Master's thesis

NTNU
Norwegian University of Science and Technology
Faculty of Medicine and Health Sciences
Department of Circulation and Medical Imaging

Bipin Chapagain

Longitudinal Changes in Peak Oxygen Uptake and Influence of Age, Gender and Self-Reported Physical Activity in a Healthy Population - THE HUNT 4 Fitness Study.

Master's thesis in MSc. Exercise Physiology
Supervisor: Bjarne Martens Nes
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ABSTRACT

Background: According to a few longitudinal studies, peak oxygen uptake(VO_{2Peak}) declines at a nonlinear rate and accelerates at older ages in both men and women. Rate of decline in VO_{2peak} per decade is higher in men compared to women, and physical activity (PA) reported at high intensity can attenuate the decline in VO_{2peak}. But only a few longitudinal studies had reported the effect of relative intensity and time spend on absolute and percentage decline of VO_{2peak}.

Objectives: The primary aim of the study is to examine the absolute (mL/kg/min) and relative (%) change in VO_{2peak} over 10 years in healthy subjects across different age groups. The secondary aim of the study is to analyze the influence of gender, age, intensity, and level of self-reported PA on change in VO_{2peak}.

Methods: Out of 3264 participants invited from HUNT 3 fitness study (prospective population-based health survey in Nord-Trøndelag, Norway, performed in 2006-08), 1443 participants completed the VO_{2peak} test. 1107 healthy participants (501 men, 606 women) were included in the study. Information on self-reported PA is collected through a questionnaire including questions on duration, frequency, and relative intensity (Borg scale 6-20). Association between PA and the change in VO_{2peak} is assessed through a general linear model.

Results: Longitudinal decline in VO_{2peak} observed across different age groups from <40 years to ≥70 years shows that the percentage (%) decline of VO_{2peak} is similar in both gender, whereas men show more decline in absolute (mL/kg/min) VO_{2peak} in each decade as compare to women. The relative rate of decline accelerated from 2 to 5 % in the 30s and 40s to > 12% per 10 years in the 70s and beyond. Inactive participants reported a more longitudinal decline in VO_{2peak} than those reported for <75min. wk^{-1}, 75-149 min. wk^{-1}, and ≥150 min. wk^{-1}. When PA is stratified by intensity and time spend, an absolute decline in VO_{2peak} is lower in participants who reported PA 75-149 min. wk^{-1} [-2 mL/kg/min (95 % confidence interval -0.3 to -0.1)]with very vigorous intensity than participants who reported PA ≥150 min. wk^{-1} [-5.9 mL/kg/min (95% confidence interval -7.1 to -4.7)]with a moderate intensity. The longitudinal decline in VO_{2peak} did not differ considerably between participants who reported PA at the very vigorous intensity with a duration of less than 75 min. wk^{-1} and participants who reported PA at moderate intensity with recommended volume.

Conclusions: Our findings conclude that the absolute longitudinal decline of VO_{2peak} is not constant across the age groups, it declines at a nonlinear rate and accelerates after 50 years of age, especially in men and regardless of any PA. The percentage decline of VO_{2peak} is similar between men and women. PA at a moderate intensity of long duration and higher intensity with shorter duration was associated with similar longitudinal declines of VO_{2peak}. Thus, the PA at vigorous and very vigorous intensity helps to attenuate the decline of VO_{2peak} with considerably lower exercise time.

Keywords: Physical activity, VO_{2peak}, PA recommendations.

PREFACE

This Master thesis report is submitted to Norwegian University of Science and Technology (NTNU), Department of Medicine and Health science, as a part of the course SPO3900, Master´s thesis. The project work has been performed under the supervision of researcher Bjarne Martens Nes, PhD, as main supervisor and Jon Magne Letnes, MD, as co-supervisor.

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ABBREVIATIONS

ACSM	American College of Sports Medicine
BMI	Body Mass Index
CHD	Coronary Heart Disease
CI	Confidence Interval
CO	Cardiac Output
CPET	Cardio Pulmonary Exercise Testing
CRF	Cardio Respiratory Fitness
CVD	Cardio Vascular Diseases
CVH	Cardio Vascular Health
EDV	End Diastolic Volume
FFM	Fat Free Mass
HR	Heart Rate
HR_{max}	Maximal Heart Rate
Min. wk^{-1}	Minute per Week
Min. d^{-1}	Minute per Day
O2	Oxygen
PA	Physical Activity
SD	Standard Deviation
SV	Stroke Volume
SV_{max}	Maximum Stroke Volume
VO_{2max}	Maximal Oxygen Consumption
VO_{2peak}	Peak Oxygen Uptake
WHR	Waist Hip Ratio

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1. INTRODUCTION

Cardiorespiratory fitness (CRF) is a health-related component of physical fitness defined as the ability of circulatory and respiratory systems to supply oxygen to skeletal muscles during sustained physical activity. It can be measured directly from the treadmill or cycle ergometer expressed as VO_{2max} (maximal oxygen uptake) or can be derived from the peak work rate expressed as VO_{2peak} (peak oxygen uptake), where peak uptake denotes the situation where the criteria for the maximal test were not met (Haskell et al., 2007). Particularly in epidemiological studies involving large populations estimated CRF derived from the peak work rate is the more common expression of fitness. VO_{2peak} and physical activity (PA) are both strongly and inversely related to cardiovascular morbidity and mortality(Kodama et al., 2009; Wen et al., 2011). Previously it has been reflected that estimated or directly measured VO_{2peak} is a stronger determinant of cardiovascular disease (CVD) risk than measures of PAWilliams (2001). However, it is very hard to distinguished PA and VO_{2peak} because an increase in PA is the main method to increase fitness. Therefore, higher VO_{2peak} can act as a negotiator for promoting better health effects on physically active individuals. Exercise training or leisure time PA commonly improves VO_{2peak} and typically measured by its frequency, intensity, and duration of which intensity may be the most important determinant of VO_{2peak} (Wisløff, Ellingsen, & Kemi, 2009).

CRF is an important predictor for CVD mortality (P. Katzmarzyk, Janssen, & Ardern, 2003; P. T. Katzmarzyk, Church, Janssen, Ross, & Blair, 2005) and increasing evidence suggest that a spectrum of health and disease outcomes are powerfully predicted by VO_{2peak} (Blair, 2009; Jackson., Sui, Hébert, Church, & Blair, 2009). Most cross-sectional studies suggest that CRF declines linearly with 5-20% per decade with increasing age (Fleg & Lakatta, 1988; Jackson et al., 1996; Pollock, Foster, Knapp, Rod, & Schmidt, 1987), a few longitudinal studies suggest that VO_{2peak} declines at a nonlinear rate which is accelerated after 45 years of age in both men and women (Fleg et al., 2005; Jackson. et al., 2009; Stathokostas, Jacob-Johnson, Petrella, & Paterson, 2004). Studies with both cross-sectional and longitudinal design, shows that the rate of decline of VO_{2peak} not only depends upon age per se, but also with lifestyle factors, the PA level of an individual. Whereas, the decline in VO_{2peak} with age is multifactorial, which is influenced by central and peripheral factors.

A reduction in PA with advancing age can cause a reduction in VO_{2peak} in older individuals (Blair, 2009). With advancing age, people tend to spend less time on more vigorous PA and results in the shift of PA levels towards less physically demanding activities (Stephens, Jacobs Jr, & White, 1985). This phenomenon may partially explain the decrease in CRF reflected in VO_{2peak}. According to a longitudinal study, baseline PA can also act as a strong predictor of VO_{2peak} after years of follow up (Jackson. et al., 2009). Moreover, as longitudinal measurements indicate, the subsequent increase in the level of physical activity helps to minimize cardiovascular and all-cause mortality (Lee, Puska, Blair, Katzmarzyk, & Group, 2012; Li & Siegrist, 2012). Therefore, lifestyle factors such as PA may be important predictors of change in VO_{2peak} with advancing age. In addition to age and level of PA, gender also has an independent effect on the absolute and relative change in VO_{2peak}. Men have higher VO_{2peak}

values in all age groups compared with women. However, the gender difference in longitudinal changes in VO_{2peak} had not been clearly defined until the Baltimore longitudinal study of aging examined the relationship between leisure-time PA and VO_{2peak} among healthy men and women across a broad age range using a cross-sectional design study (Fleg et al., 2000). Another study from Baltimore reflected that the longitudinal decline in VO_{2peak} was observed in each of the 6 age decades in both genders, where the rate of decline was larger in men than in women from the 40s onward (Fleg et al., 2005).

There are some population-based studies, which had reported for the change in VO_{2peak} with advancing age (Fleg et al., 2005; Jackson et al., 1996) but few population-based studies have describe the factors such as age, gender (Fleg et al., 2005) and self-reported PA that influences the change in VO_{2peak} (Jackson. et al., 2009). But still no longitudinal population-based study of healthy individuals has examined the association between absolute and relative rate of decline in VO_{2peak} and PA stratified by intensity and time spend on exercise. Thus, the aim of the study is to describe the absolute and percentage change in VO_{2peak} across different age groups and the factors that influence the change in the decline of VO_{2peak}. And, in this longitudinal population study of healthy individuals, we compared self-reported PA at a different intensity and duration level in relation to the absolute and percentage decline of VO_{2peak}.

1.1 VO_{2peak} as a measure of CRF and predictor of Cardiovascular health

CRF and PA have provided successful health benefits on the cardiovascular health. According to numerous studies, it has been reported that both measured and estimated CRF strongly predicts the outcomes (Harber et al., 2017; Laukkanen., Salonen, Rauramaa, Salonen, & Kurl, 2004; Letnes, Dalen, Vesterbekkmo, Wisløff, & Nes, 2018). CRF is not only a reliable measure of habitual PA (Carnethon, Gulati, & Greenland, 2005), but also a useful indicator of prognosis and health status for both symptomatic and asymptomatic patients in clinical interventional studies (McAuley, Kokkinos, Oliveira, Emerson, & Myers, 2010). Both CRF and PA is inversely associated with cardiovascular morbidity and mortality and with risk factors for cardiovascular diseases, such as diabetes, hypertension, site specific cancers and bone health.

1.1.1 CRF and Cardiovascular Health

CRF is recognized as an important risk predictor for all-cause CV mortality and morbidity. Mounting evidence suggests that a low level of CRF is associated with a higher risk of CVD and all-cause mortality (Blair. et al., 1989; Laukkanen. et al., 2004). For instance, the landmark study by Blair et al. 1989 demonstrated a strong independent association of CRF with all-cause mortality rates, where participants in the lower 20 % of CRF had significantly higher mortality rates and relative risk of mortality compared to the highest 20 %. According to collective evidence of the last three decades, CRF and health outcomes, of both healthy individuals and those with existing CVD, shows strong inverse and independent association, and lead American Health Association to make scientific statement that VO_{2peak} can be measured as a vital sign to predict health outcomes (Ross et al., 2016). Research performed on more than 2000 Norwegian subjects followed over 7 years showed strong association between reduced coronary risk and high levels of CRF (Lie, Mundal, & Erikssen, 1985). Furthermore, changes in CRF among 1756 Norwegian old men followed for 22 years, was an independent predictor of all-cause mortality and CVD mortality (Erikssen et al., 1998). A recent study confirmed these early findings by observing 9 % decrease in all-cause mortality with 1ml/kg/min increase in CRF over 11 year period (Laukkanen et al., 2016). HUNT 3 fitness study on 4527 adults with no history of CVD in a large population-based health study showed a strong and inversed association between VO_{2peak} and CHD across the whole fitness continuum in a low-risk population and concludes that increased VO_{2peak} may have substantial benefits in reducing the burden of CHD (Letnes et al., 2018)

In addition, previous studies suggest that CRF can attenuate the increased risk of death due to obesity (Lee, 2012). Several risk factors such as blood lipid profile, body composition, inflammation, and blood pressure gets improved through CRF (Fletcher et al., 2001).CRF is strongly correlated with the physiological functions of the body such as pulmonary (Benck et al., 2017), cardiovascular (Bhella et al., 2014), skeletal muscle and metabolic function (Earnest et al., 2013). In spite of being recognized as an important marker for cardiovascular health, CRF is currently only a major risk factor which is not assessed in clinical practice routinely compared with other risk factors such as smoking, obesity, high blood pressure, or high blood glucose (Ross et al., 2016).

1.1.2 PA and Cardiovascular Health

PA is associated with decreased risk for CVD and its risk factors. It was found that CHD can be lowered by 5.8 % world-wide through the elimination of physical inactivity, and also longevity can be increased by 0.68 years (Lee et al., 2012). In prospective cohort studies, PA is inversely associated with the prevalence of metabolic syndrome, obesity and other CVD risk factors, CHD, and risk of CVD mortality (Williams, 2013). Similar findings were supported by meta-analysis research, where they showed that leisure-time PA was associated with a decreased risk of metabolic syndrome (He et al., 2014). Furthermore, another meta-analysis study revealed that leisure-time PA was associated with a 20-30% reduction in risk of CHD and stroke(Li & Siegrist, 2012). In general, strong evidence indicates that PA is helpful for the protection against the development of CVD and its risk factors, and also the inclusion of PA levels improves the ability to predict risk in patients with CVD (Ingle, Carroll, Stamatakis, & Hamer, 2013). Thus, PA shows parallel benefits compared to CRF in relation to CVD outcomes and terms of risk predictions.

1.1.3 CRF and PA in relation to CV health

Both CRF and PA have an independent and important role but overlapping roles in CV health. Since CRF can be modified through changes in PA, it is regarded as a surrogate for habitual PA(Haskell et al., 2007). However, animal and human studies show that it is just more than just a marker of PA habits (Blair, Cheng, & Holder, 2001). It has been noted through the review that habitual PA is better represented by CRF than by self-report PA (Swift et al., 2013). Further, a study from Williams concluded that CRF determined by maximal exercise test had been shown to be a stronger predictor of CVD events versus PA (Williams, 2013). Occupational and leisure-time PA , conventional risk factors and VO_{2peak} assessed on 2383 factory workers (followed for 5 years) in Belgian Fitness study interpreted CRF along with smoking and HDL cholesterol as a strong and independent risk marker for CVD, while PA scores were not significant predictors of CVD incidence (Sobolski et al., 1987). Aerobic training studies performed in healthy but sedentary adults using moderate- to vigorous-intensity exercise typically increases an individual measured or estimated VO_{2peak} in the range of 15 to 25 %(Skinner et al., 2000). Whereas, conversely, inactive men placed at bed rest for 3 weeks was shown to decrease VO_{2peak} by 26 % (Saltin, Blomqvist, Mitchell, & Johnson Jr, 1968). As noted, training can help to modify the level of CRF, so such change in CRF levels can influence CV outcomes years later in terms of mortality. Thus, CRF and risk attributed to the lower levels can be modified with PA.

The decline in VO_{2peak} is usually attributable to a reduction in maximal heart rate, reduction in stroke volume or both (Montero & Díaz-Cañestro, 2015). However, age-related loss of muscle mass can also be seen in the context. Interestingly, maximal heart rate is a function of age that has an inherent aging effect in all individuals and unaffected by fitness status, irrespective of lifestyle. This highlights the fact that some physiological indexes are not influenced by activity but are under the control of the aging process. However, it is beyond the scope review to cover all the system but still some of the prospective studies showed that an individual maintaining regular PA are less prone to suffer from depression, dementia and cognitive impairment (Sofi et al., 2011).

In summary, collective scientific evidence confirms that high CRF, or improvement in CRF in healthy and diseased populations are independently linked with reduced risk of mortality and other adverse outcomes. Hence, practitioners may convey that the adult who has high CRF has a low risk of premature mortality and vice versa. The main strategy to improve CRF is to participate in an exercise training program or to increase the general PA levels.

1.2 Cross-sectional studies on VO_{2peak} across age groups.

In 1938, original work from Robinson (1938) accounted loss rate in VO_{2peak} on men with advancing age approximated 10% per decade . Early studies of athletic population generally shows relative loss rate of VO_{2peak} that is lower than 10 %; for instance, Shephard (1966) demonstrated a loss rate of 6% per decade for athletic males. Although an athletic sample from Pollock, Miller Jr, and Wilmore (1974) shows 10% decline rate, this number was raised to a 22% per decade rate of loss in athletes over 70 years of age, while the athletes under age 70 years demonstrated 6% per decade loss in VO_{2peak}. Early studies of athletic populations showed a similar decline rate in VO_{2peak} for both sedentary and active individuals (Barnard, Grimditch, & Wilmore, 1979). Additionally, another study involving athletic populations have demonstrated identical loss rate those seen in sedentary individuals (Hawkins & Wiswell, 2003). However, Pimental et al. demonstrated that the absolute rate of decline was greater in endurance-trained athletes than in sedentary men while relative (% decade) loss rate was similar between the groups endurance trained athletes and sedentary men with 10.8 and 11.2, respectively (Pimentel, Gentile, Tanaka, Seals, & Gates, 2003).

Another study from a Chinese population showed 34.8 % decline in VO_{2peak} for men from 20-29 to 60-64 age groups, whereas for women it showed 37.8 % decline in VO_{2peak} from 20-29 to 60-69 age group (Wong et al., 2008) with 10 % decline per decade for both men and women. The Chinese men and women showed lower VO_{2peak} than that of Caucasians group (Jackson et al., 1996) with 20 % lower in 25-34 and 35- 44 age groups and also 10 % lower in 45-54 and 55 over age groups. A suggested reason for this was Chinese population was considered as less physically active as compared to Caucasians, and they were shorter and had lighter body mass so that they have a lower absolute VO_{2peak}.

The HUNT study examined the distribution of VO_{2peak} across age and gender in a large population-based sample in Norway and assessed the association of CRF with the prevalence of unfavorable levels of cardiovascular risk factors. In that study, an average VO_{2peak} among women was higher than previously observed in men. The data of the study suggested that VO_{2peak} of 44.2mL/kg/min in men and 35.1 mL/kg/min in women represent the thresholds for elevated cardiovascular risk. Thus, the assessment of VO_{2peak} by gender in the study of fitness and cardiovascular risk is useful. Moreover, they observed that physically active participants age 50-59 years and inactive participant's age 20-29 years had a similar level of VO_{2peak}. The finding suggests that to limit age-dependent decline in VO_{2peak} or possibly the level of cardiovascular risk factors level with increasing age people must engage in physical exercise. Overall, each 5ml/kg/min decrement in VO_{2peak} corresponded to nearly 50 % higher prevalence of cardiovascular risk factor in both genders.

According to a study from the HUNT 3 Fitness (n=4631), women had lower VO_{2peak} than men despite being more physically active. The highest VO_{2peak} for both sexes were observed in the age group 20-29 years. Among men and women in this group, VO_{2peak} was 54.4±8.4 mL/kg/min and 43±7.7 ml/kg/min, respectively. 10 % per decade decrease in absolute and relative VO_{2peak} in both sexes during 40-69 years was observed compared to that in age 30-39 and 40-49 years. Between 60-69 years and above 70 years, the largest drop in absolute and relative VO_{2peak} in both sexes were 10% and 11 % lower in males and females compared to that of 60-69 years of age(Loe, Rognmo, Saltin, & Wisløff, 2013). Another study from seven hundred fifty-nine Norwegian reported men and women reported VO2peak for 20-29-year-old age group was 40.3 ± 7.1mL/kg/min and 48.6 ± 96 ml/kg/min in men and women respectively. 8% linear decline of VO_{2peak} was observed after 30 years in both sexes

The FRIEND registry in the U.S population developed CRF reference values derived from cardiopulmonary exercise testing (CPX) using a treadmill. They performed the study on a large cohort where they included men and women (aged 20-79 years) without CVD for determining VO_{2peak}. In FRIEND, the VO_{2peak} of men and women aged 20 to 29 years decreased from 48 and 37.6 ml/kg/min to 24.4 and 18.3 ml/kg/min for ages 70 to 79 years, respectively (Kaminsky et al., 2015). On the other hand, CPX using cycle ergometry in the next cohort from FRIEND registry reported that VO_{2peak} of men and women aged 20 to 29 years declined from 41.9 and 31 ml/kg/min to 19.3 and 14.8 ml/kg/min for ages 70 to 79 years. The rate of decline in this cohort was approximately 10 % per decade (Kaminsky et al., 2017).

1.3 Longitudinal studies on VO_{2peak} with increasing age.

Longitudinal design research has been recommended to be more valid means of assessing age-related changes in physiological function because of different inherent bias such as selection bias, information bias and confounding bias associated with cross-sectional studies (Dehn & Bruce, 1972). However, due to subject mortality and morbidity, similar bias can be susceptible to longitudinal research (Plowman, Drinkwater, & Horvath, 1979). The main problem of the longitudinal designs is that the main age effect cannot be distinguished from the two confounding effects (i.e. period and cohort effects)(Twisk, 2013). As they can easily occur together, it is very hard to extract the two types of effects. Due to the influence of both cohort and periodic effects, one should be careful with the interpretation of age-related results also in a longitudinal study. Therefore, to minimize bias, it is essential to consider the number of individuals who dropped out along the way over the study period. Despite of this limitation, longitudinal research not only offers advantages on paired observation VO_{2peak} but also factors that could account for some of the changes observed in VO_{2peak}.

Generally, it has been reported that the longitudinal rate of loss of VO_{2peak} is greater than the cross-sectional rate of loss (Buskirk & Hodgson, 1987; Dehn & Bruce, 1972). However, most longitudinal studies on sedentary and physically active individuals report similar to those produced by cross-sectional data reflecting 10% loss rates per decade from age 20 to 60 years (Astrand, Astrand, Hallbäck, & Kilbom, 1973; Plowman et al., 1979). It is interesting that despite the mixed physical activity, women in their twenties showed no loss in VO_{2peak}, but after 30 years of age, the decline rate of 10% per decade was uniformly noted (Plowman et al., 1979). These supported the belief that declines in VO_{2peak} do not begin until the third decade of life.

Kasch et al. (1999) reported a 10 % loss rate per decade for both sedentary and active individuals in a group of participants involved in a moderate exercise program for up to 32 years at various intervals. Several studies reported lower declines in VO_{2peak} for athletic individuals when compared to sedentary individuals ranging from 1-6 % per decade (Astrand et al., 1973; Pollock et al., 1987). A short follow up study of 2.3 years in middle-aged man demonstrated 1.4 % loss on active individuals (n=24) and 5.1% loss in inactive individuals (n=24) (Pollock et al., 1997). One early study of longer time frame (22 years follow up) reported lower loss rate in younger athletes (45.3 ± 2.3 years at follow up) in contrast to older athletes (68.4 ±2.7 years at follow up)(Astrand et al., 1973). Older adults were considered as ‘fit older’ because of 60 years of age and high training duration of 20-25 years, experienced a 15 % decline in VO2peak per decade.

Baltimore Longitudinal study of aging, a community-dwelling cohort free of clinical heart disease conducted series of measurements of VO_{2peak} in 375 women and 435 men ages 21 to 87 years, over a median follow up period of 7.9 years (Fleg et al., 2005) and reported a 3% to 6% decline in VO_{2peak} per 10 years in the 20s and 30s to >20% per 10 years in the 70s and beyond. The rate of decline in men was larger than in women from the 40s and onward. It was concluded that regardless of PA, especially in men, the longitudinal decline in VO_{2peak} in healthy adults is not constant across the age span but accelerates markedly with age in each successive age decade. A cohort study on 3429 women and 16889 men aged 20 to 96 years from Aerobic Center Longitudinal Study (ACLS) also showed the decline in VO_{2peak} with age is not linear (Jackson. et al., 2009). The results of this study were consistent with results reported by Fleg and associates, showing a decline at an accelerated rate after 45 years of age. The major differences between the results of Fleg et al. and ACLS model were that the ACLS model defined the influence of common lifestyle variables (smoking, self-reported PA, blood pressure, body composition) on the longitudinal decline in CRF associated with age. Altogether both studies were similar to a study from Stathokostas et al. who reported mean longitudinal yearly change in VO_{2peak} of -0.43 ml/kg/min for 34 men and -0.19 ml/kg/min for 28 women (Stathokostas et al., 2004). However, the sample size of the study from Stathokostas el al., was smaller than ACLS model and Baltimore longitudinal study of aging.

Another fitness study in Swedish working force showed absolute VO_{2peak} decreased by -6.7 % (-0.19L/min) in the total population in which men had the higher absolute VO2peak, and experienced greater decrease compare to women, whereas relative VO_{2peak} decreased by 10.8 % (4.2 ml/kg/min) (Ekblom-Bak et al., 2019). In the following study, periodic effects of a decline in VO_{2peak} were examined on the population level over different decades from 1995-2017. The greater decrease in relative VO_{2peak} was explained by the simultaneous increase in body weight.

1.5 Physiological Mechanism responsible for age related declines in VO_{2peak}.

The exact physiological definition of VO_{2peak} is expressed by Fick equation.

VO_{2peak} = Cardiac output (Q)× arterial- Venous O_2 difference(Cao_2-Cvo_2)

VO_{2peak} is the single most important factor that determines success in an aerobic endurance PA(Mitchell & Saltin, 2003). According to illustration from Fick equation, cardiac output, and O_2 extraction are two major factors that could limit VO_2 at maximal exertion(Wagner, 1996). It has been identified that a decrease in both maximal cardiac output and maximal arterial-venous O_2 difference may play a role in the reduction of VO_{2peak}(Tanaka & Seals, 1997).

1.5.1 Central factors

(a) *Maximal Cardiac Output*:

Cardiac output is defined as the volume of blood being pumped by the heart, by the left and right ventricle, per unit time and denoted by the symbol Q. It is the product of heart rate (HR), i.e., the number of heartbeats per minute (bpm) and the stroke volume (SV), which is the volume of blood pumped from the ventricle per beat.

$Q = SV_{(L/beat)} \times HR_{(beats/min)}$

Cardiac output seems to be a major factor determining oxygen delivery at maximal exercise when VO_{2peak} is limited by oxygen delivery. Although it has been reported that with advancing age, maximal cardiac output can be maintained (Rodeheffer et al., 1984), the majority of studies reinforce the idea that maximal cardiac output declines with advancing age in healthy sedentary adults (Hunt et al., 1998; Ogawa et al., 1992; Rivera et al., 1989), in proportion to the decline in maximal oxygen uptake (Proctor et al., 1998).

(b) *Maximal Heart Rate:*

Particularly in endurance-trained athletes it is viewed as the primary mechanism for the contribution of age- related reductions in maximal cardiac output and VO_{2peak} (Hagberg et al., 1985). Various cross-sectional and longitudinal studies reported that starting from the early adulthood the maximal heart rate declines with age at a rate of 3-5 % per decade (Drinkwater, Horvath, & Wells, 1975; Eskurza, Donato, Moreau, Seals, & Tanaka, 2002; Fleg et al., 2005; Jackson et al., 1996; Nes, Vatten, Nauman, Janszky, & Wisløff, 2014). The physiological mechanism believed to the reduction in the maximal heart rate with ageing is due to the slower conduction velocity (Fleg et al., 1994), a reduced responsiveness of the sinoatrial node to β adrenergic stimulation and decreased intrinsic heart rate (Jose & Collison, 1970).

(c) *Maximal SV*:

SV is obtained by subtracting end-systolic volume (ESV) from end-diastolic volume(EDV)(Edvardsen, Hansen, Holme, Dyrstad, & Anderssen, 2013)

SV= EDV - ESV

Maximal SV in older endurance exercise-trained is reduced to 80-90 % of that observed in the younger endurance-trained adults (Ogawa et al., 1992). The physiological mechanism behind such reduction is due to the changes in the determinants of SV (e.g., preload, afterload, and intrinsic contractility of the heart). Preload refers to the degree to which the ventricles are stretched prior to contracting. An increase in the venous return increases the preload, and through the Frank starling law of the heart, the SV increases (Cho, 2017). Whereas, reduction in SV is caused by decrease venous return, meaning that EDV will be lower with higher age, but also all these possible changes can be attenuated by exercise (Molmen, Wisloff, Aamot, Stoylen, & Ingul, 2012). Afterload is commonly measured as aortic pressure during systole; elevated afterload reduces SV due to increased vascular resistance, which later hinders the ventricles in ejecting blood, causing reduction in SV. Stiffness of the large elastic arteries with advancing age leads to an increase in aortic impedance as well as vascular afterload followed by decreasing the stroke volume (Chen et al., 1999). Compared to sedentary, the degree of stiffness can be attenuated in endurance trained athletes, but still large elastic arteries can get stiffened with advancing age (Tanaka et al., 2000). Therefore, an increase in ventricular afterload and aortic input impedance leads to the reduction in the maximal SV in older endurance-trained adults (Mazzaro, Almasi, Shandas, Seals, & Gates, 2005). Intrinsic contractility is lowered due to parasympathetic stimulation and hypoxia (Mesquida, Kim, & Pinsky, 2011). Decreased contractility causes increase in ESV which results in decreased SV (Domenech & Parra, 2016).

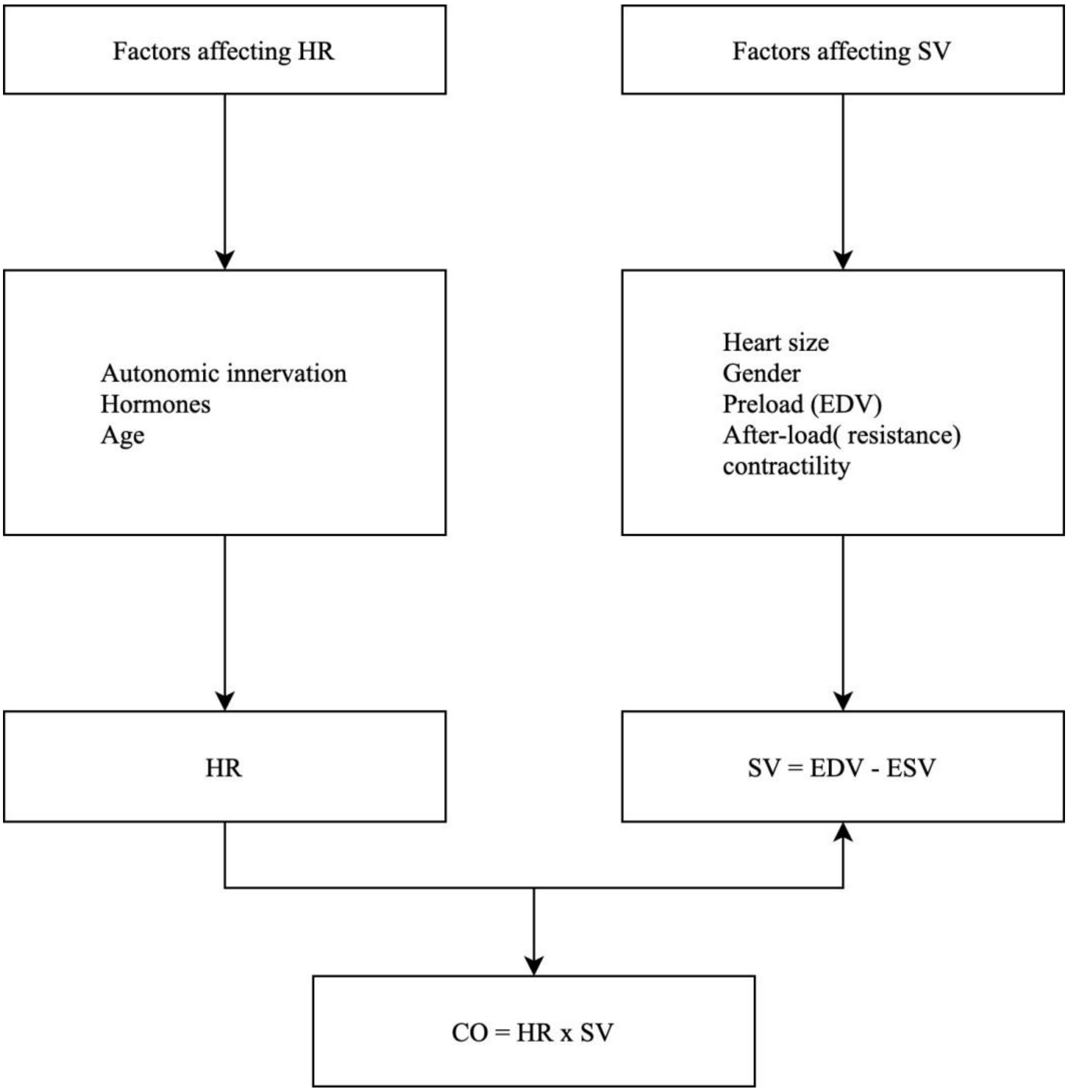


Figure 1. Major factors influencing cardiac output, heart rate and stroke volume.

1.5.2 Peripheral Factors

Skeletal muscles and respiratory muscles extract O_2 from the blood to produce ATP during maximal exercise, and is reflected by maximal arteriovenous O_2 difference. The decline in maximal arteriovenous O_2 difference with an advancing age occurs with a consistent reduction in the capillary density and mitochondrial enzyme activities, which leads to the reduction in peripheral oxygen extraction and can contribute to decline of VO_{2peak} with age in endurance trained adults (Coggan et al., 1992). Muscle oxidative enzyme activities and capillarization (per area or per fiber) are similar between young and older endurance-trained adults (Coggan et al., 1992). Thus, compared to maximal oxygen extraction, maximal oxygen delivery is likely the major contributor to age-related reduction in maximal arteriovenous O2 difference in endurance-trained adults (Wagner, 1996).

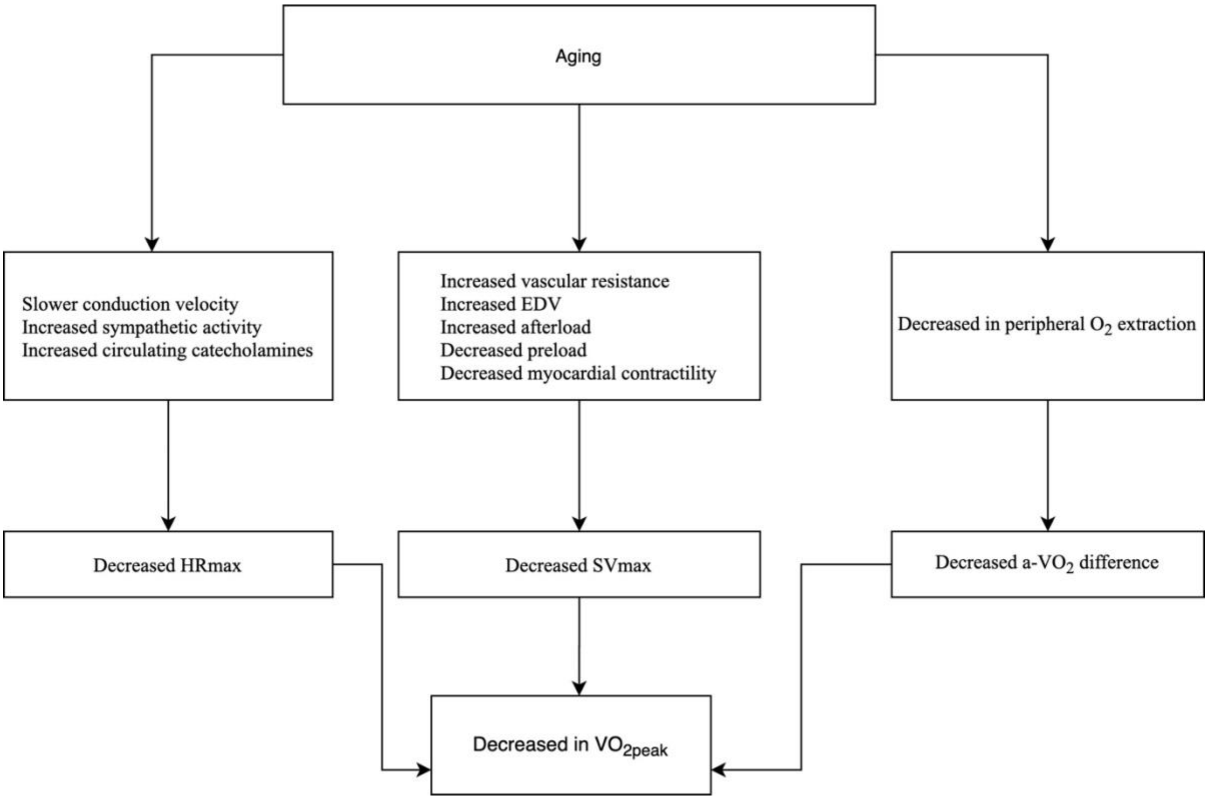


Figure 2. Physiological process on age related decline of peak oxygen uptake.

1.6 Body Composition and VO_{2peak}.

Body composition and CRF are the physiological parameters that are often associated with each other and strongly inter-related. Both body fatness and CRF predict the health outcomes, but still, the extent of independent effects to one another is debatable. Previous studies indicated body mass, fat-free mass (FFM) and % body fat and body surface area are the best predictor of VO_{2peak} (Fleg et al., 2005; Kenney & Hodgson, 1985; Lee, 2012; Miller, Wallace, & Eggert, 1993; Wong et al., 2008). In the earlier studies, Fleg and Lakatta (1988) implemented a cross-sectional design to examined the role of muscle loss in the age associated decline in VO_{2peak}. The study reported that men had higher VO_{2peak} than women across all ages; the unadjusted rate of decline of VO_{2peak} was significantly greater in men than females (3.9-2.5 mL/kg/min per decade) respectively. Similarly, the absolute rate of reduction in muscle mass was greater in men than females. Despite of higher VO_{2peak} in men than women in relative to body-weight, the muscle mass eliminated the gender difference in aerobic capacity. Therefore, the author concluded that loss of muscle mass in untrained men and women explained the half of age-associated decline in VO_{2peak}. Furthermore, this study was supported by a cross-sectional design study employed by (Toth, Gardner, Ades, & Poehlman, 1994), who initially found a greater difference in the decline of aerobic capacity in men and women. Still, after controlling for changes in body composition (FFM and fat mass), an adjusted rate of decline was 4 % per decade for both genders.

Longitudinal study from Fleg et al. (2005) mounted that age-associated changes in body weight and FFM are important determinants of longitudinal changes in VO_{2peak}. VO_{2peak} per kilogram of FFM remained stable in the younger age group of both sexes, but the accelerating decline was observed after 50 years for men and 60 years for females. The gender difference in FFM narrowed with age after the fifth decade due to a greater decline in FFM in older men than older women. Moreover, VO_{2peak} also showed an accelerating decline after the 5_{th} decades in both older men and women. Prospective studies performed over the last decade have assessed the independent and joint association between PA patterns, fitness, and outcomes. In each of the study, obese, unfit or comparatively sedentary possess high % body fat, low % FFM, and higher mortality risks. When stratified within a given category of body dimensions [BMI(Body Mass Index), WHR(Waist Hip Circumference)] subjects who were more physically active and fit had a high CRF and a lower risk for adverse outcomes compared with who are inactive or unfit (P. Katzmarzyk et al., 2003; LaMonte & Blair, 2006).

Another cross-sectional study from the Chinese population reported a negative correlation between fat mass and VO_{2peak} in men and women, where more than 50 % cross-sectional decline in VO_{2peak} was due to fat mass, lean mass and age. Study concluded that age, fat mass and lean mass were independent determinants of VO_{2max} in Chinese adults (Wong et al., 2008). A recent study in the Indian population showed a strong negative correlation between % body fat and VO_{2peak} (r= -0.987) (Sharma, Kamal, & Chawla, 2016) where, aerobic fitness of individuals with high BMI had a lower level of aerobic fitness and vice versa. According to a study from ACLS of 3148 healthy adults, the development of hypertension and dyslipidemia was predicted by changes over time in body fatness and CRF, but changes in CRF were superior to increases in body fatness or predicting future risk of these disorders (Lee, 2012).

Thus, the effect of body fat on cardiorespiratory functions demonstrates the importance of low CRF in young adults with increased body fat can be a factor for developing cardiovascular comorbidities later in middle age. BMI, % body fat, and WHR can be used in clinical settings to predict CRF as it is rapid and inexpensive methods.

1.7 ACSM recommendation for PA.

ACSM (American College of Sports Medicine) recommendation suggest that all adults of different ages need to perform regular moderate-intensity exercise at most of the days to achieve at least 150 minutes of exercise per week, or should perform vigorous intensity exercise of at least 75 minutes per week (Haskell et al., 2007). Thus, the recommendations suggest that aim may be reached different approaches, either by short duration-vigorous intensity or by long duration-moderate intensity. This was supported by cross-sectional population based study from the HUNT3 fitness study, where it showed direct association between higher VO_{2peak} and PA at moderate intensity-long duration and high intensity-short duration, and also suggest that exercising at very vigorous intensity even with considerably lower exercise time than expressed in ACSM recommendation, may be beneficial for VO_{2peak} (Nes et al., 2012). Table1. shows the PA recommendations based on ASCM (Garber et al., 2011).

Table 1 Evidence based recommendations from ACSM for cardiorespiratory exercise.

Cardiorespiratory exercise	Evidence based recommendations
Frequency	• ≥ 5 days per week × moderate exercise • ≥ 3 days per week × vigorous exercise • Combination of moderate and vigorous exercise on ≥ 3-5 days per week is recommended.
Intensity	• For most healthy adults, moderate and /or vigorous intensity is recommended. • For deconditioned person, light to moderate intensity exercise may be beneficial.
Duration	• For healthy adults, 30-60 min·d^{-1} (150 min. wk^{-1}) of purposeful moderate exercise or 20-60 min·d^{-1} (75 min. wk^{-1}) of vigorous exercise is recommended. • Combination of both moderate and vigorous exercise per day is recommended. • For sedentary persons, < 20 min·d^{-1} (<150 min. wk^{-1}) of exercise can be beneficial.
Volume	• Volume of ≥ 500-1000 MET min. wk^{-1} is recommended.

1.8 Aims and Hypothesis.

Aims and objectives of the research:

The main objective of the thesis is to describe the absolute (ml/kg/min) and relative (%) change in VO_{2peak} over 10 years in apparently healthy subjects of a wide age range. The secondary aims are to describe the influence of gender, age and self-reported PA level on change in VO_{2peak}.

We hypothesized that:

- VO_{2peak} declines over 10 years in all adult age-groups, but the reduction is more pronounced in older compared to younger age-groups.
- The relative change is similar across gender, and higher total PA attenuate the age-related decrease in VO_{2peak}.

2. METHODS

2.1 HUNT Fitness study

The Nord-Trøndelag Health study is a prospective population based health survey in Mid-Norway that has been performed each decade since 1984-86. The HUNT study consists of four cross-sectional waves; HUNT 1 (1984-86), HUNT 2 (1995-97), HUNT 3 (2006-08) and HUNT 4 (2017-19). All citizen in Nord-Trøndelag County aged 20 years or older at different time periods were invited to participate in the studies. The population of Nord-Trøndelag is considered to be adequately representative of the total Norwegian population(Cuypers et al., 2012).

In the HUNT 3 study, 93,860 individuals were invited to participate, from which 50,807 (54.1%) accepted the invitation, completed questionnaires, and attended a clinical examination. Furthermore, 12,609 participants with no previous history of lung or CV disease, sarcoidosis, cancer or hypertension or use of hypertensive medications were invited for cardio-pulmonary exercise testing (CPET) in a sub study (HUNT3 Fitness Study). In total 5633 showed up for exercise testing and 4631 completed the exercise test. Similarly, in HUNT 4, 56 044 participated in the study from September 2017 to February 2019. Former HUNT3 Fitness Study participants were invited to new measurements with CPET and echocardiography.

2.2 Study population

In the present longitudinal study, participants participating in both HUNT 3 Fitness Study and HUNT 4 Fitness study were included. Three thousand two hundred sixty-four participants from HUNT 3 fitness study participated in HUNT 4 baseline. Out of those 3264, a total of 1901 participants accepted the invitation to the HUNT 4 Fitness Study. One hundred twenty-five participants were excluded prior to study because of unwillingness to participate, not able to perform exercise testing, cardiovascular (including pacemaker) or pulmonary exclusion criteria, or other illness. One thousand seven hundred seventy-six participants were included for HUNT 4 Fitness study, and further 271 participants were excluded due to failure to complete the test or other causes. Fifteen thousand five participants were measured for VO_{2peak}, out of which 1107 healthy participants without diabetes, cancer, and hypertension were included in the study.

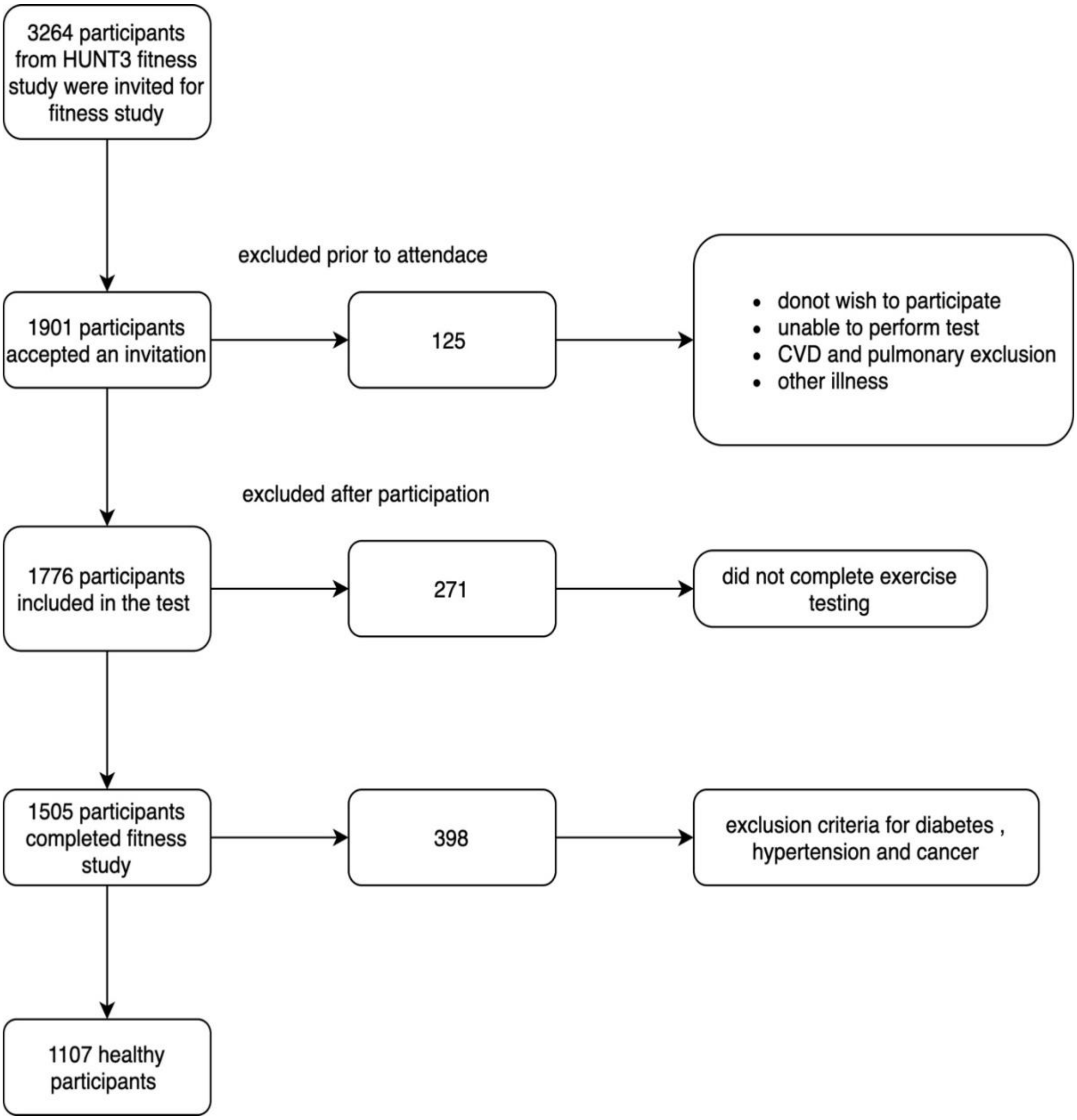


Figure 3. Flow chart representing study population and excluded participants of HUNT 4 fitness study

2.3 Exercise testing procedures (VO_{2peak} measurements).

Participants were asked to perform a 10-min warmup at a moderate relative intensity before initiating an individualized ramp protocol wearing a face covering mask and HR monitor. A portable mixing chamber gas analyzer (Metamax II; Cortex Biophysik, Leipzig, Germany) was used for continuous gas analysis. Speed and/or inclination were increased regularly when the participants reached an oxygen uptake that was stable over the 30s, until they reached exhaustion. For each submaximal level, speed, inclination, and VO_2 were registered in addition to their subjective level of exertion at the Borg scale 6-20. If the measurements showed a plateau in oxygen consumption as well as a respiratory exchange ratio above 1.05, then the test was defined as reaching VO_{2max}. A persons VO_{2peak} was calculated as mean of the three successively highest 10s VO_2 registrations. Testing was performed under the supervision of trained personnel, and calibration of equipment was executed regularly with volume and gas calibrated at standard intervals several times per day.

2.4 Measurement of other covariates.

For adults, other clinical measures such as height, weight, waist-hip circumference, hip-width, blood pressure, resting heart rate, and maximal heart rate were also measured. Body mass index (BMI kg/m^2) was calculated from standardized measures of height and weight.

2.5 PA Questionnaires.

Information on self-reported PA was collected from a detailed questionnaire. Baseline questions for self-reported PA was related to frequency, duration and intensity of leisure time PA. The question on frequency was stated "How often do you exercise?" and the options for the response was: "never ", "less than once a week", "once a week", "two to three times a week" and "almost every day". The question on duration was stated as "How long do you exercise as average minutes per session?" and included four options "less than 15 minutes", "between 15 and 30", "between 30 and 60", and "more than 60". Question on intensity was "How hard do you exercise?" with the options "I take it easy, I don't get of breath or break a sweat", "I push myself until I am out of breath or break a sweat", "I practically exhaust myself". Borg rating of perceived exertion scale was used in an in-house questionnaire for the HUNT4 Fitness Study to assess exercise intensity, where participants were asked to report their usual intensity level during exercise on a 6 to 20-point scale. The reason for choosing the well-known and validated Borg scale of perceived exertion is that it gives more detailed information on relative exercise intensity (Kurtze, Rangul, Hustvedt, & Flanders, 2008).

2.5.1 Categorization of PA.

Participants who responded to the frequency question as "none" or "less than once a week" were classified as "inactive". Total exercise time in minutes per week was then determined by multiplying the median duration of exercise with the median frequency of sessions. For instance, participants who reported between "30 and 60 min" and "two to three times a week "was interpreted as 45 min × 2.5 = 112.5 $min \cdot wk^{-1}$. According to PA recommendations from American College of Sports Medicine and the American Health Association, total exercise time was subdivided into <75, 75-149 and ≥ 150 $min \cdot wk^{-1}$. Borg scale was used for the classification of intensity, with a range from 6 (very, very light/no exertion at all) to 20 (extremely hard or maximal exertion). Ratings from 6 to 11 were classified as low intensity, 12 to 13 as moderate intensity, 14 to 20 as vigorous intensity, according to recommendations. In a following analysis, participants who reported a relative intensity of 14 to 20 on the Borg scale were sub divided into vigorous (Borg scale 14-15) and very vigorous (16-20).

2.6 Statistical Analysis

Descriptive statistics of the total population tested for VO_{2peak} were presented as means and standard deviation (SDs) for continuous variables and percentage and frequency count for categorical variables. The data set was examined for erroneous outliners and missing values. Absolute change in VO_{2peak} was calculated by subtracting HUNT3 VO_{2peak} from HUNT4 VO_{2peak} (HUNT4-HUNT3), and the percentage change in VO_{2peak} was calculated by (HUNT4-HUNT3/HUNT3) VO_{2peak} ×100.

A general linear model was used to examine the independent associations of longitudinal changes in VO_{2peak} and PA recommendations. Association between PA recommendations and change in VO_{2peak} per decade were estimated with absolute or percentage change in VO_{2peak} as a dependent variable and total exercise time categorized according to PA recommendations (inactive, below, and at or above) as a categorical independent variable and age as a covariate. The inactive group was used as a reference, and the precision of the estimate expressed as 95 % confidence intervals (CI).

In further analysis, the associations between the level of PA stratified by intensity and change in VO_{2peak} is reported where self-reported intensity of the participants was stratified as a categorical variable. Total exercise time (<75min.wk^{-1}, 75-149min.wk^{-1}, ≥150min.wk^{-1}) was combined with BORG scale categories (low, moderate, vigorous and, very vigorous) yielding four groups for each exercise time. A general linear model was used to assess the independent contribution of intensity within the group of different exercise time as PA recommendations. We entered change in VO_{2peak} as the dependent variable, Borg scale as a categorical independent variable with exercise time (min. wk^{-1}) as continuous variable and covariate. Linear regression analysis was performed to examine the contribution of changes in body weight and changes in BMI on the longitudinal decline of VO_{2peak}. Pearson correlation was used to see the correlation between different two variables.

The statistical analysis was performed using SPSS statistics version 26 (SPSS INC, Chicago Illinois, USA).

2.7 Ethics

A written consent was signed by all participants in the HUNT study, and the study current has been approved by the Regional committee for medical research ethics (2019/7243).

3. RESULTS

3.1 Descriptive characteristics

Descriptive characteristics of the participants from the HUNT 4 Study are presented in Table 2. The mean (± SD) VO_{2peak} was 42.2 (± 9.1) and 34.3 (± 7.5) mL/kg/min, and 3.5 (± 0.7) and 2.3 (± 0.5) L/min for men and women, respectively. In total, 5.2 % of the participants were classified as inactive, where the proportion of inactive men and women were 2.9% and 2.3%, respectively. Mean percentage change in VO_{2peak} was similar within men and women, meanwhile men had more decrease in mean absolute and relativeVO_{2peak} with -0.38 (± 0.48) L/min and -4.9 ± 6.16) mL/kg/min compared to women with mean change -0.21 (± 0.31) L/min and -3.8 (± 4.8) mL/kg/min.

Table 2: Descriptive characteristics of the participants from the HUNT 4 fitness study

	HUNT 4 Study		
Variable	Total	Men	Women
N	1107	501	606
Age	58.1 (± 11.7)	58.4 (± 11.9)	57.8 (± 11.7)
Anthropometrical data			
Height (cm)	172 (± 9.1)	179 (± 6.5)	165 (± 5.8)
Weight (Kg)	76.1 (± 13.4)	84.4 (± 11.0)	69.2 (± 11.2)
BMI (kg/m2)	25.6 (± 3.5)	25.1(± 3.8)	26.3 (± 3.1)
Waist (cm)	91.9 (± 5.9)	94.9 (± 10.3)	89.4 (± 11.3)
Hip (cm)	99.1 (± 5.9)	101.7 (± 4.8)	97 (± 5.8)
W/H ratio	0.92 (± 0.07)	0.93 (± 0.07)	0.91(± 0.06)
Blood pressure (mmHg)			
Diastolic	74.9 (± 9.4)	78.1 (± 9.5)	72.2 (± 8.5)
Systolic	128 (± 17.9)	130 (± 17)	126 (±18.4)
HRmax (beats/min)	173 (±13.9)	173 (± 14.6)	172 (±13.3)
Total cholesterol	5.61 (± 0.96)	5.68 (± 1.09)	5.6 (± 1.03)
HDL	1.32 (± 0.29)	1.63(± 0.36)	1.49 (± 0.37)
Triglycerides	1.69 (± 1.05)	1.32 (± 0.74)	1.48 (± 0.91)
Smoking status, n (%)	N (%)	N (%)	N (%)
Never	597 (53.9)	277 (55.3)	320 (52.8)
Former	341 (30.8)	142 (28.3)	199 (32.8)
Sometimes	72 (6.5)	43 (8.6)	29 (4.8)
Daily	77 (7)	28 (5.6)	49 (8.1)
Treadmill data			
VO_{2peak} mL/kg/min	37.9 (± 9.1)	42.2 (± 9.1)	34.3 (± 7.5)

L/min	2.8 (± 0.8)	3.5 (± 0.7)	2.3 (± 0.5)
RER	1.1 (± 0.05)	1.1 (± 0.05)	1.1 (± 0.05)
Borg rating at VO_{2peak}	18.3 ± 1.2	18.3 ± 1.1	18.2 ± 1.3
Exercise Data	N (%)	N (%)	N (%)
Inactive	58 (5.2)	32 (2.9)	26 (2.3)
Duration, n (%)			
<15 mins	12 (1.1)	7 (14)	5 (0.8)
15-29 mins	101 (9.1)	45 (9)	56 (9.2)
30-60 mins	696 (62.9)	285 (56.9)	411 (67.8)
>1 hr	232 (21.1)	128 (25.5)	104 (17.2)
Intensity on Borg scale			
Low (6-11)	84 (7.6)	37 (7.4)	47 (7.8)
Moderate (12-13)	294 (26.6)	110 (22.0)	184 (30.4)
Vigorous (14-15)	461 (41.6)	213 (42.5)	248 (40.9)
Very vigorous (16-20)	239 (21.6)	127 (25.3)	112 (18.5)
Frequency			
Once a week	129(11.7)	66(13.2)	63 (104)
2-3 times a week	579 (52.3)	262(52.3)	317 (52.3)
Nearly everyday	334(30.2)	138(27.5)	196 (32.2)

Continuous variables are presented as mean (± SD), Categorical variables are presented as N (%)
BMI = Body mass index.
W/H = Waist-Hip ratio.
HDL = High density lipoproteins
mL/kg/min = milliliter per kilogram per minute
L/min = Liter per minute
RER = Respiratory exchange ratio
HR_{max} = Maximal heart rate.

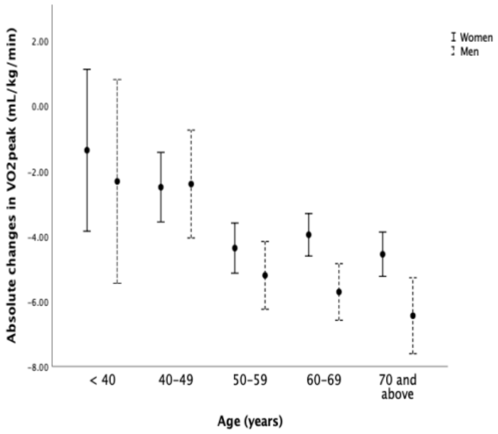
3.2 Absolute and percentage changes in VO_{2peak} by age and gender.

Table 3. shows the mean VO_{2peak} of HUNT 4 fitness study across different age groups in men and women, followed by absolute and percentage changes in VO_{2peak} expressed in mL/kg/min and L/min. Men had steeper mean VO_{2peak} in all the age groups than women. The absolute decline in VO_{2peak} in men is higher as compared to women after 50 years of age, whereas the percentage decline of VO_{2peak} was similar in both genders across different age groups. The percentage decline in VO_{2peak} in both genders was not significant until the 4th decades. But, on the 5th age decades, the rate of the decline in VO_{2peak} accelerated, with a pronounced difference of 5.2 % decline per decade for women and 7.3 % decline per decade for men as shown in Table 3. Besides, the rate of decline was flattened after the 5th decades in women, but not in men (Fig 4. A and B).

Table 3. Absolute and percentage changes in VO2peak across different age groups in men and women.

	Age group HUNT4				
	<40 years	40-49 years	50-59 years	60-69 years	≥70 years
Women/ Men (n)	38/27	96/73	162/129	166/141	96/90
VO_{2peak} (mL/kg/min) [a]					
Women	43.3 (±7.2)	40.5 (±6.3)	35.9 (±6.4)	31.4 (±5.3)	27.6 (±4.3)
Men	53.2 (±8.2)	48.7 (±6.6)	45.2 (±7.8)	38.6 (±7.3)	34.4 (±6.3)
VO_{2peak} (L/min)					
Women	2.79 (±0.45)	2.83 (± 0.44)	2.50 (±0.38)	2.17 (±0.28)	1.81 (±0.28)
Men	4.46 (±0.58)	4.18 (±0.62)	3.81 (±0.59)	3.23 (±0.51)	2.73 (±0.50)
Change[b]					
VO_{2peak} (mL/kg/min)					
Women	-1.3 (-3.8, 1.1)	-2.5 (-3.5, -1.4)	-4.3 (-5.1, -3.5)	-3.9 (-4.6, -3.3)	-4.5 (-5.2.-3.8)
Men	-2.3 (-5.4, 0.8)	-2.4 (-4.1, -0.7)	-5.2 (-6.2, -4.1)	-5.7 (-6.58, -4.8)	-6.4 (-7.6.-5.2)
VO_{2peak} (L/min)					
Women	-0.03 (0.2,0.1)	-0.05 (0.1,0.02)	-0.20(-0.3, -0.1)	-0.30(-0.3, 0.2)	-0.40 (-0.4, -0.3)
Men	-0.06 (0.2,0.1)	-0.09 (0.2,0.04)	-0.30(-0.4, -0.2)	-0.50(-0.6, 0.4)	-0.60 (-0.7, -0.5)
Percentage change (%)[b]					
VO_{2peak} (mL/kg/min)					
Women	-1.9 (-7.9, 0.4)	-4.9 (-7.4, -2.3)	-10.1 (-11.9, -8.2)	-10.7 (-12.3, -8.9)	-13.5 (-15.5,11.5)
Men	-3.3 (-8.7, 2.1)	-2.5 (-7.5, 2.5)	-9.8 (-11.9, -7.8)	-12.3 (-14.3, 10.3)	-14.1 (-17.5,12.2)
VO_{2peak} (L/min)					
Women	-0.2 (-4.9, 4.4)	-0.8 (-3.3, 1.6)	-7.4 (-9.1, -5.8)	-9.9 (-11.4, -8.3)	-15.9 (-17.7,14.1)
Men	-0.9 (-5.1, 3.2)	-0.02 (-5.1, 5.1)	-8.2 (-10.2, 6.3)	-13.1 (-14.8, -11.4)	-16.9 (-19.3,14.4)

VO_{2peak} = Peak oxygen uptake
% change = Percentage change
mL/kg/min = milli-liter per kilogram per minute
L/min = Liter per minute
[a] VO_{2peak} in HUNT4
[b] Change from HUNT3 to HUNT4
Values in parenthesis in each decade represent the 95 % CI derived from the observed data



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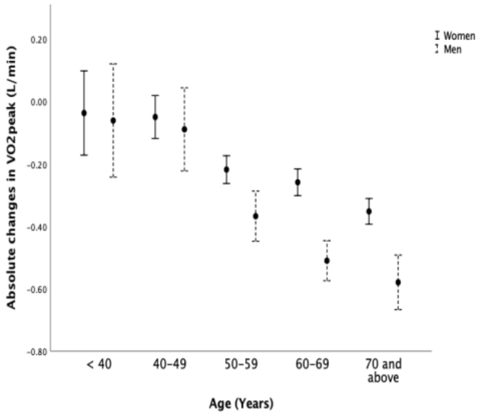

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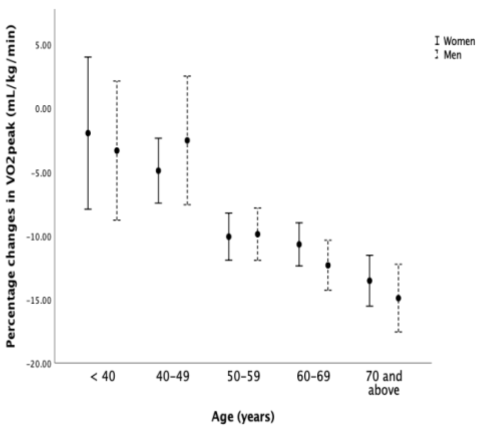

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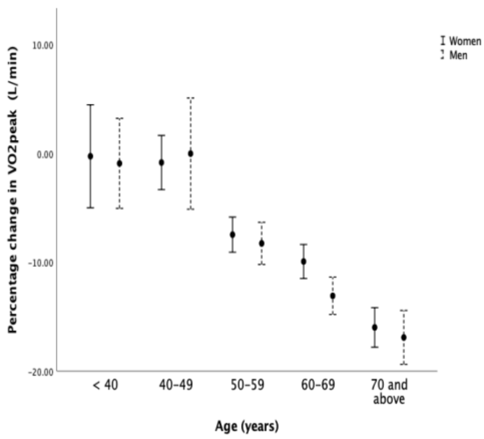

D.

Figure 4. Longitudinal decline in VO_{2peak} across different age groups in men and women.

In Fig 4. A and B represent the absolute changes in VO_{2peak} in mL/kg/min, and L/min, C and D represent the percentage changes in VO_{2peak} across different decades from <40 to 70 and above years of age. The vertical bar represents the 95 % CI.

3.3 Physical activity and changes in VO_{2peak}.

Absolute and percentage changes of VO_{2peak} (95% CI) based on adherence to PA with adjustment for age is shown in Table 4. The absolute and percentage decline of VO_{2peak} was lesser in "at or above" recommendation groups. When comparing the main effects, the groups "at or above" and "below" PA recommendation had a significant mean difference of changes in VO_{2peak} ($p < 0.05$). Although the "inactive" group had a higher decline in VO_{2peak} compared to the other two groups, the mean difference of changes in VO_{2peak} was not significant ($p > 0.05$) compared to the group "below" recommendation¨. Overall, percentage decline based on adherence to PA is similar in both men and women, whereas men show more absolute decline in VO_{2peak} compare to women.

Table 4. Absolute and percentage change in VO_{2peak} adherence to PA.

	PA recommendations *	$N_{a\psi}$	Absolute change in VO_{2peak}		Percentage change in VO_{2peak}	
Women			mL/kg/min	L/min	mL/kg/min	L/min
	Inactive	30	-4.6(-6.4, -2.9)	-0.21(-0.32, -0.14)	-13.1(-17.4, -8.8)	-9.0(-12.9, -5.1)
	Below	147	-4.5(-5.3, -3.8)	-0.23(-0.28, -0.18)	-11.9(-13.9, -10.0)	-9.2(-10.9, -7.4)
	At or above	426	-3.4(-3.9, -3.0)	-0.20(-0.23, -0.18)	-8.4(-9.6, -7.3)	-7.7(-8.7, -6.7)
Men						
	Inactive	36	-6.0(-8.0, -4.1)	-0.45(-0.60, -0.30)	-13.6(-18.1, -9.1)	-12.2(-16.5, -7.9)
	Below	125	-5.8(-6.9, -4.8)	-0.40(-0.48, -0.32)	-12.8(-15.2, -10.4)	-10.7(-13.0, -8.4)
	At or above	339	-4.4(-5.0, -3.7)	-0.36(-0.41, -0.31)	-8.4(-9.9, -6.9)	-8.6(-10.0, -7.2)

PA recommendations*=American college of sports medicine recommends that the most adult engage in moderate-intensity Cardio respiratory exercise training for ≥ 30 minute per day on ≥ 5 days per week for a total of ≥ 150 minute per week, vigorous intensity cardio respiratory exercise training for ≥ 20 minute per day on ≥ 3 days per week (≥ 75 min per week),
$N_{a\psi}$ = Number of participants with adjusted for age,
Values at parentheses represents the 95% CI.
Inactive = Participants who reported exercise less than once a week.

Mean VO_{2peak} in HUNT4 based on descriptive statistics according to Borg scale rating in men and women are presented in Table 5. Very vigorous-intensity groups in both men and women had higher mean VO_{2peak} (± SD) with 47.1 ± (8.1) mL/kg/min and 3.94 (± 0.73) L/min reported for men, 38.1 (±8.3) mL/kg/min and (2.57± 0.51) L/ min reported for women. Compared to women, men had higher mean VO_{2peak} in all the intensity groups ($P<0.05$).

The effects of self-reported PA by stratified intensity and time spent on absolute and percentage changes in VO_{2peak} (adjusted for age) (95% CI) is reported in Table 6. Participants performing PA at the vigorous and very vigorous intensity in each of the three groups (<75,75-149, ≥150 min. wk^{-1}) shows a lower decline in absolute and percentage change in VO_{2peak}. Two groups (i.e., 75 min. wk^{-1} and ≥ 150 min. wk^{-1}) inducing PA at vigorous and very vigorous intensity shows a similar rate of decline in both absolute and relative VO_{2peak}. Further, PA performed at very vigorous intensity by 75-149 min. wk^{-1} group had a lower decline in the absolute and relative VO_{2peak} than the PA performed at moderate intensity by ≥ 150 min. wk^{-1} groups (Fig 4). For instance, the absolute mean decline of VO_{2peak} performed at moderate intensity by ≥ 150 min. wk^{-1} group is -5.9 ml/kg/min with CI (-7.1, -4-1); on the other hand, PA performed at very vigorous intensity by 75-149 min. wk^{-1} groups is -2.0 ml/kg/min with CI (-3.1, -1). When comparing to inactive groups, the mean decline of absolute and percentage VO_{2peak} was lower in all the three groups (<75,75-149, ≥150 min. wk^{-1}). Also, all the participants of the three groups, who performed PA at low intensity had similar decline in the absolute and relative VO_{2peak}.

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Table 5. Mean VO_{2peak} of the participants according to relative intensity categorized based on BORG scale.

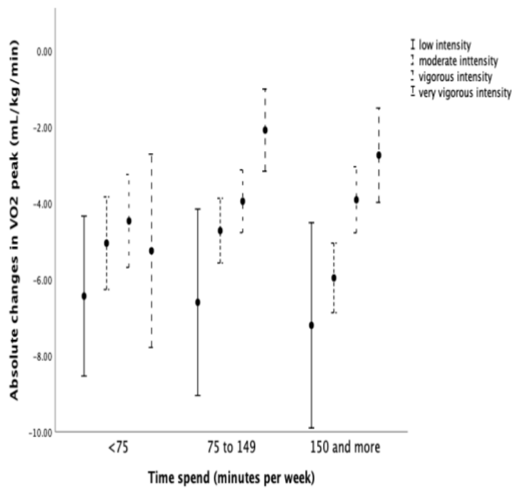
	Borg scale*(6-20)	Men	Women
VO_{2peak} (mL/kg/min)			
	Low Intensity	35.0 (± 7.04)	28.5 (± 4.90)
	Moderate Intensity	37.7 (± 7.10)	31.6 (± 6.50)
	Vigorous Intensity	43.1 (± 9.01)	35.6 (± 6.80)
	Very vigorous Intensity	47.1 (± 8.10)	38.1 (± 8.30)
VO_{2peak} (L/min)			
	Low intensity	2.99 (± 0.66)	2.01 (± 0.35)
	Moderate intensity	3.23 (± 0.65)	2.19 (± 0.44)
	Vigorous intensity	3.58 (± 0.76)	2.45 (± 0.47)
	Very vigorous intensity	3.94 (± 0.73)	2.57 (± 0.51)

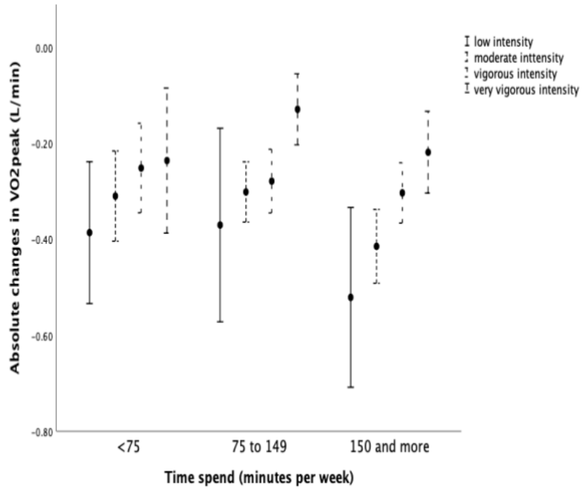
*All the values are presented as mean ± SD,
*Low intensity (6-11), Moderate intensity (12-13), vigorous intensity (14-15), very vigorous (16-20)

Table 6. Influence of self-reported PA, stratified by intensity and time spent on longitudinal changes in VO_{2peak}.

Time spent (min. wk-1)	Intensity (Borg scale)	Na	Absolute change in VO_{2peak}		Percentage change in VO_{2peak}	
			mL/kg/min	L/min	mL/kg/min	L/min
<75	Low	24	-6.4(-8.5, -4.3)	-0.38(-0.49, -0.27)	-16.0(-20.7, -11.2)	-12.7(-15.8, -9.2)
	Moderate	67	-5.0(-6.3, -3.8)	-0.31(-0.40, -0.22)	-12.2(-15.1, -9.0)	-9.4(-12.2, -7.1)
	Vigorous	75	-4.4(-5.5, -3.2)	-0.25(-0.33. -0.16)	-9.6(-12.3, -6.9)	-7.1(-9.8, -4.5)
	Very vigorous	22	-5.2(-7.4, -3.1)	-0.24(-0.41, -0.12)	-11.4(-16.4, -6.5)	-7.7(-12.0, -2.3)
	Total	**188**				
75-149	Low	22	-6.6(-8.7, -4.4)	-0.37(-0.53, -0.20)	-16.7(-22.6, -10.9)	-12.4(-18.5, -6.4)
	Moderate	108	-4.7(-5.7, -3.7)	-0.30(-0.37, -0.22)	-11.7(-14.3, -9.0)	-10.6(-13.4, -7.9)
	Vigorous	175	-3.9(-4.7, -3.1)	-0.27(-0.33, -0.22)	-8.5(-10.5, -6.4)	-7.8(-10.0, -5.7)
	Very vigorous	100	-2.0(-3.1, -1.0)	-0.12(-0.20, -0.51)	-3.8(-6.5, -1.0)	-2.9(-5.8, -0.1)
	Total	**405**				
≥ 150	Low	18	-7.2(-9.9, -4.4)	-0.50(-0.7, -0.30)	-17.2(-23.4, -11.1)	-16.5(-22.1, -10.8)
	Moderate	97	-5.9(-7.1, -4.7)	-0.41(-0.5, -0.32)	-14.6(-17.2, -12.0)	-13.3(-15.8, -10.9)
	Vigorous	194	-3.9(-4.7, -3.0)	-0.30(-0.3, -0.34)	-8.1(-9.9, -6.2)	-8.8(-10.5, -7.1)
	Very vigorous	113	-2.7(-3.8, -1.6)	-0.2(-0.3, -0.13)	-4.9(-7.3, -2.4)	-5.1(-7.3, -2.4)
	Total	**422**				

Na= Number of participants responded for intensity (Borg scale) question. 30 participants were reported as inactive with 0 min. wk-1. 54 missing variables for BORG scales were reported.





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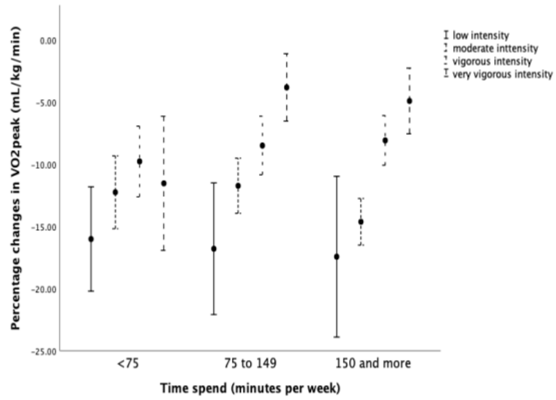
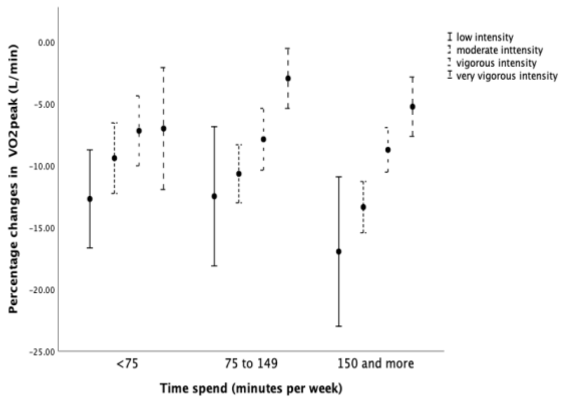




C

D

Figure 5. Absolute and percentage change in VO_{2peak} stratified by intensity and total exercise time.

Fig 5. illustrates the absolute and percentage changes in VO2peak (95% CI) adjusted for age according to the relative intensity of exercise, and total exercise duration in minutes per week. Low, moderate, vigorous, and very vigorous corresponds to 6-11,12-13,14-15 and 16-20 on the Borg scale 6-20. A and B shows the absolute change in VO_{2peak} stratified with intensity and time spend, C and D show the percentage change in VO_{2peak} stratified with intensity and time spend. VO_{2peak}, peak oxygen uptake.

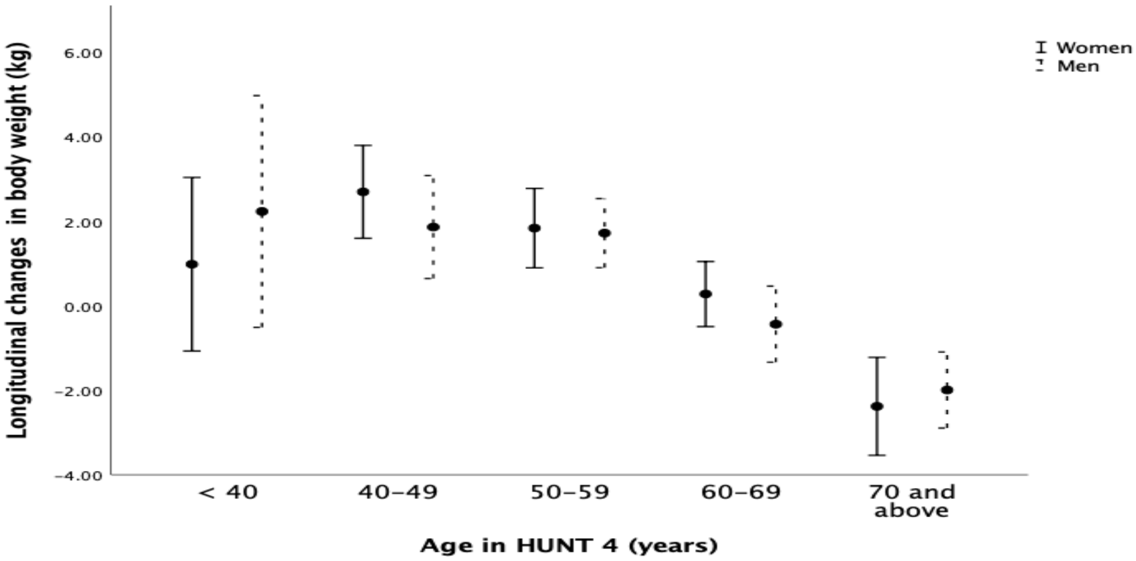
3.4 Body composition and longitudinal decline of VO_{2peak}.

Descriptive characteristics of body weight, BMI, body fat-mass, and FFM across different age groups are presented as mean (± SDs) in Table 7. The table also represents the longitudinal changes in BMI and body weight from HUNT 3 across different age decades. According to descriptive analysis, men had higher mean body weight in all the age groups, whereas females had slightly lower BMI (kg/m^2) than men across the different age groups. In all decades, men showed more amount of fat-free mass than women, but body fat mass was similar until the 50s, but after 40s, women had more amount of body fat mass.

Table 7. Body composition characteristics across different age groups in men and women.

	Age in HUNT 4				
	<40	40-49	50-59	60-69	≥70
Body-weight (kg)					
Men	84.2 (± 9.9)	86.0 (± 11.0)	85.2 (± 11.2)	84.7 (± 11.7)	79.5 (± 9.1)
Women	64.5 (± 9.5)	70.5 (± 11.9)	70.4 (± 12.2)	69.9 (± 10.8)	65.5 (± 9.8)
BMI (kg/m^2)					
Men	25.5 (± 2.5)	26.3 (± 2.7)	26.2 (± 3.1)	26.3 (± 3.5)	25.7 (± 2.5)
Women	23.2 (± 2.4)	24.8 (± 3.6)	25.6 (± 4.2)	25.6 (± 3.7)	24.4 (± 3.2)
Body-weight$_b$ (kg)					
Men	2.23(-0.5,4.9)	1.8(0.6,3.0)	1.7(0.9,2.5)	-0.4(-1.3,0.4)	-1.9(-2.8, -1.1)
Women	0.98(-1.0,3.0)	2.6(1.5,3.7)	1.8(0.8,2.7)	0.3(-0.5,1.04)	-2.3 (-3.5, -1.0)
BMI$_b$ (kg/m^2)					
Men	0.5(-0.26,1.32)	0.52(0.15,0.88)	0.54(0.28,0.8)	0.01(-0.23,0.3)	-0.35(-0.63, -0.07)
Women	0.23(-0.5,1)	0.87(0.5,1.2)	0.77(0.42,1.1)	0.31(0.03,0.58)	-0.56(-0.98, -0.15)
Body-fatmass (kg)					
Men	16.6 (± 5.3)	18.8 (± 6.2)	18.9 (± 7.1)	20.5 (± 8.3)	19.6 (± 5.7)
Women	17.2 (± 5.7)	20.9 (± 8.3)	23.3 (± 9.2)	24.3 (± 8.2)	22.0 (± 7.0)
FFM (kg)					
Men	67.6 ± 7.2	67.1 ± 8.2	66.3 ± 6.8	64.1 ± 5.7	59.9 ± 6.4
Women	47.3 ± 3.9	49.5 ± 5.6	47.7 ± 5.1	45.5 ± 4.8	43.3 ± 4.7

BMI$_b$= changes from HUNT 3 to HUNT 4 (HUNT4- HUNT3)
Body weight$_b$ = changes from HUNT 3 to HUNT 4 (HUNT4- HUNT3)
FFM = Fat free mass.
kg =kilogram
kg/m^2= Kilogram per meter square
Values in parenthesis represent the 95 % CI from observed data.



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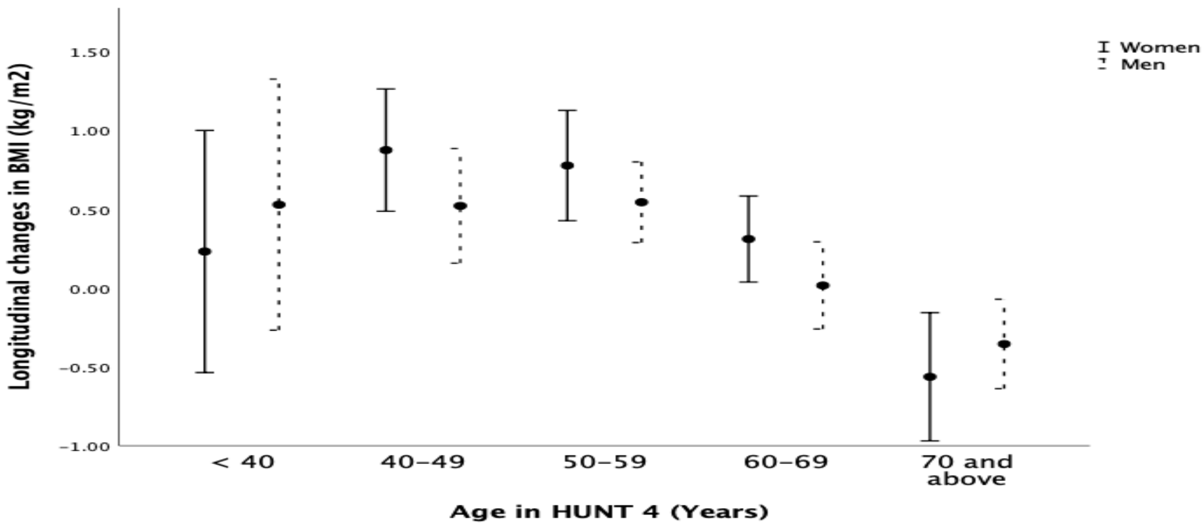
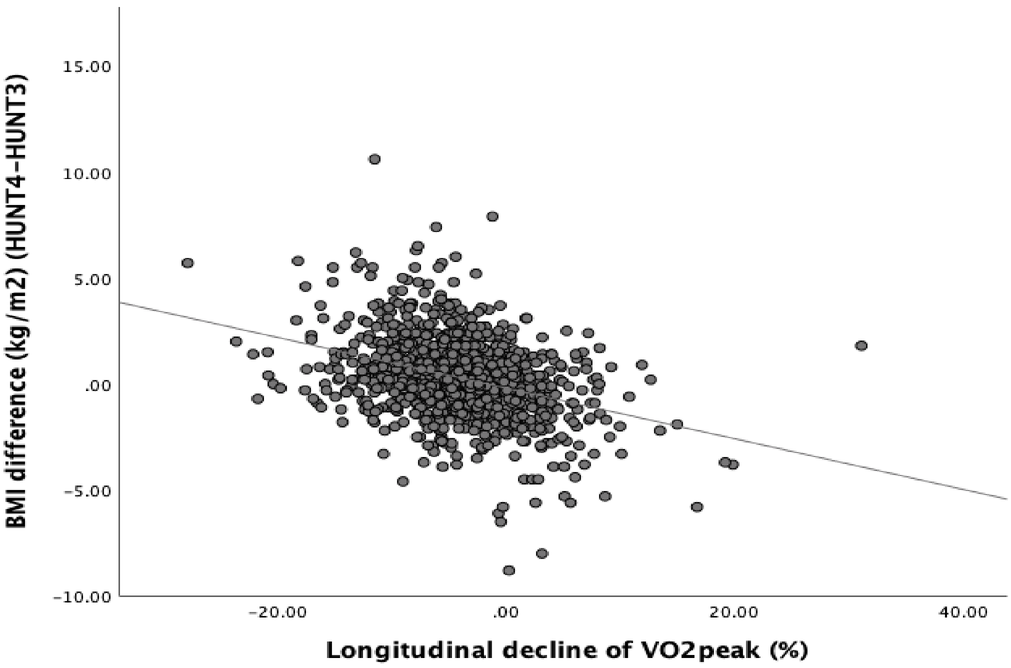


B.

Figure 6. Longitudinal changes of body weight and BMI across different age groups in men and women.

Longitudinal changes in BMI and body weight across different age groups in men and women is presented in fig 6. Fig 6. A. illustrates the longitudinal change in body weight across different age decades; whereas, Fig 6.B represents longitudinal change in BMI across age groups. Although men had higher body weight, longitudinal mean changes in BMI and body weight is similar between both genders were observed.



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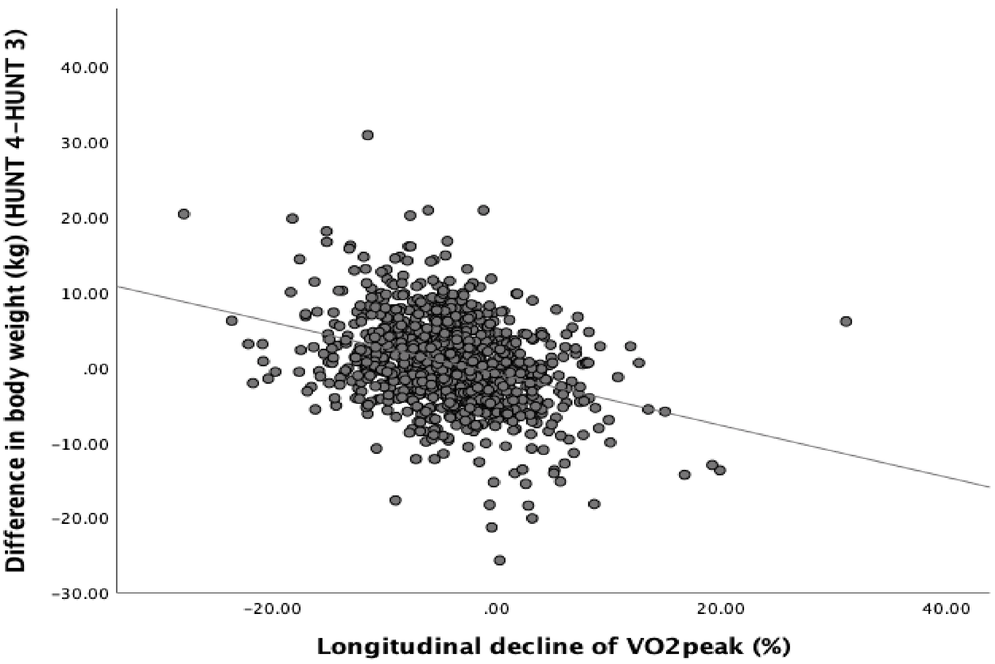

B.

Figure 7. Correlation between longitudinal (%) decline of VO_{2peak} and changes in body weight and BMI.

Correlation between longitudinal decline of VO_{2peak} (%) and change in body weight and BMI are shown in Fig.7. A. illustrates, scatter plot diagram showing a correlation between mean change in body weight and longitudinal decline of VO_{2peak} (r_2=0.11)[equation Y= -2.5x –

8.9(P<0.05)]. B. illustrates, scatter plot diagram showing correlation between mean change in BMI and longitudinal decline of VO_{2peak} (r^2=0.12) [equation Y = -0.7x -9.2 (p<0.05)].

3.5 Longitudinal changes in HR_{max} across different age groups in men and women.

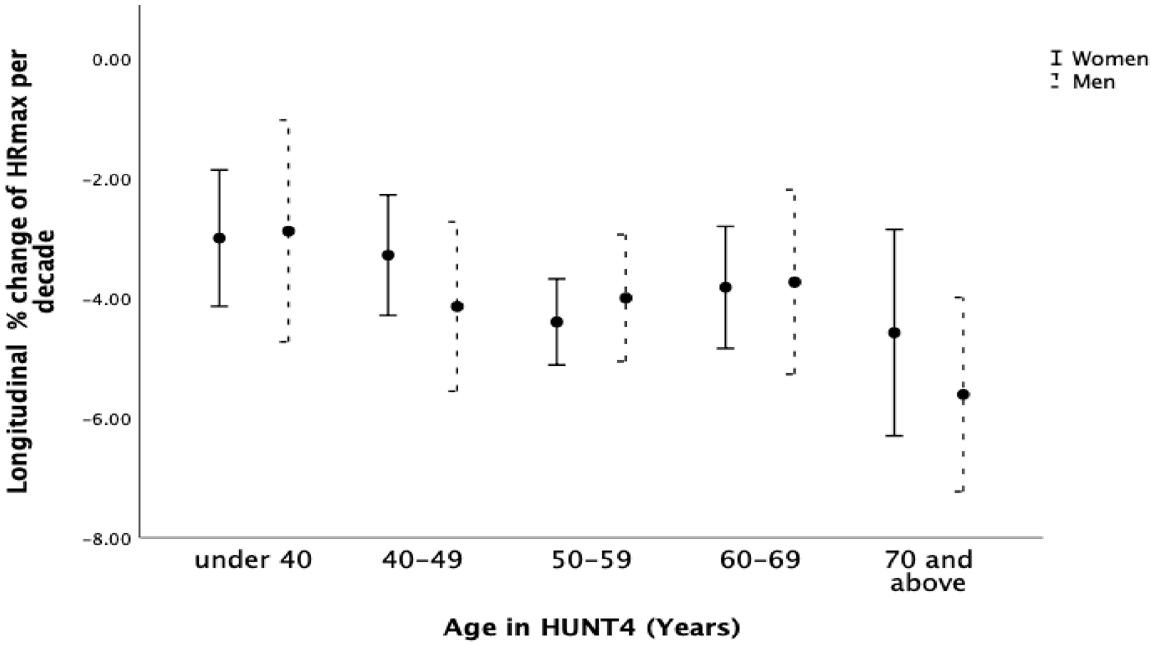

Figure 8. Longitudinal (%) changes in HRmax across different age groups in men and women.

Longitudinal changes of HRmax across different age groups in men and women is presented in Fig 8. The rate of decline was similar between men and women. HR_{max} declines at the rate of 2 to 4 % at 30s, 40s, and 50s to >6 % at 70 years and beyond.

4. DISCUSSION.

4.1 Major findings of the study.

The present apparently healthy sample of 501 men and 606 women free of cardiovascular diseases, are among diseases the largest and most heterogeneous samples in which longitudinal changes in VO_{2peak} have been measured. The main findings of the present study are that the longitudinal decline in VO_{2peak} observed in each of 5 age-decades in both the gender shows that the rate of decline accelerates from 2 to 5% in 30s and 40s to >12 % per 10 years in the 70s and beyond. Although the rate of decline did not accelerate pronouncedly after 60 years of age, the results of the study showed that the longitudinal decline of VO_{2peak} in men and women in the HUNT 4 fitness study was not linear. The absolute decline in VO_{2peak} was larger in men in every decade as compared to women. However, a similar pattern of percentage decline was observed in both genders. The findings of this study showed differences with the longitudinal decline of VO_{2peak} that reported from Fleg and associates, who studied 435 men and 375 women in Baltimore longitudinal study (Fleg et al., 2005). Even though both the study studied healthy populations, the Baltimore longitudinal study observed the rate of decline that accelerated from 3 to 6 % per 10 years in the 20s and 30s to >20% per 10 years in the 70s and beyond. The longitudinal decline is similar until the 30s and 40s in our study (i.e., 2-5 % decline in VO_{2peak}), but after 50s our study showed comparatively slower decline (i.e. >12% per 10 years in 60s and beyond). Our study had a more fit population with relatively smaller differences in the mean changes of body weight than study from Fleg and associates, which can be the reason for the difference in the longitudinal decline of VO_{2peak}. When evaluating the association between changes in VO_{2peak} and PA recommendation, the participants reporting PA at or above recommended volume had a slower decline in VO_{2peak} as compare to “below” and “inactive” groups (Table 4). Furthermore, when intensity was stratified by time spend to illustrate the absolute and percentage changes in VO_{2peak}, the age-adjusted model shows no notable difference in the decline of VO_{2peak} among the people who reported PA at the very vigorous intensity with low volume (<75min.wk^{-1}) and people who reported PA at moderate intensity with high volume (Table 6 / Fig 5).

4.2 Gender differences in longitudinal decline of VO_{2peak}.

Despite being physically active, in every age group, women had lower mean VO_{2peak} at follow up compared to men. The mean VO_{2peak} for men and women was 42.2 mL/kg/min, and 37.9 mL/kg/min respectively, which is 10 % lower for men and 9.4 % lower for females than at baseline in the HUNT3 fitness study. The percentage decline of VO_{2peak} was similar in both gender across different age groups as in other studies (Buskirk & Hodgson, 1987; Fleg et al., 2005; Jackson. et al., 2009). When expressed per kilogram of body weight, VO_{2peak} was considerably higher in men than women; in addition, its longitudinal decline shows steeper decline than females across all age decades, which is consistent with the findings from other studies. For instance, a longitudinal study from Sthatokostas et al. reported the mean longitudinal change of -0.19 ml/kg/min per minute per year for female and 0.43 ml/kg/min per minute per year for male which is approximately similar with the present findings.

4.3 Association between physical activity and longitudinal changes in VO_{2peak}.

To our knowledge, this is the first longitudinal study to examine the association between longitudinal changes on VO_{2peak} that stratified intensity and time spend based on PA recommendations in healthy men and women. Participants following recommendations showed higher VO_{2peak}, in men and women, compared to the inactive or below recommendation category. Furthermore, the association between VO_{2peak} and Borg scale rating illustrates that PA at low intensity and moderate intensity had a small difference in VO_{2peak} (35 mL/kg/min vs. 37.7 mL/kg/min for men, 28.5 mL/kg/min vs. 31.6 ml/kg/min for women). In contrast, PA at high and very high intensity had substantially greater VO_{2peak} than PA at low and moderate intensity (43.1 mL/kg/min and 47.1 mL/kg/min for men, 35.6 mL/kg/min, 38.1 mL/kg/min for women). These findings is similar to cross-sectional results from HUNT 3 fitness study (Nes et al., 2012). When the association between level of PA (stratified by intensity and time spent based on PA recommendation) and longitudinal changes in VO_{2peak} is assessed, the participants with moderate intensity – longer duration had similar decline in absolute and relative VO_{2peak} as contrast to high or very high intensity- below the 75 recommended minutes. Inactive groups showed more reduction in longitudinal VO_{2peak}, whereas the participants reporting PA at low and moderate intensity at less than recommended volume did not show a significant difference from the group with low and moderate intensity at or above recommended volume. Interestingly, PA at low and moderate intensity in every group shows uniform decline contrast to vigorous and very vigorous intensity. Hence, individuals that reported PA at very vigorous intensity, regardless of total time spent, obtained a slower decline in VO_{2peak}.

Various studies have shown that the higher level of VO_{2peak} is not necessarily associated with the time spent on PA at low intensity (Swain, 2005; Wenger & Bell, 1986). Our results somehow support that, regardless of the number of hours spent on exercise, the low and moderate intensity exercise was not associated with the slower decline of VO_{2peak}. Hence, an increase in intensity to a greater extent than an increase in exercise time positively alters the VO_{2peak} levels and slower the longitudinal decline of VO_{2peak}.

4.4 Possible Mechanisms.

4.4.1 Cardiac adaptation.

Aging and alteration in physical activity both clearly contributes to the reduction in VO_{2peak}. Mechanism for age-related decline can be explained by central and peripheral adaptation to aging. According to various other studies, centrally HR_{max} declines approximately 3-5 % per decade independent of the level of PA and gender (Kasch et al., 1999; Marti & Howald, 1990; Toth et al., 1994). In our study, the longitudinal decline of HRmax observed in each of 5 age decades observed in both genders showed that the rate of decline was 2 to 4% in the 30s, 40s and, 50s to >5 % per 10 years in the 70s and beyond (Fig 8). Longitudinal percentage change in HR_{max} showed a positive correlation ($p<0.01$) with longitudinal percentage change in VO_{2peak}, which means that a higher percentage change of HRmax was associated with an increased decline of VO_{2peak}. While in inactive people or sedentary individuals, maximal SV clearly declines with age, the role of PA preventing this decline is not clear, as several studies have reported no changes in SV_{max} with age in athletic individuals (Hagberg et al., 1985; Heath, Hagberg, Ehsani, & Holloszy, 1981) while others have (Rivera et al., 1989). However, older adults, whether physically active or inactive, to increase maximal cardiac output through an increase in SV_{max} rely on Frank-sterling mechanism. Regardless of positive adaptations, the maximal reduction of CO in athletic older adults contributes to the age-related reductions in VO_{2peak}. On the basis of various investigations, the relative contribution of the reduction in HR_{max} to reduced maximal cardiac output ranges from 40-100 % (Hagberg et al., 1985; Rivera et al., 1989). Therefore, reduced HR_{max} is more likely to play a vital role in central adaptations to aging that contribute to longitudinal reductions in VO_{2peak}.

4.4.2 Influence of Changes in body composition on reduction of VO_{2peak}.

Changes in body weight and BMI showed a negative correlation ($p<0.01$) to a longitudinal decline of VO_{2peak}. It indicates that participants that increased in body weight or BMI from HUNT 3 to 4 relatively had a larger decline in absolute and relative VO_{2peak} (Fig.7). Still, there was no significant gender difference in BMI. In our study, no pronounced difference in the changes in body weight (kg) and BMI (kg/m_2) across age groups was observed (Fig 6. A and B). Total mean BMI for men and women was 25.1 and 26.3 kg/m_2 respectively (Table 7), whereas longitudinal changes in BMI and body weight for each different age group was similar in both genders. The reason for the smaller decline of BMI across different age groups may be because our study involves comparatively fit population compare to other longitudinal studies (Fleg et al., 2005; Jackson. et al., 2009). Meanwhile, it can also act as a reason for the slower decline in longitudinal VO_{2peak}, as many other studies showed that increase in BMI decreases CRF over the years (Myers et al., 2015; Rauner, Mess, & Woll, 2013). Interestingly, when linear regression analysis was performed, 11.7 % variance in longitudinal changes in VO_{2peak} was explained by mean changes in body weight. In comparison, 12.6 % variance is explained by mean changes in BMI in men and women combined (Fig 7. A and B).

Furthermore, in our study body fat mass and fat-free mass was measured to see the association with VO_{2peak}, the results showed a strong negative correlation ($p<0.01$) ($r = -0.65$) between body fat mass and VO_{2peak}. These findings indicate that participants with increased body fat would have less VO_{2peak} compared with a participant with low body fat. FFM showed a positive correlation ($p<0.01$) ($r=0.42$) with VO_{2peak} measured in HUNT 4 fitness study. Though this is not a strong relation, but the positive correlation coefficient indicates that participants with more FFM may have higher VO_{2peak}. Therefore, inactive or inadequate PA is not only associated with an increase in body fat mass, also it decreases amount of relative muscle mass. The involvement of more muscle in PA improves venous return by pumping action of muscle (Mondal & Mishra, 2017). Hence loss of FFM and increase in body fat mass can enhance the age-related reduction of VO_{2peak}.

4.5 Practical implications.

Age-related reduction of VO_{2peak} is inevitable; however, it can be attenuated by life-style modifications, such as the involvement of regular PA. As we observed in our study, people who perform PA at or above recommendations had a slower decline in relative and absolute VO_{2peak} compared to below and inactive participants. Furthermore, including vigorous-intensity PA, even with a lower volume than the recommended 75 min. wk^{-1} can have a similar effect on attenuating age-related reduction of VO_{2peak} as that of low or moderate-intensity PA with higher total time spend. Moreover, PA at vigorous intensity with recommended volume will comparatively slower the decline of VO_{2peak} than PA at low or moderate intensity with recommended volume. Therefore, our results showed that PA performed at vigorous or very vigorous intensity within recommended exercise time is most beneficial for slowing the age-related decline of VO_{2peak}.

Generalization of these findings can be applied for healthy individuals of any age who are physically inactive or performs a certain level of PA on a regular basis. ACSM recommends a specific program such as resistance, flexibility, cardiorespiratory and neuro-motor exercise for healthy adults of all ages. Spreading short bouts of PA with recommended volume of exercise should be a goal for all adults to attenuate the longitudinal decline for absolute and relative VO_{2peak}. The PA performed in this manner can have a positive effect on physical and mental health too. However, particularly in inactive or sedentary adults moderate or vigorous-intensity PA with less than recommended volumes would like to have benefited too.

Regular PA is associated with healthy living, increased CRF, and reduced morbidity. It can also act as a potential primary prevention for many CVD and its outcomes, although not fully exploited (Piepoli et al., 2016). As the evidence show a modest increased in CRF by exercise is easily achieved over a few months of regular PA, it can be an efficient way of reducing cardiovascular risk.

4.6 Strength and Limitations.

A longitudinal, population-based design, a wide age span, and objectively measured VO_{2peak} are the major strengths of the study. Furthermore, the use of Borg scale rating as a relative intensity measured is more powerful than compared to most of the population-based study considering absolute intensity levels. Most of the studies generally have used total MET value (1 MET $\approx$3.5 ml/kg/min) as a measure of intensity, and it can be assumed that the relative intensity of exercise was often higher than referred (Asikainen et al., 2002; O'Donovan et al., 2005). METs may not unveil the true exertion, instead it can be a replacement for fitness in the individuals. Since older and unfit individuals may have problem adhering to a given MET level, which may be close to their maximal aerobic capacity (i.e., 1MET $\approx$ 21 ml/kg/min), prescribing PA intensity on a relative scale is more efficient. Therefore, used of relative intensity (i.e., Borg scale) by personal perception of exertion relative to participants CRF be more important tool for interpretations of PA in a diverse population. Selection bias is another limitation because more fit people were more likely to show up in the HUNT 4, and that can lead to under estimation of the association between PA and change in VO_{2peak}. However, relatively few dropouts and missing data during follow up of this study had important implications for the interpretation of the results of longitudinal analysis. The self-questionnaires method used for collecting information can have a risk of misclassification, which can be a limitation of the study. Moreover, our findings indicate that the self-reported questionnaire applied could assess the association between the level of PA and longitudinal decline of VO_{2peak} in a biologically plausible dose-response manner. However, the observational nature of the study prevents firm conclusions regarding causal relationships.

5. CONCLUSION

In summary, our study supports the hypothesis that the longitudinal decline of VO_{2peak} is not linear, and the rate of decline accelerates from 2 to 5 % in the 30s and 40s to >12 % per 10 years in the 70s and beyond. Although all the adult age groups showed a decline in VO_{2peak} over ten years, older adults showed more fall in the VO_{2peak} as compared to younger ones. Men had a higher decline of absolute VO_{2peak} than women across different age groups, whereas the percentage change was similar between both genders. As it seems that age-related reduction in VO_{2peak} is inevitable, PA at vigorous intensity at any age can lead to higher VO_{2peak} levels, an advantage that is maintained over the years helps to attenuate the reduction of VO_{2peak}. PA at vigorous intensity within the recommended volume is more likely to be beneficial on age-related decline of VO_{2peak} compared to low or moderate-intensity, regardless of time spend on exercise. The indirect and significant relationship between body fat mass and peak oxygen uptake indicates that PA at a certain level of intensity and volume can attenuate the increase in body fat mass and contribute to slow the decline of VO_{2peak}. Given the importance of VO_{2peak} in activities of daily living and as a predictor of health and longevity, increased and maintained a higher level of VO_{2peak} should be encouraged.

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