the effect of PA on risk of MI is mediated by CRF.

4 Material and methods

4.1 Study design and participants

This study is a longitudinal cohort study. I used data from the fifth (2001) wave of the Tromsø study, connected to follow up data on MI from the Tromsø Study endpoint register through 2014. The study population is all available adult participants from Tromsø 5 who had information on sex, age, waist circumference, resting heart rate, self-reported physical activity from two separate physical activity questionnaires (PAQ)s, educational, smoking and alcohol. Those who have previously been diagnosed with MI was excluded from the analysis. One of the PAQs were only answered by those under 70 years, thus in total, this resulted in a study sample of 5175 participants.

4.2 Data access and ethical approval

All participants in Tromsø 5 have provided written informed consent, and the Tromsø Study surveys have been carried out in accordance with the Declaration of Helsinki. The current study is approved by the Regional Ethics Committee (REK) North (reference number: 14289). My main supervisor had responsibility of applying for access to data from the Tromsø study.

Outcome: myocardial infarction

Myocardial infarction was retrieved from the Tromsø Study endpoint register and was recorded as the first incident occurring between baseline through study end at 31.12.2014. MI was determined by International Classification of Diseases (ICD) 8 codes 410–414; ICD 9 codes 410–414 and ICD 10 codes I20-I25 of patients discharges from University Hospital of North Norway, as well as being linked to the Norwegian Cause of Death Registry to identify possible out of hospital fatal MIs. Data on mortality was retrieved from the Norwegian Cause of Death Registry, where date of death was used as censoring, in addition to moving from Tromsø municipality and emigration from Norway. All participants were followed until

incident MI, death, moving from Tromsø Municipality, emigration, or end of follow-up, whichever came first.

Exposure: physical activity

Self-reported physical activity was measured using the leisure time Saltin-Grimby Physical Activity Level Scale (SGPALS) (42) and were answered by those under 70 years in Tromsø 5. The SGPALS asks a single question, presented in Table 1.

Table 1 SGPALS = Saltin-Grimby Physical Activity Level Scale.

"Describe how much you move and your physical exertion during leisure time? If your activity varies greatly between, e.g., between summer and winter, estimate an average. The question only concerns the last year", where participants place themselves in one out of four alternatives	
1	Read, watch television or other sedentary behaviour?
2	Walk, bicycling or move in another way least 4 hours per week? (This includes walking or bicycling to work or strolls etc)
3	Exercise sports, heavy gardening or similar (Note that the activity shall last at least 4 hours per week)
4	Heavy exercise or participation in competitive sports regularly an several times per week?

As few participants answered rank 4 (n=87), rank 4 and 3 were collapsed as highly active, rank 2 as moderately active and rank 1 as inactive.

Mediator: cardiorespiratory fitness

Cardiorespiratory fitness was derived from a non-exercise formula by Nauman *et al* (21) and is expressed as maximal oxygen uptake in $ml \cdot kg^{-1} \cdot min^{-1}$. The following formula was applied: 78.00 – (0.297 x age) – (0.270 x waist circumference (WC)) – 0.110 x resting heart rate) + (2.674 x PA) for women and 105.91 – (0.334 x age) – (0.402 x WC) – (0.144 x resting heart rate) + 3.102 x PA). This formula is found to explain 50% of the variance in directly

measured CRF through indirect calorimetry (21). The PA index used in this formula is a dummy variable representing inactive (0) and active (1) (21), which is coded from the Cohort of Norway (CONOR) PAQ, which is presented in Table 2. Total hours of PA were summed by light and hard intensity, where those reporting 3 hours per week of either light and hard or a combination leading to ≥3 hours per week were determined as active, and those below as inactive (meeting current lower bound physical activity guidelines, 150 minutes/2.5 hours per week (8). Although 3 hours per week sums up to 180 minutes per week, the categorical nature of the CONOR-PAQ allows 3 hours per week as the lowest minutes per week over the PA guidelines.

Table 2 CONOR-PAQ used in the fifth wave of the Tromsø study

How have your level of leisure time physical activity been for the last year? Imagine a weekly average for the year. Travel to work is regarded as leisure time. Answer both questions	
Light (no sweating/breathless)	Hard (sweating/breathless)
None (0)	None (0)
Under 1 hour (0.5)	Under 1 hour (0.5)
1-2 hours (1.5)	1-2 hours (1.5)
4 or more hours (3)	4 or more hours (3)

Covariates

I chose sex, age, WC, education, smoking and alcohol as covariates. As sex, WC and age are included in the calculation of CRF, these were not included separately into the statistical models when assessing mediation. Resting heart rate (RHR) was measured three times while in a seated position. Prior to the RHR measurements, the participants were sitting down quietly for five minutes. I used the mean of the two last recordings as RHR. Waist circumference was measured 2 cm above the umbilicus and expressed in cm. Smoking, education and alcohol were retrieved from questionnaires. Smoking was categorized as current, previous, and never smoker. Education was reported as years of education, which was grouped as primary school (≤9 years), high school (10-12 years), university <4years (13-15 years) and university ≥4 years (≥16 years) for descriptive purposes. Self-reported education in the Tromsø Study is found to provide acceptable accuracy compared with Statistics Norway

(43). Alcohol intake was reported as frequency by answering how often alcohol was consumed during the last year, with 8 answering alternative: 1) never, 2) not during the last year, 3) a few times, 4) 1 time per month, 5) 2-3 times per month, 6) 1 time per week, 7) 2-3 times per week, 8) 4-7 times per week.

4.3 Statistical methods

I used cox regressions to assess the association between PA and MI, adjusted for age, sex, education, smoking, alcohol intake and WC. There was an interaction of sex in the association between PA and MI ($p<0.001$), thus, analyses of physical activity and MI were also performed stratified by sex. I performed a sensitivity analysis to assess the influence of reverse causation by excluding to two first years of follow up from study attendance. I also assessed the association between eCRF and MI using cox models where 1) eCRF was computed as a continuous variable per metabolic equivalent of task (MET, 3.5 $ml \cdot kg^{-1} \cdot min^{-1}$) higher unit, and as a categorical variable in low (<30 $ml \cdot kg^{-1} \cdot min^{-1}$), moderate (30-39 $ml \cdot kg^{-1} \cdot min^{-1}$) and high (≥40 $ml \cdot kg^{-1} \cdot min^{-1}$) eCRF. To assess whether eCRF mediated the association between physical activity and MI, a model including both PA and eCRF was performed with similar covariate adjustments (education, smoking, and those included in eCRF: age, sex, and WC). When including a potential mediator in a regression analysis, the association between the exposure (here: PA) and the outcome (here: MI), the association will either be weaker or disappear, depending on 1) whether the hypothesized mediator is in reality a mediator and 2) whether the hypothesized mediator partly or fully mediates the association between the exposure and the outcome, respectively. Thereafter, Vanderwheele´s (44) four-way decomposition analysis was performed to assess the proportion mediated from 1) the pure direct effect, 2) the interaction only, 3) the mediation-interaction and 4) the pure indirect effect (44). In the four-way decomposition, eCRF was computed as a continuous variable at the mean (37 $ml \cdot kg^{-1} \cdot min^{-1}$). As PA was measured using another PAQ (Physical Activity Questionnaire) (SGPALS) than the PAQ included in the calculation of CRF (CONOR-PAQ), these two PAQs have different measurement properties and were thus considered appropriate to include in one model. Data analyses were performed using the Statistical Package for Social Sciences (SPSS, Version 26, IBM, Armonk, NY, United States) and Stata Version 17.0 ((StataCorp LLC, Texas, United States) with alpha set to <0.05.

5 Results

5.1 Baseline characteristics

A flowchart of included participants is illustrated in Figure 2, and participants characteristics are presented in Table 3. In total 5175, participant were included in the analyses, of which 2291 (44,3%) and 2884 (53,7 %) were men and women, respectively. The mean age was 53.41 years at study attendance. 296 (183 men and 113 women) suffered an incident of MI during the median 13.26 years (interquartile range 0.49, 25th 13.08 to 75th 13.57) follow-up time.

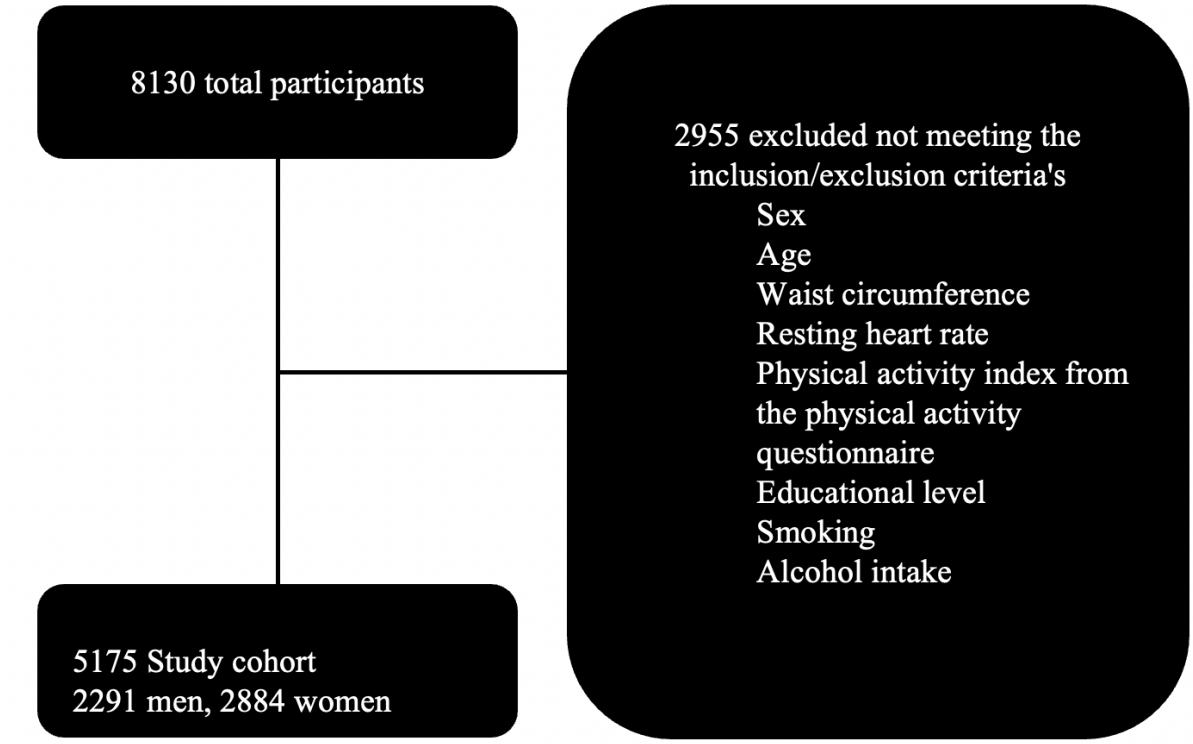

Figure 2 displays a flow-chart of included participants in this thesis.

Table 3. Descriptive characteristics of the participants.

	All participants (N=5175)	**Men (n=2291)**	**Women (n=2884)**
MI, n (%)	296 (5.7)	183 (7.8)	113 (3.9)
Follow up time, median (25th, 75th)	13.26 (13.08, 13.57)	13.26 (13.11, 13.58)	13.25 (13.06, 13.57)
Age (years)	53.41 (12.10)	53.75 (12.26)	53.13 (11.97)
<40 years, n (%)	634 (12.3)	261 (11.4)	373 (12.9)
40-49 years, n (%)	1264 (24.4)	570 (24.9)	694 (24.1)
50-59 years, n (%)	980 (18.9)	338 (14.8)	642 (22.3)
≥60 years, n (%)	2297 (44.4)	1122 (49.0)	1175 (40.7)
WC (cm), mean (SD)	88.13 (12.45)	94.64 (10.16)	82.96 (11.65)

RHR (beats·min^{-1}), mean (SD)	71.36 (12.37)	69.47 (12.65)	72.86 (11.93)
PA level			
Inactive, n (%)	1023 (19.8)	485 (21.2)	538 (18.7)
Moderate, n (%)	3375 (65.2)	1327 (57.9)	2048 (71.0)
High, n (%)	777 (15.0)	479 (20.9)	298 (10.3)
eCRF (ml·kg^{-1}·min^{-1}), mean (SD)	37.1 (7.59)	41.7 (7.0)	33.3 (5.78)
Low (<30 ml·kg^{-1}·min^{-1}), n (%)	906 (17.5)	90 (3.9)	816 (28.3)
Moderate (30-40 ml·kg^{-1}·min^{-1}), n (%)	2521 (48.7)	874 (38.2)	1647 (57.1)
High (≥40 ml·kg^{-1}·min^{-1}), n (%)	1748 (33.8)	1327 (57.9)	421 (14.6)
Smoking			
Smoker, n (%)	1604 (31.0)	708 (30.9)	896 (31.7)
Previous smoker, n (%)	1833 (35.4)	939 (41.0)	894 (31.0)
Never smoker, n (%)	1738 (33.6)	644 (28.1)	1094 (37.9)
Education (years), mean (SD)	11.7 (4.2)	11.7 (4.2)	11.7 (4.2)
Primary School, n (%)	1858 (35.9)	783 (34.2)	1075 (37.3)
High School, n (%)	1457 (28.2)	691 (30.2)	766 (26.6)
University <4 years, n (%)	831 (16.1)	385 (16.8)	446 (15.5)
University ≥4 years, n (%)	1029 (19.8)	432 (18.9)	597 (20.7)
Alcohol intake			
Never, n (%)	268 (5.2)	71 (3.1)	197 (6.8)
Not during the last year, n (%)	229 (4.4)	108 (4.7)	121 (4.2)
A few times, n (%)	1119 (21.6)	353 (15.4)	766 (26.6)
1·month^{-1}, n (%)	735 (14.20)	309 (13.5)	426 (14.8)
2-3·month^{-1}, n (%)	1003 (19.4)	492 (21.5)	511 (17.7)
1·week^{-1}, n (%)	971 (18.8)	495 (21.6)	476 (16.5)
2-3·week^{-1}, n (%)	714 (13.8)	384 (16.8)	330 (14.4)
4-7·week^{-1}, n (%)	136 (2.6)	79 (3.5)	57 (2.0)

WC=Waist circumference, RHR=Resting heart rate, PA=Physical activity, eCRF=estimated cardiorespiratory fitness, MI=myocardial infarction.

5.2 PA and MI

The associations between PA and MI, and eCRF and MI are presented in Table 4 and Figure 3. There was a non-linear association between PA and MI, where reporting being moderately and highly active were associated with~35% and lower risk of MI compared to reporting being inactive (rank 2 vs 1: HR: 0.65, 95%CI: 0.49-0.85, rank 3 vs 1: HR: 0.66, 95%CI: 0.45-0.97). When including eCRF in the model, the results were attenuated in those reporting being moderately active (0.72, 95%CI: 0.55-0.94) and those reporting being highly active displayed no lower risk of MI compared with those reporting being inactive (HR: 0.83, 95%CI: 0.57-1.22).

Table 4. Hazard ratio of lower risk of MI by higher PA level, and by higher eCRF.

I	**Physical Activity**		
Total	**Inactive**	**Moderately Active**	**Highly Active**
N (MI)	*1023 (76)*	*3375 (178)*	*777 (42)*
Without eCRF	Reference	0.65 (0.49-0.85)	0.66 (0.45-0.97)
With eCRF	Reference	0.72 (0.55-0.94)	0.83 (0.57-1.22)
Sex			
Women, n(MI)	*506 (32)*	*1975 (73)*	*290 (8)*

Without eCRF	Reference	0.59 (0.39-0.90)	0.44 (0.20-0.96)
With eCRF	Reference	0.90 (0.63-1.29)	0.98 (0.62-1.54)
Men, n(MI)	*485 (44)*	*1327 (105)*	*479 (34)*
Without eCRF	Reference	0.71 (0.50-1.02)	0.77 (0.49-1.21)
With eCRF	Reference	0.69 (0.45-1.05)	0.57 (0.26-1.25)
	Estimated Cardiorespiratory Fitness		
Continuous*	(per 3.5 ml·kg^{-1}·min^{-1})	0.90 (0.85-0.95)	
	<30 ml·kg^{-1}·min^{-1}	**30-39 ml·kg^{-1}·min^{-1}**	**≥40 ml·kg^{-1}·min^{-1}**
Total, N (MI)	*906 (75)*	*2521 (149)*	*1676 (72)*
	Reference	0.81 (0.61-1.07)	0.64 (0.47-0.90)
Sex			
Women, n(MI)	*816 (57)*	*1647 (55)*	*421 (1)*
	Reference	0.56 (0.38-0.83)	0.05 (0.01-0.39)
Men, n(MI)	*90 (18)*	*874 (94)*	*1327 (71)*
	Reference	0.47 (0.29-0.79)	0.25 (0.15-0.42)

*Table 4 Data are presented as hazard ratio with 95% CI, adjusted for sex, age, waist circumference, alcohol intake, education, and smoking. *eCRF is modelled as a continuous variable, hazard ratio are displayed per MET (3.5 ml·kg^{-1}·min^{-1}) higher eCRF where the reference is always one unit lower (e.g., 4 METs versus 3 METs). PA=physical activity, CI=confidence interval, MET=metabolic equivalent of task, eCRF=estimated cardiorespiratory fitness.*

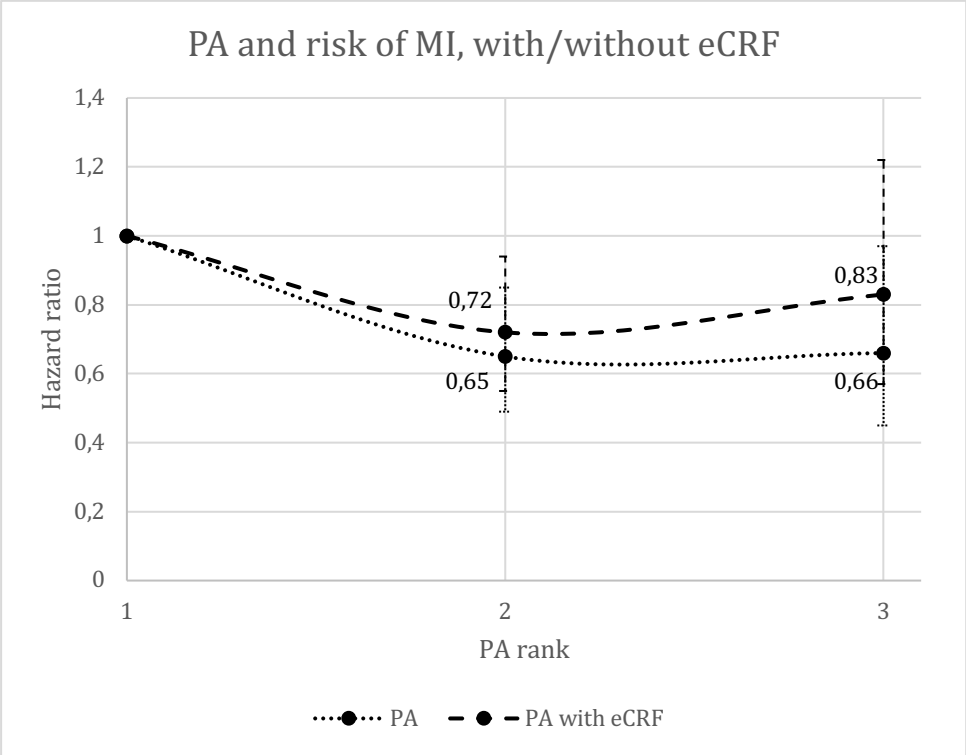

Figure 3 *display the relationship between higher level of PA and HR with/without eCRF, adjusted for adjusted for sex, age, waist circumference, alcohol intake, education, and smoking. PA=Physical activity, eCRF=estimated cardiorespiratory fitness, MI=myocardial infarction. Large-dotted line is with eCRF, and small-dotted line is without eCRF.*

When stratifying by sex, there were no association of higher PA level and MI risk in men (rank 2 vs 1: HR: 0.71, 95%CI: 0.50-1.02, rank 3 vs 1: HR: 0.77, 95%CI: 0.49-1.21), while results for women were consistent with the result in the total sample (rank 2 vs 1: HR: 0.59, 95%CI: 0.39-0.90, rank 3 vs 1: HR: 0.44, 95%CI: 0.20-0.96, Table 3 and Figure 4). Finally, there was a linear association between eCRF and MI, where every MET (3.5 $ml \cdot kg^{-1} \cdot min^{-1}$) higher eCRF was associated with 10% (HR:0.90 95%CI:0.85-0.95) lower risk of MI, and also linearly lower MI risk by higher grouped eCRF level (reference=low) (Table 4 and figure 5).

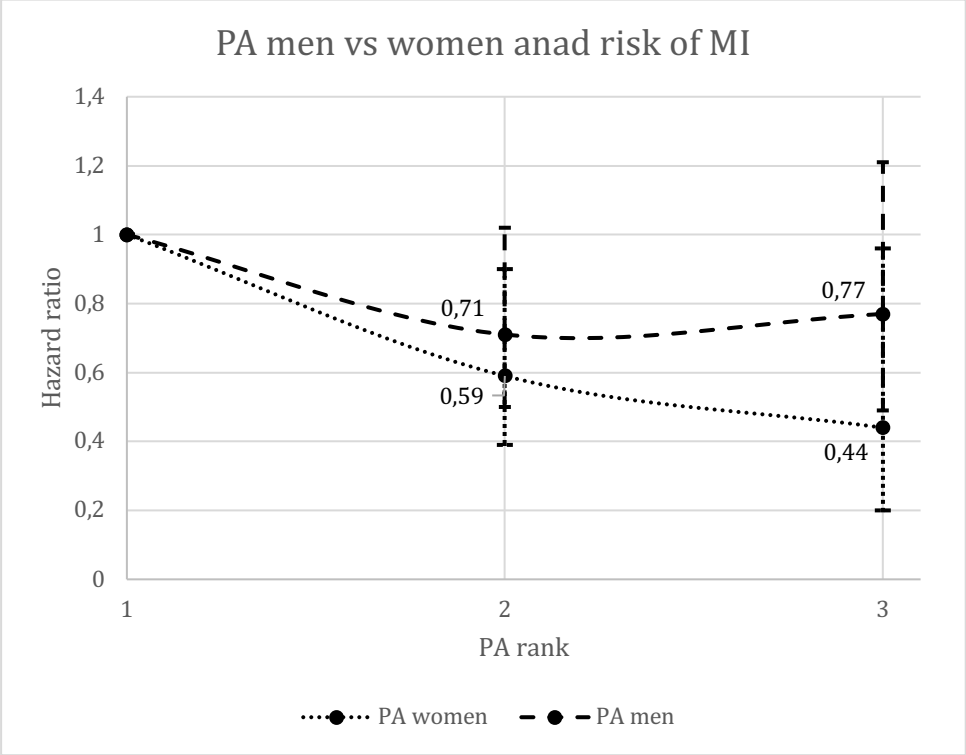

Figure 4 *display the relationship between higher level of PA and HR for MI without eCRF, compared to rank 1 by sex. PA = Physical Activity, HR = Hazard Ratio, eCRF = estimated Cardiorespiratory Fitness, MI=myocardial infarction.*

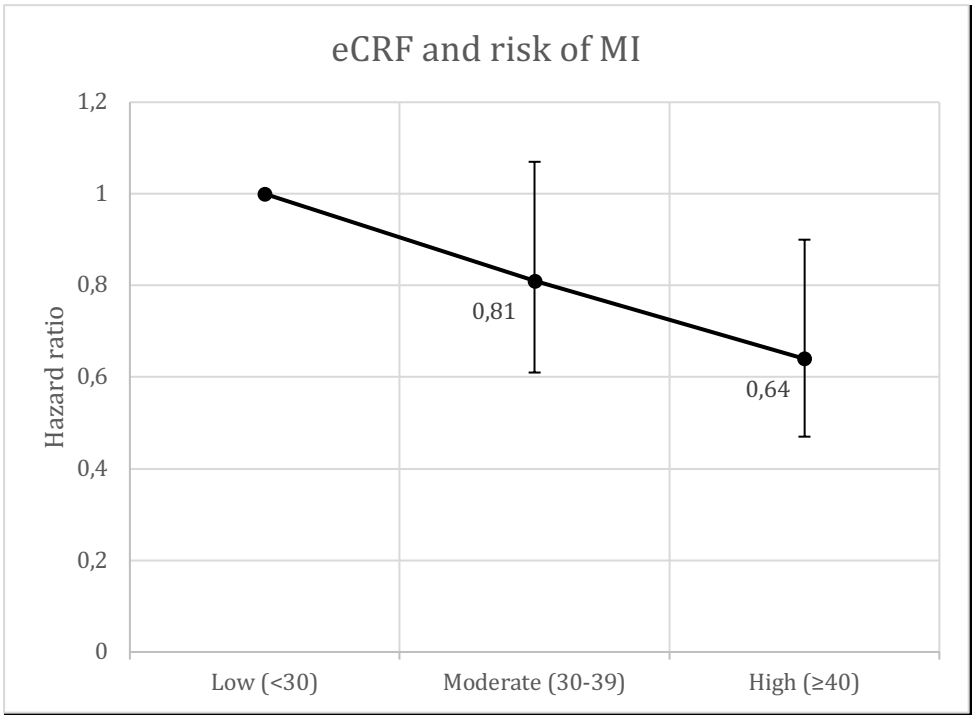

Figure 5 *displays the linear association between eCRF and MI. eCRF=estimated Cardiorespiratory fitness. MI=Myocardial Infarction.*

Sensitivity analyses

In a sensitivity analysis where I excluded those having less than 2 years follow up time from study attendance, results remained unchanged for inactive (reference) versus moderately active (HR:0.67, 95%CI: 0.49-0.90), and slightly attenuated for inactive versus highly active where 95%CI crossed 1.00 (HR: 0.71, 95%CI: 0.47-1.08).

5.3 4-way decomposition mediation analysis

The 4-way decomposition analysis of the mediating effect of eCRF on the association between PA and MI are presented in Table 5 and Figure 6. When decomposing the effect of eCRF in the association between PA and MI of inactive (reference) versus moderately active (B: -0.25, 95%CI: -0.41, -0.09), the direct effect of PA on MI (whether PA directly influences MI risk independently of eCRF) were non-significant (proportion of the beta coefficient: 22 %, 95%CI: -31, 75%, p=0.50), indicating that eCRF fully mediated the association between PA and MI. The reference interaction, that is the excess relative risk due to the interaction (whether the association between PA and MI is dependent on level of eCRF) contributed with the largest proportion (60%, 95%CI:19-102%) of the association of lower MI risk. The

mediated interaction, that is whether eCRF both influence risk of MI directly and interact in the association between PA and MI, contributed negatively with -34% (95%CI: -55, -14%), indicating that A) eCRF influence MI risk directly and B) that eCRF act as an effect modifier in the association between PA and MI (*i.e.,* whether higher PA is associated with lower MI risk is dependent on the level of eCRF). The pure indirect effect, which is the effect of PA that influence eCRF and thereafter influence risk of MI, mediated 52% (95%CI: 19-85%) of proportion of the association of lower MI risk.

Table 5 *4-way decomposition analysis of the mediating effect of eCRF on the association between PA and MI.*

	Inactive (rank 1) versus:			
4-way decomposition	**Moderately active (Rank 2)**		**Highly Active (Rank 3)**	
	Beta coefficient (B)	*Proportion (%)*	*Beta coefficient (B)*	*Proportion (%)*
Total effect	-0.25 (-0.41, -0.09)	100%	-0.29 (-0.56, -0.01)	100%
Controlled direct effect	-0.05 (-0.21, 0.10)	22 (-31, 75)	-0.10 (-0.39, 0.19)	36 (-35, 106)
Reference interaction	-0.15 (-0.25, -0.05)	60 (19, 102)	-0.22 (-0.35, -0.09)	76 (-14, 166)
Mediated interaction	0.09 (0.03, 0.14)	-34 (-55, -14)	0.28 (0.12, 0.43)	-97 (-211, 18)
Pure indirect effect	-0.13 (-0.19, -0.07)	52 (19, 85)	-0.24 (-0.34, -0.14)	84 (-5, 173)

When decomposing the effect of eCRF in the association between PA and MI of inactive (reference) versus highly active (B: -0.29, 95%CI: -0.56, -0.01), the direct effect of PA on MI was non-significant (proportion of the beta coefficient: 36 %, 95%CI: -35, 106%, p=0.50), indicating the eCRF fully mediated the association between PA and lower risk of MI. Both the reference interaction (proportion of the beta coefficient: 76%, 95%CI: -14, 166%, p=0.10, whether the association between PA and MI is dependent on level of eCRF) and the mediated interaction (-97%, 95%CI: -211, 18%, p=0.10, whether eCRF both influence risk of MI directly and interact in the association between PA and MI) were non-significant. The pure indirect effect, which is the effect of PA that influence eCRF and thereafter influence risk of MI, mediated 84% (95%CI: -5, 177%) of the association of lower MI risk.

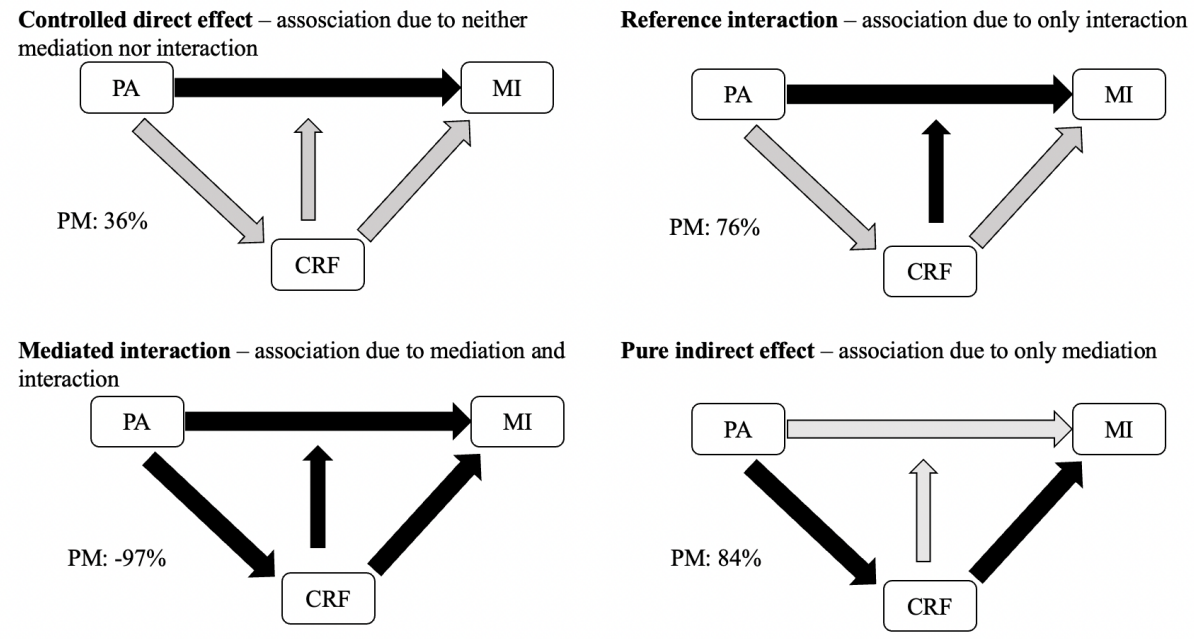

Figure 6 *Presents the pathways in table 5 rank 3vs1. Black pathways represent the proportion mediated (PM) by the components of the 4-way decomposition. PA=physical activity, CRF= cardiorespiratory fitness. MI=Myocardial infarction.*

6 Discussion

This thesis uses a longitudinal cohort study-design, assessing the association between PA and risk of MI. Higher level of PA was associated with lower risk of MI in a curve-linear fashion. Further, higher eCRF was also associated with lower risk of MI. Finally, when assessing the mediating effect of eCRF in the association between PA and MI, eCRF appeared to fully mediate the association between PA and lower risk of MI.

Regarding the effect of PA on MI, the results is in line with the existing literature (10-12), and further showcases that an increase from an inactive lifestyle to a more active lifestyle have substantial health benefits. Furthermore, as mentioned, eCRF was also associated with lower MI risk, which appeared to be in a linear fashion. For example, every MET-hours higher eCRF was associated with an additional 10% lower risk of MI. This is consistent with previous studies assessing CRF and MI (45, 46). For example, Nauman *et al* reported that low eCRF was an independent risk factor high risk for ischemic heart disease, and this relationship is also reported as dose-response dependent (21).

When decomposing the mediating effect of eCRF in the association between PA and MI, the direct pathway between PA and the risk of MI was non-significant. This indicate that CRF

fully mediate the association between PA and risk of MI, *i.e.,* the lower risk of MI in those being more active is likely an effect having higher CRF, where the association between higher PA and higher eCRF showed up to 84% proportion mediated when decomposing the association between those being highly active and those being inactive.

However, I also observed a mediated interaction in the models, where the mediated interaction accounted for 97% of the proportion mediated. This indicates that although higher PA is associated with higher eCRF, which thereafter influences MI risk, this also seem to be dependent on initial eCRF level. In other words, the effect of PA on the association with lower MI risk is also dependent on level of eCRF. This concours with the exercise physiology literature, where initial effect on improving CRF following PA participation is higher if baseline CRF level is low. And if already having high CRF, the effect on improving CRF is lower compared to those having low CRF level (47).

Indeed, this explanation is also in line with the results of decomposing the mediation of eCRF in the risk of MI when comparing those being moderately active and inactive. Here, the proportion of the reference interaction, that is whether the PA-MI association is dependent of eCRF, was significant accounting for 60% of the association (this proportion in highly active versus inactive were non-significant), meaning that if having lower risk of MI if being moderately active depends on the initial CRF level of the participants. In other words, small doses of PA can result in lower risk of MI if the initial CRF level is low, but if already having high fitness level, it is less likely that going from inactive to a moderately active lifestyle will lower risk of MI. For these individuals with already high CRF level, a higher dose of PA would be needed to potentially further lower their risk of MI, which likely already is lower than those with low CRF level. This is consistent with a recent mediation analysis that examined the mediation of CRF on the association between PA and mortality (41).

The results observed here strengthens the implication of the physical activity guidelines issued by the American Heart Association (17) and by the WHO (8), which recommends that all adults should participate in 50-300 min of moderate intensity, or 75-150 minutes of vigorous PA every week. Moreover, this mediation analysis sheds further light on the effect of PA on MI. For example, although there is a curvilinear association of PA on risk of MI, this is mediated by CRF, *and* it is also dependent on initial CRF level. In simple words for implementation in public health; some activity will lower risk of MI, but higher intensity PA that improves CRF will likely result in even lower risk of MI. Consequently, public health

initiatives aimed at lowering CVD risk and the societal burden of CVD should include incentives to increase population levels of PA and may expect higher trade-off if the PA is of sufficient volume to increase CRF.

For clinical practice, this may also have implications. As effects of PA that improves CRF is highly consistent in the literature (27, 33-40), clinicians have the necessary means to improve CRF of their patients, which will most likely lower their risk of MI. Moreover, as the non-exercise prediction formula for eCRF (21) as used here can easily be applied in clinical settings (by measuring WC and RHR, PA in addition to age and sex), practitioners have the necessary tools to tailor their exercise intervention to improve CRF, which can be adoptable according to patients´ estimated initial CRF. However, considering that higher intensity PA may be harder to sustain over time, potential exercise interventions must be seen in combinations with other lifestyle interventions (e.g., diet, hypertension/statin medication *etc.*), and can also be adoptable for gradually increasing the intensity of the exercise as their patients improve their CRF. This application of CRF, and accordingly PA intervention, is in line with the recommended routine assessment of CRF lined out by the American Heart Association (17). Consequently, this can also be adopted by other countries for lowering the global burden of CVD.

6.1 Strengths

This thesis has several strengths. The main strength is the large sample size included in the analysis. In addition, there was a very high response rate for Tromsø 5 (78.53%), thus, there may be low influence from selection bias, and this provides generalizable results for adults. Moreover, as this study included a non-exercise prediction formula for CRF, this also likely minimised selection bias as previous studies using CRF measured by indirect calorimetry usually display a 50% non-response (19). It has previously been argued that representativeness should be avoided when assessing causal associations in population studies, as heterogeneous samples may be more influenced by confounding than homogeneous samples (48). However, recent examples have illustrated that although causal associations are detectable in homogeneous samples that are not representable of the general population (49), others have illustrated that non-representativeness influences the effect estimates of the causal association and this may have implications when adopting it in the general population (50). Consequently, this study of high representativeness shed light on how CRF acts in the association of PA and MI. Nevertheless, selection bias may never be

fully eliminated; thus, influence of selection bias cannot be ruled out. Furthermore, the Tromsø Study endpoint register for incident of MI as used in this study is found be valid and complete when compared to the Norwegian National registry for CVD (51). Thus, misclassification of MI is likely low, which further strengthens the results.

6.2 Limitations

This thesis also has several limitations that should be addressed. First of all, the information used to calculate PA was gathered using PAQs and therefore there is a possibility of information bias and misclassification of PA level. It is likely that self-reported PA is overestimated by individuals (52). Overestimation of an exposure will introduce regression dilution bias (53), and thus underestimate the effect magnitude on the outcome. For example, a recent meta-analysis of device-measured PA reported larger effect magnitudes on mortality (54) than previous studies using self-reported PA (54). Consequently, it is likely that the effect of PA on MI risk in this thesis is underestimated.

Similarly, as the eCRF formula in this thesis also includes a PAQ, regression dilution bias is also likely evident in the eCRF variable. For example, the eCRF formula is derived form a non-exercise formula and is found only to explain ~50% of variance in directly measured CRF trough indirect calorimetry. This may have influenced the mediation analyses as both the exposure and the mediator are influenced by regression dilution bias. Consequently, the results observed here should be replicated in studies using more accurate assessment of PA and CRF. However, measuring PA by self-report is low-cost and can ensure high participation rate. Thus, results from self-report still have high value, and may be used by public health authorities.

Furthermore, as eCRF and PA is derived from baseline, there is a possibility for a change in theses covariates until incident (MI), thus, influence of time-dependent confounding cannot be ruled out. However, this may also be interpreted as a strength, as previous studies have indicated that a single baseline measurement of eCRF may suggest long term risk of MI, and baseline high PA level is reported to display similar lower risk of mortality as increasing PA from low to high levels (55-57). Thus, a baseline assessment may be sufficient to examine the dose-response associations with future health outcomes in many settings. Another limitation is that eCRF includes a PAQ; although there are different PAQs for the exposure and the mediator variable, their initial face validity suggest that they measure the same construct. Thus, collinearity including PA in both the exposure and mediator variable may have

influenced the mediation analysis. Therefore, this thesis should be replicated using a mediator that measured CRF, preferably by indirect calorimetry and a test to exhaustion, or at least by an exercise test testing the performance in *e.g.,* running/cycling. Although the population sample is large, it may have some limited generalizability beyond western high-income countries. Similarly, the results derived from the formula estimating CRF may lack generalizability across ethnicities beyond those participating in the original study by Nauman *et al* (21), and this may further influence the mediating analysis.

7 Conclusion

In this thesis, higher PA was associated with lower risk of MI. The lower risk of MI from PA is fully mediated by eCRF, indicating that the reason for observing lower MI risk from PA is explained by higher CRF. Public health authorities aimed at lowering burden of CVD should provide incentives that facilitate as much PA as possible for improving CRF of the population. This may also have implication in clinical practice as CRF is increasingly viewed as a clinical vital sign in routine assessment for CVD, where increasing CRF through participation in PA may be vital for improving CRF and ultimately lower CVD risk. Finally, these results should be replicated using a gold-standard measurement of CRF through indirect calorimetry.

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9 Tables

10 Figures