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Physical activity, weight gain, and risk of mortality in adults

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Photography: Ryhor Bruyeu, Mostphotos

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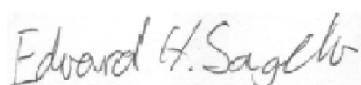
A handwritten signature in black ink that reads 'Edvard H. Sagelv'.

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List of Papers

Paper I

Sagelv EH, Ekelund U, Pedersen S, Brage S, Hansen BH, Johansson J, Grimsgaard S, Nordström A, Horsch A, Hopstock LA, Morseth B. Physical activity levels in adults and elderly from triaxial and uniaxial accelerometry. The Tromsø Study. *PLoS One*. 2019;14(12):e0225670.

Paper II

Sagelv EH, Hopstock LA, Johansson J, Hansen BH, Brage S, Horsch A, Ekelund U, Morseth B. Criterion validity of two physical activity and one sedentary time questionnaire against accelerometry in a large cohort of adults and older adults. *BMJ Open Sport Exerc Med*. 2020;6(1):e000661.

Paper III

Sagelv EH, Ekelund U, Hopstock LA, Aars NA, Fimland MS, Jacobsen BK, Løvsletten O, Wilsgaard T, Morseth B. Do declines in occupational physical activity contribute to population gains in body mass index? Tromsø Study 1974–2016. *Occup Environ Med*. 2021;78(3):203-10.

Paper IV

Sagelv EH, Ekelund U, Hopstock LA, Fimland MS, Løvsletten O, Wilsgaard T, Morseth B. The bidirectional associations between leisure time physical activity change and body mass index gain. The Tromsø Study 1974-2016. *Int J Obes (Lond)*. 2021;45(8):1830-43.

Paper V

Sagelv EH, Hopstock LA, Morseth B, Hansen BH, Steene-Johannessen J, Johansson J, Nordström A, Saint-Maurice PF, Løvsletten O, Wilsgaard T, Ekelund U, Tarp J. Device-measured physical activity, sedentary time, and risk of mortality. (*In review*).

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Abbreviations

ANOVA=analysis of variance

ANCOVA=analysis of covariance

BMI=body Mass Index

CI=confidence interval

CPM=counts per minute

HAI=Healthy Ageing Initiative

HR=hazard ratio

IPAQ=International Physical Activity Questionnaire

IPD=individual participant data

Kcal=kilocalories

MET=metabolic equivalent of task

MVPA=moderate-and-vigorous physical activity

NHANES=National Health and Nutrition Examination Survey

NNPAS=National Norwegian Physical Activity Survey

OR=odds ratio

PAEE=physical activity energy expenditure

PAFID=Physical Activity Frequency, Intensity and Duration

PAL=physical activity level

PAQ=physical activity questionnaire

REE=resting energy expenditure

SGPALS=Saltin-Grimby Physical Activity Level Scale

TEE=total energy expenditure

VM=vector magnitude

VO₂=oxygen uptake

WC=waist circumference

WHO=World Health Organization

Summary

Why: As low physical activity levels associate with ill health and mortality, continuous monitoring of physical activity levels is needed to inform policy. Identifying aetiology causes for the obesity epidemic is important to prevent population weight gain. However, there are still uncertainties on how physical activity and weight at population level associate over time, and how physical activity and sedentary time collectively influence premature death.

Aims and methods: To describe prevalence of device-measured physical activity in adults (40-84 years) in the Seventh Tromsø Study survey 2015-16 (Tromsø7) (Paper I). To examine accelerometry-criterion validity for two physical activity questionnaires (PAQ)s and one sedentary time questionnaire (Paper II). To examine whether occupational (Paper III) and leisure time physical activity (Paper IV) changes from one examination to the next are associated with subsequent body mass index (BMI) changes from the second to a third examination, across Tromsø Study surveys from 1974 to 2016 in prospective cohort designs. To examine associations between device-measured physical activity, sedentary time, and mortality in a one-step individual participant data meta-analysis of four prospective cohort studies (Tromsø7, The Healthy Ageing Initiative 2012-2019, The Norwegian National Physical Activity Survey 2008-09, The National Health and Nutrition Examination Survey 2003-06) (Paper V).

Findings and conclusions: About 70% of all adults met current lower-limit physical activity guidelines of 150 minutes per week of moderate and vigorous physical activity (Paper I). Processing PAQs in crude groups may attenuate biases associated with self-reported physical activity as it provided clearer patterns of higher device-measured physical activity by higher grouped ranking, while continuous scales of the PAQs showed small correlation magnitudes with device-measured physical activity (Paper II). Population levels of occupational (Paper III) and leisure time (Paper IV) physical activity appear insufficient to prevent weight gain but rather it appears the association is reverse, population weight gain leads to physical activity declines (Paper IV). Physical activity, at any intensity, associates with a substantial lower mortality risk and meeting current lower-limit guidelines ameliorates the higher mortality risk associated with high sedentary time (Paper V).

Importance: This thesis highlights the public health gain of increasing population levels of physical activity, and of preventing population weight gain to avoid physical activity declines.

Sammendrag

Hvorfor: Siden fysisk inaktivitet er assosiert med høyere risiko for sykdom og tidlig død er overvåking av fysisk aktivitetsnivå i befolkningen et viktig redskap i utforming av folkehelseiltak. Identifisering av årsaker for fedmeepidemien er et viktig bidrag i utforming av tiltak for å forebygge vektøkning i befolkningen. Imidlertid er det usikkert hvordan sammenhengen mellom fysisk aktivitet og vekt i befolkningen utspiller seg over tid, og hvordan fysisk aktivitet og stillesittende atferd i kombinasjon påvirker risiko for tidlig død.

Hensikt og metoder: Å beskrive fysisk aktivitetsnivå hos voksne (40-80 år) i den syvende Tromsøundersøkelsen 2015-16 (Artikkel I). Å undersøke kriterievaliditet (akselerometri) for to SFA-spørreskjemaer om fysisk aktivitet og et om stillesittende tid (Artikkel II). Å undersøke om arbeidsaktivitets- (Artikkel III) og fritidsaktivitetsendring (Artikkel IV) fra et måletidspunkt til det neste er assosiert med påfølgende endring i kroppsmasseindeks fra det andre måletidspunktet til et tredje, i Tromsøundersøkelser fra 1974 til 2016 i prospektive kohortdesign. Å undersøke sammenhengen mellom fysisk aktivitet, stillesittende tid og dødelighet i en ett-steg-individnivådata-meta-analyse av fire prospektive kohortstudier (Tromsø7, The Healthy Ageing Initiative 2012-2019, Kartlegging av fysisk aktivitet og fysisk form i Norge 2008-09, The National Health and Nutrition Examination Survey 2003-06) (Paper V).

Funn og konklusjoner: Sytti prosent av voksne oppfyller den nedre anbefalingen om 150 minutter i uka med moderate og hard fysisk aktivitet (Artikkel I). Grovkategorisering av SFA-spørreskjemaer kan forbedre skjevheten i data som vanligvis er assosiert med SFA siden det viste klarere mønstre av høyere monitormålt fysisk aktivitet, mens kontinuerlige skalaer for SFA viste svake korrelasjoner med monitormålt fysisk aktivitet (Artikkel II). Fysisk aktivitetsnivå i hverken arbeid (Artikkel III) eller fritid (Artikkel IV) ser ut til å kunne forebygge vektøkning i befolkningen, men sammenhengen ser heller ut til å være motsatt, en økning i vekt fører til lavere fritidsaktivitet (Artikkel IV). Fysisk aktivitet, uansett intensitet, er assosiert med en betydelig lavere risiko for tidlig død og ved å møte den nedre anbefalingen elimineres den økte risikoen av mye stillesitting (Artikkel V).

Relevans: Denne avhandlingen fremhever folkehelsegevinsten av å øke fysisk aktivitetsnivå i befolkningen, og viktigheten av å unngå vektøkning i befolkningen for å unngå nedgang i fysisk aktivitetsnivå.

1 Introduction

Physical activity is associated with a myriad of health benefits (1), including lower risk of mortality, major non-communicable diseases, and ill-health, such as cardiovascular disease, stroke, hypertension, type-2 diabetes mellitus, breast and colon cancer, metabolic syndrome, depression, and severe falls in elderly (2, 3). Physical activity is also recommended for rehabilitation and/or as secondary prevention of multiple diseases (4). A recent review identified physical activity as an effective treatment in 26 different chronic diseases, including psychiatric-, neurological-, metabolic-, cardiovascular-, and pulmonary diseases, musculoskeletal disorders and cancer (4). The economic burden of physical inactivity is enormous. In 2013, cumulative global healthcare costs related to physical inactivity added to 53.8 billion US dollars (46.6 billion Euros and 461.7 billion Norwegian kroner) (5). Considering the relatively inexpensive costs of performing physical activity, the public health, and economic gains of increasing population levels of physical activity is high.

1.1 Physical activity

1.1.1 Concept and definition

The traditional definition of physical activity from 1985 by Caspersen, Powell and Christenson (6) reads; “*Physical activity is any bodily movement produced by skeletal muscles that results in energy expenditure*”. Exercise, as defined for epidemiological research by Caspersen *et al.* (6), is; “*a subset of physical activity that is planned, structured, and repetitive and has as a final or an intermediate objective the improvement or maintenance of physical fitness*” (6). Physical fitness is; “*a set of attributes that are either health- or skill-related*” (6). Before this, physical activity and exercise were used interchangeably in the literature (6). Consequently, exercise is always physical activity. However, while physical activity can be exercise, it may not always be; for example, if the activity is not planned or structured with a goal to maintain or improve fitness (6). To improve health, exercise may be a solution for many people, but small bursts of physical activity that are not intended for maintaining or improving fitness may also provide health benefits, such as transportation by walking, cycling, or running, or grocery shopping, playing with kids, light or heavy manual work, *etc.* This notion is important, especially for public health messaging and policy implementation.

This classical definition was recently critiqued by Piggin (7), who suggested a more holistic approach towards the physical activity definition. According to Piggin (7), the physical activity definition by Caspersen *et al.* (6) only focuses on health-related research and epidemiology, which excludes aspects of physical activity, such as cognition, physical literacy, social cohesion and education (7). Furthermore, Piggin postulates that since physical activity must be performed by skeletal muscles, it narrows the view to only assess biomechanical characteristics, and ignores the human motivation (7). Finally, he suggests that if physical activity must result in energy expenditure, it excludes all aspects besides energy expenditure that can be a product of physical activity (7).

However, the classical definition of physical activity by Caspersen *et al.* (6) covers all aspects of all physical behaviours relevant for epidemiology. Therefore, for this thesis, the definition by Caspersen *et al.* (6) will be used for physical activity, while Piggin's (7) description can be considered as effects associated with physical activity.

1.1.2 Sedentary behaviour

Two decades ago, a new research paradigm emerged, where sedentary behaviour was suggested a health risk (8). As with physical activity and exercise, sedentary behaviour and physical inactivity is often used interchangeably in the literature (8). Nevertheless, sedentary behaviour is now commonly defined as “*any waking behaviour characterized an energy expenditure ≤ 1.5 metabolic equivalent of task (MET)s while in a sitting or reclining posture*” (8), and thereby distinctly different from physical inactivity, which is “*performing insufficient amounts of moderate and vigorous physical activity (i.e., not meeting specified physical activity guidelines*” (8).

1.1.3 Energy expenditure

All work produced by the body arise from metabolic processes, which involve energy transfer and results in heat energy, *i.e.*, heat production (9). Energy expenditure can be expressed as work completed using the unit, joule (6), which is 1 Newton metre (N·m). However, as noted by Caspersen *et al.* (6), calorie, normally as kilocalories (kcal), has historically been used to express energy expenditure, which is heat production equivalent to increasing 1 litre water temperature by 1 degree Celsius at sea level. The conversion between kilojoules and kcals is multiplication by 0.2388, or *vice versa* by division by 4.1868, if converting from kcals to kilojoules (6).

Total energy expenditure (TEE) is divided into the subcomponents resting energy expenditure (REE) and thermogenesis. Resting energy expenditure is the energy expenditure at rest (lying supine, ~3-4 hours post-absorptive) and is slightly higher than basal metabolic expenditure (12-18 hours post-absorptive state) (9). Thermogenesis is further divided into postprandial (thermic effect of food) and physical activity energy expenditure (PAEE) (9).

The average TEE in men and women are ~3300 kcals (14 MJ) and ~2400 kcals (10 MJ) per day, respectively (10). Total energy expenditure is influenced by body composition, physical activity, sex, age, nutrient intake, and genes (10). However, in general, TEE and REE increases from infancy to adulthood (~20 years), then remains stable in adult life until ~60 years, and subsequently drops during older age (10, 11).

Fat-free mass, which is metabolic active tissue, explains ~80 % of the variance in REE (12), and also 80% of TEE at population level (10). Fat-free mass also explain the difference in TEE between men and women (~1000 kcals/~4 megajoule (MJ)·day⁻¹) (10). The remaining variance is explained by postprandial thermogenesis and PAEE (10, 12). The surface area law describes that REE changes with body surface area (m²), implying that those with higher body size produce more heat energy (9). However, TEE and REE do not increase proportionally with body mass, as fat mass is not a metabolic active tissue (*i.e.*, it does not produce heat) (10, 12). To correct for body mass, TEE can be scaled to body weight (kcal·kg⁻¹·min⁻¹), or allometrically scaled to 0.75 (kcal·kg^{-0.75}·min⁻¹) for heat production (9, 13). However, such scaling differ by physical activity, as it include both weight-bearing and non-weight-bearing activities (14).

The most variable component of TEE is PAEE. Elite endurance athletes expend ~6400-8300 kcals per day/~27-35 MJ per day (15-18). The highest reported daily TEE is believed to be ~14000 kcals per day (60 MJ per day), observed following ultramarathon running over 27 hours (~16000 kcals/~67 MJs) (19). Although such high TEE (and such a large proportion as PAEE) is achievable by humans (19), the general rule of thumb in distribution of TEE is 60-75% from REE, 10% from postprandial thermogenesis and 15-30% from PAEE (9), indicating that the vast majority of the population perform much lower amounts of physical activity (10) than elite endurance athletes (15-18).

1.1.4 Physical activity classifications

1.1.4.1 Physical activity domains

The most common differentiation of physical activity domains is usually between occupational and leisure time, where leisure time physical activity can include sport participation, conditioning exercise (aerobic, anaerobic or resistance-based exercise), household activities (cleaning, grocery shopping, yard work *etc.*) and transportation (as walking, running, cycling *etc.*) (6).

1.1.4.2 Physical activity volume: intensity, frequency, and duration

The intensity of physical activity is the energy cost of the activity per time unit and is summed up to physical activity volume by including duration and frequency. Physical activity volume is usually expressed as PAEE or time in a specific intensity. An important distinction is the difference between absolute and relative intensity.

Relative intensity is the intensity relative to an individual's maximal capacity or peak cardiorespiratory measurement. Relative intensity accounts for interindividual differences, such as body mass, sex, and fitness. This can be expressed as percentage of maximal heart rate or maximal oxygen uptake (20), or using a less precise measure of oxygen uptake or heart rate reserve (difference between resting and normally estimated maximal oxygen uptake or heart rate) (21).

Due to feasibility issues (the need for individual calibration to fitness), expressing relative intensity is unavailable for most large observational studies. Therefore, most observational studies on physical activity express absolute intensity as energy expenditure, or as a proxy for energy expenditure, in physical activity index score systems (6). The most common index score is MET, which was developed to aid researchers in processing physical activity measurements into an interpretable measure, and to allow for crude comparisons of physical activity across studies (22). One MET represent REE and corresponds to 3.5 millilitre VO_2 per kilo body mass per minute ($\sim 1 \text{ kcal}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) (22). In this regard, physical activity can be provided in multiples of METs. For example, a 3 MET intensity corresponds to three times more energy expenditure ($3 \text{ kcal}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}/10.5 \text{ ml } \text{VO}_2\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) than at rest. As METs are absolute intensity, they will vary between individuals (22).

Alternatives for standardized MET-values include corrections for age, sex and body mass by using the ratio of measured or estimated REE and TEE, such as corrected METs (23). Another common physical activity index score is physical activity level scores (PAL-scores), also the ratio of REE and TEE (24). However, such approaches are not as accurate as relative intensity measures, as this assumes that TEE is only dependent on body mass and physical activity (13, 14, 25) but this also depends on fitness (10, 11, 26).

In observational studies, intensity is usually split into crude intensity categories over the physical activity continuum; sedentary behaviour, light-, moderate- and vigorous intensity physical activity. The corresponding MET-values are <1.5 (VO_2 : $5.25 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) for sedentary behaviour (8), 1.5-2.9 (VO_2 : 5.25 - $10.4 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) for light-, 3-5.9 (VO_2 : 10.5 - $20 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) for moderate- and ≥ 6 (VO_2 : $\geq 21 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) for vigorous intensity (27). These intensity splits may be traced back to the first physical activity guidelines in the United States in 1995 (27).

1.1.5 Physical activity guidelines

In 1978, the American College of Sports Medicine published their first physical activity guidelines (28). These were quite specific and involved performing aerobic exercise 3-5 days per week at 50-85% of maximal oxygen uptake (60-90% of maximal heart rate) for a duration of 15-60 minutes per session, and should be performed in activities involving large muscle mass, such as running, hiking, swimming, cycling, rowing, cross-country skiing or endurance games or activities (28). In 1994, the first international guidelines on physical activity were published, stating; *“Take 30 minutes of moderate intensity physical activity, such as a sustained brisk walk, on at least five days of the week. Ideally, these 30 minutes should be one period of sustained activity, but shorter bouts of 15 minutes are also beneficial”* (29).

During the 1990s, accumulating evidence indicated that *exercise* guidelines were potentially not capturing all health benefits associated with physical activity (30). Consequently, a paradigm shift from *“exercise for fitness”* towards *“physical activity for health”* emerged, and indicated that the benefits of performing physical activity may be achieved with less physical activity than these early guidelines (30). It was also suggested that most health benefits were achieved by changing from inactive to slightly active, and that health/benefit curves may level off at higher physical activity levels (30),

The recent 2020 physical activity guidelines from the World Health Organization (WHO) suggest adults should undertake 150-300 minutes of moderate- or 75-150 minutes of vigorous physical activity (MVPA) per week, or a combination of these two (31). Further, adults are also recommended to perform muscle-strengthening activities (*i.e.*, resistance exercise) twice per week (31). Finally, adults are also recommended to reduce their sedentary time, but no time specific range or threshold is mentioned except that those with high sedentary time are recommended to reach the upper 300 minutes of MVPA per week to ameliorate the health consequences of high sitting time (31). Although these guidelines update and replace the previous 2010 WHO guidelines (32), they are only a slight adjustment from the previous guidelines. Specifically, the previous guidelines recommended a minimal threshold of 150 minutes of moderate-, or 75 minutes of vigorous physical activity (32), while the 2020 guidelines present a range (150-300, or 75-150 minutes per week, respectively) (31). The previous guidelines also suggested that physical activity should be performed in continuous bouts of at least 10 minutes (32). Now, every minute counts towards the guidelines (31). Finally, the new 2020 guidelines also recommend reducing sedentary behaviours (31), which was not a recommendation in the 2010 guidelines (32). In Norway, the national guidelines follow those of the WHO, and was updated in 2022 (33).

1.1.6 Some physical activity measurements in epidemiology

As physical activity epidemiology research grew as a field, so too did the exploratory studies of measuring physical activity during free-living (34). An early concern was that the regression dilution bias of self-reported methods would influence study results, and that higher precision in measurement of physical activity could reveal greater magnitudes when examining associations with health outcomes (34). Many methods for measuring physical activity have been used over the years, including calorimetry, work classification, survey self-report by participants, behavioural observation, physiological proxy-markers, such as cardiorespiratory fitness, and devices such as heart rate monitors, pedometers and accelerometers (34). Up until 1985, both devices and calorimetry provided higher precision than self-reported methods, but remained unfeasible for use in large scale cohort studies (34).

There are three main challenges in measuring physical activity for application in epidemiological research: 1) measuring all aspects of physical activity; 2) the variation of physical activity by time; and 3) measurement error. Measurement precision is a considerable concern in modern physical activity epidemiology, especially with the substantial weight of

evidence regarding the effect of physical activity on health (35). Therefore, higher measurement precision is necessary to advance current knowledge within the field of epidemiology. Although higher measurement precision holds great promise, overlooking bias deriving from measurement errors may lead to misinterpretation of results.

1.1.6.1 Self-reported physical activity

Self-reported physical activity is the most used measurement tool (36). They are, by human nature, prone to self-desirability bias; as physical activity is a desired behaviour, humans will overestimate their physical activity level (36). However, the degree of bias from self-desirability may vary by complexity and data processing of the self-reported measurement tool, and by demographic factors (37).

Another issue with self-reports is recall, as memorizing all physical activity performed over time is challenging (36). This may also be influenced by the complexity of the self-reported measurement tool (37). As exercise and physical activity have been used interchangeably in the literature (6), this is likely also an issue for participants when they recall their own behaviour. In the 1970s, when Morris and colleagues asked participants why they did not perform physical activity, the participants stated that they did not perceive themselves as sporty enough to perform *exercise* (38). However, this may vary by culture (37), and the perception of physical activity during the 1970s may have changed from how it is perceived today. As such, an inherent cohort effect may be present between seminal and more recent studies.

The most feasible tool is a physical activity questionnaire (PAQ). It is easy to administrate, has low costs and low participant burden (depending on complexity) (36). Physical activity questionnaires are administrated in-person, which allows participants to write their answers, or it may also be collected during telephone interviews, where the researcher asks each question and records the response for the participants. The first PAQs were simple tools with crude categorisations of physical activity levels, such as the PAQ developed by Saltin and Grimby in 1968 (39, 40). This was later named the Saltin-Grimby Physical Activity Scale (SGPALS) (41).

Today, there are many PAQs available with considerable differences. As the outputs between various PAQ's are often expressed differently, it can be challenging to compare between studies. When physical inactivity emerged on the international agenda in the 1990s, this issue was already present (42). Consequently, the International Physical Activity Questionnaire

(IPAQ) was developed, aimed at measuring physical activity on a global scale, consisting both of a short and long version which captured all aspects of physical activity (43). However, as with all PAQs, when compared with higher criterion methods, such as accelerometry, IPAQ shows low validity, with a correlation (Pearson, Spearman) of ~0.3 (43). Similar small correlations magnitudes are found when comparing PAQs to doubly labelled water in estimating PAEE (44). Although imprecise, the reliability of the IPAQ can be considered acceptable, meaning that it produces fairly stable intraindividual estimates over time (43). Therefore, PAQs are the most applicable tool for global surveillance of physical activity (42), due to the low cost and logistics of measuring physical activity in large scale studies.

1.1.6.2 Device-measured physical activity

Device-measurements of physical activity were previously named “objective” measures, to differentiate them from subjective self-reported methods. However, when being employed more frequently, many issues with device-measured physical activity emerged. As such, device-measured physical activity is commonly considered to involve many researcher-specific subjective choices, such as during data collection or calculating measurements to express physical activity (45), which may lead to investigator bias. The major advantage of devices, when compared with self-report methods, is that recall- and social-desirability bias are minimized. However, when placing devices on participants, a response bias (*i.e.*, the Hawthorne effect) may apply (46).

Accelerometers are the most used devices to measure physical activity. To measure physical activity, accelerometry utilises the principle that acceleration is a proxy for body movement, and can thus be measured as the force applied to the body, given as physiological outputs from contracting muscles (47). The first accelerometer intended to measure physical movements was reported in 1961 (47). It was small, weighting 50 grams with a dimension of 40 x 40 x 15 mm³, and three steel plates of strain gauges measuring the electrical force of movements (47). It could be placed on multiple locations of the body, but was intended to be placed at the lower back (47). The intended use was in sports medicine, measuring different movements in the laboratory (47). Whether it was appropriate for measuring physical activity levels in free-living is questionable.

Accelerometers intended for use in epidemiology started to appear in the 1980s (48, 49), but needed a more advanced methodological framework to be successfully employed in large scale

studies (34). Through the 1990s, more commercial accelerometers appeared (13). In 2015, ActiGraph (Pensacola, Florida, United States) was the most frequently used accelerometer and was included in ~50% of all published studies (50).

Accelerometers can measure acceleration in different directions. Triaxial accelerometry (vertical, coronal and sagittal) are expected to capture more physical activity than uniaxial accelerometry (vertical) (51). However, when comparing triaxial and uniaxial accelerometry in standardized activities in the laboratory, they appear to produce similar physical activity estimates in adults (52). In free-living environments, a higher intensity physical activity is observed in women (53) and during sporting activities (54) using triaxial, compared with uniaxial accelerometry.

To date, there is no gold standard to measure all aspects of physical activity (55), thus, one must carefully choose what measurement tool is best suited for both the research question and feasibility. Intuitively, one would assume accelerometry to provide higher precision in measuring many aspects of physical activity compared with self-reported physical activity. For example, doubly labelled water has a measurement error of 2-8% against respiratory indirect calorimetry from chambers (56), and as such, it is considered the gold standard for measuring PAEE during free-living (24). Usually, PAEE from doubly labelled water correlates with PAQs at ~0.3, and with accelerometry-measured PAEE at ~0.5 (44, 57, 58). Therefore, accelerometry-measured physical activity is more accurate than self-reported physical activity in measuring PAEE, although both methods cannot account for all PAEE.

1.1.7 Physical activity levels and prevalence

In 2012, physical inactivity was coined a global pandemic (59), as 30% of all adults worldwide were insufficiently active (60), of which 5.3 million (9%) of all deaths could be avoided if all were sufficiently active (2). To monitor this disease risk, the Global Observatory for Physical Activity was launched, with information on physical activity surveillance in 68 countries worldwide (61, 62). This was a large step towards global surveillance of physical activity.

The first description of physical activity levels were performed by Bedale in 1923 in school aged children (63). In this study, Douglas bags (the gold standard for indirect calorimetry) were used to measure energy expenditure of 45 different activities in children for 800 repeated experiments, in order to ascertain the average energy costs of the activities, and thereafter

undertook direct observation of the children when playing in the school yard (63). The report details all aspect of this research, including the school environment, time table, anthropometrics, as well as detailed descriptions of the physical activity level, which is freely available online (63).

When reporting prevalence, one usually display the prevalence of physical inactivity, which is the proportion of a population that do not meet the current lower-limit physical activity guidelines of 150 minutes of MVPA per week (31). However, prevalence can also be reported for the population that is physically active (*i.e.*, active for ≥ 150 minutes of MVPA per week). Physical activity guidelines have changed over time, according to the evolving evidence. This provides a challenge in tracking the prevalence of this risk factor over time and complicates calculations to determine whether physical activity has changed over time in a population. Moreover, to compare previous data with newer data, one should preferably use the same measurement tool. The measurement tools (mostly PAQs) are not necessary designed to display the proportion meeting the current guidelines. For example, in the recent global estimate of physical inactivity (64), data were included if measured with the IPAQ (43) or the Global Physical Activity Questionnaire (65). Both these questionnaires ask about physical activity performed in at least 10-minute bouts (43, 65), and are thus not capturing the new guideline where every physical activity bout length counts (31). It should be noted that the global estimate was reported in 2018 (64), preceding the updated 2020 guidelines (31).

1.1.7.1 Prevalence of physical inactivity

The recent global estimate reports that ~30% of the world's population is insufficiently active (64), with most being inactive in high-income and western populations (~35-40%), and the lowest proportion in Oceania and sub-Saharan (~20%) (64). In Europe, the estimated prevalence of physical inactivity across 35 countries ranges from 93% to 4% (66). In Norway, 30% are inactive (67).

As accelerometry is not implemented in all regions in the world due to cost (64), accelerometry estimates of physical inactivity are only available for mostly high-income countries. In Norway, accelerometry estimates display that 68% of the population are insufficiently active, using the 2010 WHO guidelines (68). In Sweden, 79% (69), or 99% (70), are insufficiently active, in the United States (71), United Kingdom (72, 73) and Portugal (74), 95% are inactive, while 85% are inactive in Germany (75), with the 2010 guidelines (68).

However, accelerometry are highly influenced by the subjective choices when processing accelerometry data. If changing the cut-off for acceleration corresponding to MVPA (*i.e.*, ≥ 3 METs), 85% (73) or 82% (72) are inactive in the United Kingdom. When using the updated 2020 WHO guidelines without the strict ≥ 10 -minute bout criteria (31), 31% in Norway, 36% in Sweden, 46% in the United Kingdom and 38% in Portugal are inactive (69).

1.1.7.2 Physical activity levels and correlates

One can also assess physical activity levels as total physical activity and minutes at certain intensities, which may describe differences in physical activity beyond the prevalence estimate, which may be of public health relevance. Physical activity varies by demographic factors (76). In self-reported data, determinants in high-income countries that likely influence physical activity are health status, self-efficacy towards physical activity and history of physical activity through adulthood (76). Correlates of physical activity include age, sex, educational level, ethnic origin, BMI, perceived effort of physical activity and social support (76); higher age is associated with lower physical activity levels, men are more active than women and higher BMI is inversely associated with physical activity levels (76). In low- and middle-income countries, similar correlates are reported, however, physical activity is mostly performed as means of transportation or as a part of their occupation rather than during leisure time as in high-income countries (76). These correlates are consistent in accelerometry-measured physical activity in high-income countries (68-75, 77), and in Chinese adults (78).

1.2 Obesity and the role of physical activity

1.2.1 The obesity epidemic

Although being underweight ($< 18.5 \text{ kg/m}^2$) is a health concern in many low-income countries, in general, global BMI is rapidly increasing (79). Given the trajectories of current data (79), the obesity epidemic may soon constitute as a pandemic. Obesity ($\geq 30 \text{ kg/m}^2$) is among top five risk factors for non-communicable diseases (80). Overweight ($25\text{-}29 \text{ kg/m}^2$) is also associated with higher risk of death; high BMI accounts for 4 million deaths globally, with 40% (~ 1.6 million) of these deaths not being among obese individuals (81). For every 5 BMI-unit (kg/m^2) increase, the risk of death increases 30-40% in those who are overweight or obese (82). From 1975 to 2014, obesity increased from 3% to 11% worldwide, with a particularly rapidly rise

from the 1990s onwards (79). In high-income countries, overweight prevalence is now almost 75%, while in South Asia and Africa it remains around 20-30% (79).

1.2.2 Physical activity and population weight gain

Weight changes are caused by energy imbalance (83-85), *i.e.*, weight gain is a result of higher energy intake than expenditure and *vice versa* for weight loss (84, 85). This basic principle is illustrated in numerous systematic reviews and meta-analyses of randomized controlled trials (86-89), including those that solely imposed restricted negative energy balance for weight loss (90-94). Additionally, this change is independent of whether the negative energy balance is achieved through higher energy expenditure or lower energy intake (95, 96). However, long-term weight loss, or weight maintenance after weight loss, is often unsuccessful (86-89), as people regain their initial weight, usually within a year (97).

Weight regulation is challenging at individual level, where changing energy intake and expenditure involves genetic, physiological and behaviour factors (98). Consequently, identifying the aetiology causes for the obesity epidemic for successful prevention of population weight gain has high priority (84). As inter-individual variability is large, early researchers pursued genetic predisposition or metabolic dysfunction as aetiology causes (99). However, as population weight gain seems universal in western high-income countries (79), environmental factors are most likely the driving causes (99).

In the 1990s, declines in physical activity at population level were suggested to also contribute to weight gain (99). Such a hypothesis is supported in the literature. Occupational physical activity has declined in western high-income countries (100-104), and at population level, occupational physical activity contributes with higher PAEE than that from leisure time (100, 105). At the same time, many occupations include limited physical activity (100, 104), and as such, leisure time physical activity may hold greater promise for interventions to prevent population weight gain.

A previous modelling study reported that a daily ~100 kcal (418 KJ) decrease of energy intake, or increase in energy expenditure, could theoretically prevent population weight gain (84). This is equivalent to 15 minutes of walking per day (84), and can be achievable for the vast majority of the population.

A recent systematic review concluded that physical activity could prevent population weight gain in adults (106). However, this is still under debate (107). For example, although many of the included studies in the recent review (106) displayed a negative association between higher physical activity and weight gain (108-135), many other studies found no association (136-146). These inconsistent results may be attributed to methodology and study designs differences (107). For example, many studies that examined this association used one baseline measure of physical activity and weight status at different time points, where some studies reported an association (110, 113, 116, 117, 120, 122, 127, 135), while others reported no association (137, 140, 141, 143-146). However, a baseline measure of physical activity does not take the reciprocal relationship of both changes in physical activity and weight into account (107).

Other studies measured physical activity at multiple time points and examined the association with weight gain. Similarly, some observed a negative association between increasing physical activity or maintaining high physical activity and lower weight gain (108, 109, 111, 112, 114, 115, 118, 119, 121, 123-126, 128-134, 147, 148), while others observed no association (136, 138, 139, 142, 149). Even two studies conducted by the same group of researchers displayed inconsistent findings (115, 138). However, computing change in both physical activity and weight at the same time points is basically a cross-sectional analysis of change scores, and thus the direction of the association remain unexamined (107).

Initial weight is a strong determinant of future weight gain (107). In one study, only baseline weight and not baseline physical activity, was associated with higher odds of being obese at follow up, with mutual adjustment of baseline weight and physical activity (136). However, some of the studies in the recent review (106) did not adjust their analyses for baseline weight (109, 110, 112, 120, 125, 128, 130-132, 141). Unadjusted baseline weight may overestimate the effect of physical activity on future weight gain (107).

Observational data are susceptible for reverse causation, thus, there is also the possibility that the association between physical activity and weight change is reversible (107). There are fewer studies examining whether weight change is associated with physical activity change, but consistent observations indicate that weight change is more likely to result in decreasing physical activity than *vice versa* (115, 138, 142, 146, 149-151). A mendelian randomization study indicated that increases in weight were causally associated with physical activity declines

in children (152), however, this has not been examined in adults using mendelian randomization.

A final option in the association between physical activity and weight is that the associations are bidirectional; that physical activity causes weight change *and* weight change causes physical activity change (107), and thus can be exponential over time. If there are bidirectional associations, then the pertinent question is in what direction is the magnitude of associations the greatest (107). In other words, whether physical activity is involved in the aetiology of the obesity epidemic, and if so, in what direction (84, 99). One study reported associations in both directions; accelerometry-measured physical activity were associated with changes in adiposity (waist circumference and fat mass measured with bioimpedance), and changes in adiposity were associated with physical activity declines (153). When modelling the adiposity markers as the exposure and physical activity as the outcome, the associations were three times greater (standardized beta (β), waist circumference: -0.25, 95% confidence interval (CI): -0.36 to -0.15, fat mass: -0.27, 95%CI: -0.36 to -0.18) than *vice versa* (waist circumference: $\beta = -0.07$, 95%CI: -0.12 to -0.02, fat mass: -0.09, 95% CI: -0.14 to -0.04) (153). An option in longitudinal designs is to use three or more time points, where weight change can regress on previous physical activity change, which may be more suitable for examining directions of associations.

1.3 Physical activity and mortality

Population attributable fractions indicate that physical inactivity causes 3.9-5.3 million deaths annually (2, 154). Consequently, increasing population levels of physical activity may have the capacity to improve longevity. This evidence is one of the reasons why there are concerns regarding the worldwide prevalence of physical inactivity (59).

Alongside cardiovascular disease, mortality was the first outcome to be examined in physical activity epidemiology (155, 156). In 1953, Morris *et al.* (155, 156) published a two-series publication on how different occupations were associated with coronary heart disease and mortality. The first of the two-series revealed that drivers of London's double-decker buses had higher rates of coronary heart disease and mortality from coronary heart disease, than conductors (155). This was also evident in postmen versus desk workers in the London mail service (155). The second of the two-series presented their hypothesis; that these associations are likely explained by higher physical activity levels by conductors walking up and down the stairs of the busses, and postmen walking to deliver mail, than their inactive colleagues driving

the busses and sitting in the front desk of the mail service (156). However, there were concerns that these results may have been confounded by adiposity (157). Consequently, Morris *et al.* (157) collected the uniform trousers of similar participants from the London transport service, which revealed that drivers had larger uniforms, and therefore likely more adiposity than conductors, suggesting that the association was confounded by adiposity. Nevertheless, later studies by Morris *et al.* (158, 159) indicated that physical activity is associated with lower rates of coronary heart disease and mortality, independent of adiposity.

In the following years, more studies emerged with similar findings, but in different occupations with varying degree of physical activity, such as farmers versus other occupations (160), railroad workers with different physical activity of work (161) and longshoremen with different physical activity of work (162, 163). One study also included different intensities of occupational physical activity, and found lower incidents of mortality with higher intensity of occupational physical activity (164).

These seminal studies were primarily case-control studies that compared an active occupational physical activity group with an inactive occupational group. As occupational physical activity was in decline in the 1950-70s (165), epidemiologists started to examine whether leisure time physical activity was associated with lower mortality risk (38). In the 1980s, Paffenbarger *et al.* (166) reported a lower risk of mortality with higher leisure time physical activity among individuals with high socioeconomic status, in Harvard alumni. Although dose-response associations were previously observed in the aforementioned occupational physical activity intensity studies (162-164, 167), the Harvard alumni study was the first to display a clear dose-response association: for every additional 500 kcals per day of physical activity, the relative risk of mortality was lower, and levelled off at 3500 kcals per day (166). Moreover, physical activity seems to modify, albeit not eliminate, associations with other established risk factors, including those smoking over 20 cigarettes per day (166).

In the 1990s, studies examining the plausible mechanisms started to appear (38). In 1989, Blair *et al.* showed that baseline higher cardiorespiratory fitness was associated with lower mortality risk (168), and later also with changes in cardiorespiratory fitness, where increasing cardiorespiratory fitness was associated with lower mortality risks (169). In the 1990s, a Norwegian study showed similar findings of cardiorespiratory fitness and mortality (170). In the beginning of the 2010s, a large prospective cohort study indicated that even low intensity

physical activity (*i.e.*, below moderate intensity of 3 METs, $10.5 \text{ mlVO}_2 \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) was associated with lower risk of mortality (171). A commentary to the study stated that the health benefits of physical activity were causally associated, and this was irrefutable (172).

However, most of this evidence derives from self-reported physical activity, which is prone to regression dilution bias, and thus the associated lower risk of mortality could be underestimated. A recent meta-analysis reported a lower risk of mortality that was twice in magnitude (35) compared with that from self-reported physical activity (173). This indicates that the association between physical activity and mortality may be greater than what can be estimated from self-reported physical activity, and as such, studies using device-measured physical activity and examining the association with mortality are warranted.

A dose-response association between physical activity and mortality is well known (166, 167). However, the recent meta-analysis of device-measured physical activity indicates that there is still a need for additional research to better understand the dose-response association between physical activity and mortality (174). For example, examining the dose-response association in different populations may reveal additional evidence on how this association manifest in these individuals, such as in older adults (174).

1.3.1 Sedentary behaviour and mortality

Research on sedentary behaviour can be traced to Levine, Eberhardt and Jensen (175), who suggested that the absence of non-exercise activity thermogenesis results in higher fat storage from food intake, as PAEE sums up a small proportion of daily TEE. The study by Levine *et al.* (175) showed how the body attempts to maintain homeostasis by increasing light physical activity, such as standing and fidgeting, in order to increase TEE in response to overeating, suggesting that an increase in non-exercise activity thermogenesis could aid in fighting the obesity epidemic (175). This relationship may have been further ‘extrapolated’ to suggest that sitting and/or sedentary behaviour is a health risk independent of physical activity, *i.e.*, PAEE (176). In physical activity epidemiology nomenclature, thermogenesis is divided into postprandial thermogenesis or PAEE (9). Consequently, non-exercise thermogenesis as defined by Levine *et al.* (175) is still PAEE, as defined in physical activity epidemiology.

In 2003, a study in rodents reported suppressed lipoprotein lipase activity (LPL; an enzyme important for uptake of triglycerides into muscle cells) following prolonged hours of unloading

hind limb muscles, which were upregulated following subsequent ambulatory physical activity (177). This finding indicated that the regulation of LPL activity may be controlled by reducing sedentary time (177). This later framed a new concept, '*inactivity physiology*', suggesting that some physiological mechanisms operate differently during low- and vigorous-intensity physical activity (178).

Thereafter, epidemiological studies started to appear, framing a new concept different from physical inactivity (*i.e.*, sedentary behaviour), where higher sedentary time was associated with a higher risk of ill health, including mortality (179-181). These early population studies indicated similar findings as those from the first experimental animal studies; the risk of ill health from prolonged sedentary time was independent of higher intensity physical activity, *i.e.*, MVPA (179, 181). Not long after the initial epidemiological studies were published, sedentary behaviour guidelines were launched in many countries (182), including Norway (183). Despite warnings that the evidence was premature (184), guidelines on sedentary behaviour were launched faster than the development of physical activity guidelines (28). Moreover, this disparity reached the lay public; an analysis of mass media coverage from 2000-2012 indicated that 40% of all mass media reports on sedentary behaviour stated that "*physical activity levels are irrelevant if you sit too much or for prolonged time*" or that "*sitting abolishes the beneficial health effects of physical activity*" (185). Furthermore, media outlets and researchers even postulated that "sitting is the new smoking" (186, 187). Naturally, smoking and sitting are incomparable; the risk of high sitting time (>8 hours) is reported to be 4% (188) to 20% (189). The mortality risk of smokers versus people who never smoked is 280%; for heavy smokers this increases to 408% (186). Consequently, smoking displays a 9- to 20-fold higher risk of mortality, than sitting for prolonged hours (186).

In all studies towards the mid-2010s that reported "sedentary behaviour was independent of MVPA for disease" (179), physical activity was included as a covariate in their analyses. Rothman presented the concept of biological interaction in 1974 (190), suggesting that some causes for disease may work in combination, *i.e.*, as joint effects. In 2016, a meta-analysis by Ekelund *et al.* (191) examined whether self-reported sedentary time and physical activity may work synergistically. In this study, higher levels of physical activity, about 60 minutes per day, eliminated all mortality risks associated with sedentary time (191), which was reproduced some years later in a prospective cohort study (192). Another meta-analysis by Ekelund *et al.* (193) of device-measured physical activity confirmed this association, where ~40 minutes of MVPA

appeared sufficient to eliminate the excess risk of high sedentary time (193). Although it is likely that a certain amount of MVPA eliminates mortality risks associated with high sedentary time, examining the combined joint dose-response association in multiple study populations, such as older adults, is still warranted to fully understand the biological interaction between these exposure factors (174).

1.3.2 Individual participant data meta-analysis

Recent meta-analyses of device-measured physical activity that have examined the dose-response association with mortality (35, 194), and studies that examined the joint associations of physical activity and sedentary time with mortality (191, 193) were individual participant data meta-analyses (195, 196). Individual participant data meta-analyses harmonize all exposure and covariate data, thus making data between the included studies comparable (195, 196). A meta-analysis by Ekelund *et al.* (35) included eight prospective cohort studies, and reported 52% lower risk of mortality for participants in the second quartile of total physical activity compared with the first quartile, and spline models displayed that the risk of mortality levelled off at ~24 minutes of MVPA per day and ~300 minutes of light physical activity per day. Finally, sedentary time of more than 9.5 hours per day was associated with higher risk of mortality (35). The meta-analysis by Ekelund *et al.* (191), from 2016, combined data from 13 studies and more than 1 million participants, to examine the joint association of self-reported physical activity and sedentary time on mortality. The harmonized physical activity exposure in this study was MET-hours per week (191). Over 35 MET-hours per week eliminated the association between sedentary time and mortality, equivalent to about 60 minutes of MVPA per day.

Another individual participant data meta-analysis by Ekelund *et al.* (193) from 2020 included eight prospective cohort studies of device-measured physical activity and examined the joint association between physical activity, sedentary time, and mortality. Here, about 40 minutes of MVPA per day eliminated the association between sedentary time and mortality (193). An individual participant data meta-analysis by Chastin *et al.* (194) included six prospective cohort studies and used compositional data analysis to examine the joint association of MVPA, light physical activity, sedentary time, and sleep, with mortality. They reported that higher MVPA was associated with the lowest risk of mortality, while the ratio of light physical activity and sedentary time did not modify the association between MVPA and mortality. However, higher amounts of light physical activity, and thus lower amounts of sedentary time, were also

associated with a lower risk of mortality (194). When restricting analyses to studies using hip-worn accelerometers, the results indicated that the amount of sedentary time modified the association between MVPA and mortality, with no lower risk of mortality associated with higher MVPA, when exceeding 11-12 sedentary hours per day (194).

Two approaches of individual participant data meta-analyses are commonly used; a one-step and a two-step approach (196). The latter is fairly similar to aggregated meta-analyses, where estimates are obtained from each study cohort separately and further synthesized with meta-analytic procedures (196). The difference compared with solely aggregated meta-analyses is the harmonized protocols making data processing of exposure, confounder, effect modifier, and outcome data similar, thus avoiding inconsistencies in the included studies (195, 196). This results in comparable estimates of the individual studies, thus allowing for firmer conclusions (195). The abovementioned studies all used two-step approaches (35, 191, 193, 194). Although this provides many strengths to the interpretation of studies, it still has some limitations. For example, summary study-level data may force categorisation of exposure groups; Ekelund *et al.* from 2019 (35) and from 2020 (193) included study-specific centiles of physical activity. In the highest quartile (35) and tertile (193) of MVPA, MVPA ranged from ~20 to ~60 minutes of MVPA per day. Such large variations in physical activity estimates makes interpretation of the results difficult and makes it challenging to translate such findings into public health targets and clinical decision-making.

In comparison, the one-step approach pools individual participant data into one dataset, and thus analyses all the data as one study (196). This approach offers greater flexibility in analyses when compared with two-step approaches, especially as it increases statistical power to explore effect modification, interactions and confounding beyond what can be obtained from meta-analytic estimates of study-level data (195, 197, 198). One-step approaches can also be obtained as special cases of two-step approaches and can also be conducted without requiring a systematic review to identify all available studies, which can be unfeasible due to restrictions on data sharing, time, and resources (195, 197). A recent study conducted a one-step approach of self-reported physical activity and mortality, where occupational physical activity was associated with lower risk of mortality in men, but not in women (199). Such one-step approaches have not been conducted with device-measured physical activity.

Regression dilution bias is evident in self-reported physical activity (36) and self-reported sedentary time (200), and accelerometry-measured physical activity is associated with lower risk of mortality using a two-step individual participant data meta-analysis (35, 193, 201) compared with self-reported data (173). Therefore, one-step individual participant data approaches may provide additional exposure-interaction-outcome associations between physical activity, sedentary time, and mortality.

1.4 The aims of this thesis

The individual papers' contribution to this thesis is illustrated in Figure 1.1. The following specific aims were examined in this thesis:

- 1) To describe the levels and prevalence of accelerometry-measured physical activity.
 - a. A secondary aim was to compare the levels and prevalence from uniaxial and triaxial accelerometry-measured physical activity.
- 2) To examine the validity of two PAQs and one sedentary time questionnaire, processed as crude categorisation ranks and as continuous scales of physical activity, against accelerometry-measured physical activity as the criterion.
- 3) To examine whether occupational physical activity changes predict future BMI changes.
 - a. A secondary aim was to examine whether occupational physical activity changes predict future weight changes.
- 4) To examine whether leisure time physical activity changes predict future BMI changes.
 - a. A secondary aim was to examine whether BMI changes predict future leisure time physical activity changes.
- 5) To examine whether the association between sedentary time and mortality is modified by being physically active (*i.e.*, meeting current lower-limit physical activity guidelines).
 - a. There were two secondary aims:
 - i. To examine whether the association between physical activity and mortality is modified by sedentary time.
 - ii. Examine the joint association of MVPA and sedentary time on the risk of mortality.

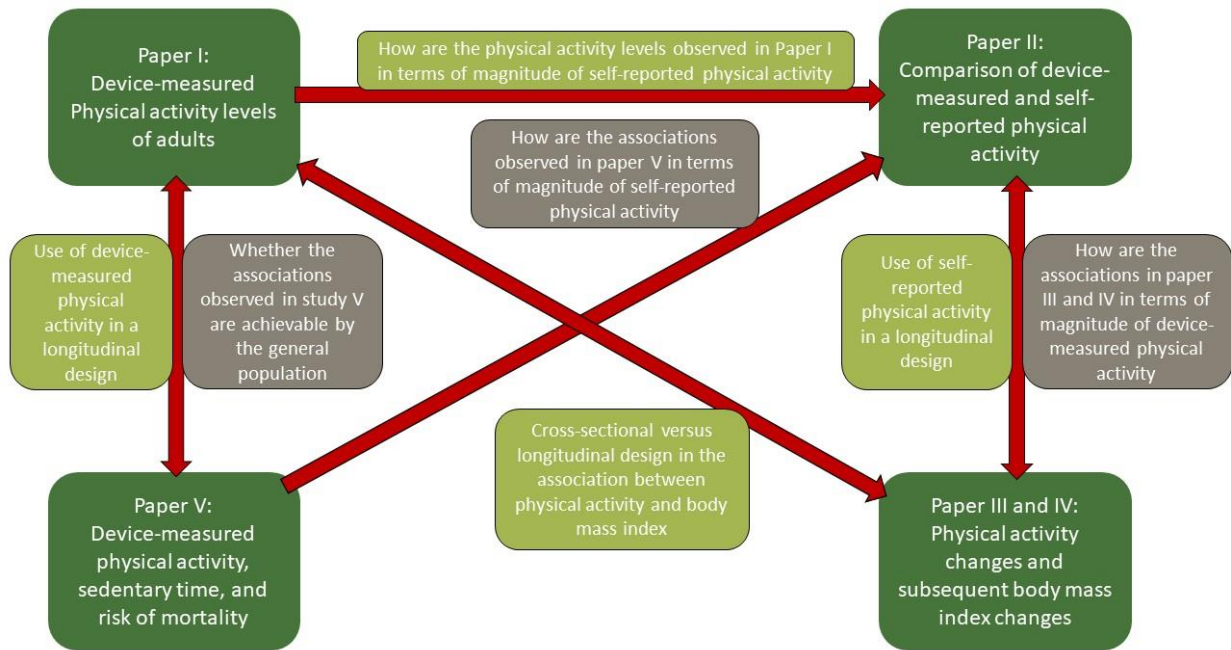


Figure 1.1. The combined contribution of the papers in this thesis.

Light green boxes: the prospective continuation of a previous paper

Grey boxes: the retrospective continuation of a paper

2 Methods

2.1 Design and study populations

2.1.1 Paper I

Paper I was a cross-sectional study including participants of the seventh survey of The Tromsø Study in 2015-16 (Tromsø7) (202). Of the 32591 individuals over 40 years that were invited to Tromsø7, 21083 (65%) attended. A sub-sample (n=13304) was invited for a second visit with extended examination. This included 20% the 40–59-year age group, and 50% in the 60–84-year age group, which were both randomly drawn from the total sample (N=21083). Additionally, 3154 participants from the total sample were also invited for follow-up on extended examinations, as they had attended the sixth survey of The Tromsø Study in 2007-08 (Tromsø6) (203). Of the 13304 who were invited to the second examination of Tromsø7, 8346 (63%) attended. Due to logistical reasons, 6778 (81% of those attending examination 2) were invited to wear an ActiGraph GT3X-BT (ActiGraph, LLC, Pensacola, Florida, United States) accelerometer for eight consecutive days, of which 6333 (93%) accepted the invitation. Six accelerometers were lost, 37 returned accelerometers with a technical error (unreadable data due to accelerometer malfunction), and 165 did not provide sufficient wear time. We ended up with a sample of 5918 aged 40-84 years, who provided valid accelerometry wear time and had information on sex, age, BMI and education.

2.1.1.1 Additional analysis Paper I

An additional analysis for paper I was performed to examine at what relative intensity (percentage of maximal oxygen uptake) participants in paper I would be performing different absolute intensity of physical activity.

2.1.2 Paper II

Paper II was a cross-sectional study using data from Tromsø7. Of the 6332 participants who agreed to wear an accelerometer (see 3.2.1, Paper I), 4040 completed both the leisure time and occupational time SGPALS (39), 5902 completed the Physical Activity Frequency, Intensity, and Duration (PAFID) questionnaire (204), 5186 and 5088 completed the IPAQ (43) week and weekend sitting question, respectively (4896 completed both). No additional inclusion/exclusion criteria were set.

2.1.2.1 Additional analyses Paper II

Additional analyses in paper II were included to examine the associations between accelerometry-measured physical activity and the SGPALS separately in the leisure time and occupational questions. Additionally, the limits of agreement between accelerometry-measured sedentary time and the IPAQ sitting question were evaluated by Bland-Altman plots (205) using uniaxial accelerometry with 1) the Hecht wear time algorithm (206) and 2) the Troiano wear time algorithm (71).

2.1.3 Paper III

Paper III was a prospective cohort study of participants attending ≥ 3 consecutive Tromsø Study surveys between the first survey of The Tromsø Study (1974, Tromsø1) and Tromsø7. If participants attended >3 surveys, the three most recent consecutive surveys were included. We included participants who provided information on physical activity from the first and the second examination, had information on sex, birth year, smoking and education at the second examination, as well as weight and height at both the second and third examinations. Exclusion criteria was set for women who were pregnant during examination 2 and/or 3.

The overall cohort comprised 11308 participants from five sub-cohorts: Tromsø 5-7 (2001-16, $n=1166$), Tromsø 4-6 (1994-2008, $n=2212$), Tromsø 3-5 (1976-2001, $n=3827$), Tromsø 2-4 (1979-1995, $n=9679$) and Tromsø 1-3 (1974-1987, $n=3570$). As some participants were included in multiple sub-cohorts, the overall cohort was not a sum of the total number in the sub-cohorts.

2.1.4 Paper IV

Paper IV was a prospective cohort study with analyses that mirrored those in paper III; participants attending ≥ 3 consecutive Tromsø Study surveys, where the three most recent consecutive surveys were included if participants attended >3 surveys. Participants were included if they provided information on physical activity during the first and the second examination, had information on sex, birth year, smoking and education at the second examination, as well as weight and height at both the second and third examinations. Exclusion criteria were set for pregnancy during examination 2 and/or 3. Additionally, we reversed our analyses to examine whether BMI changes predicted subsequent physical activity changes, using the same analytical framework.

As the leisure time SGPALS was substituted with a PAQ developed for the Cohort of Norway (207) in Tromsø4 (1994-95), sub-cohorts including Tromsø4 were not included in paper IV to preserve the strength of using the same PAQ across all surveys. Consequently, three sub-cohorts were included: Tromsø 5-7 (2001-16, n=2206), Tromsø 2-4 (1979-95, n=9691) and Tromsø 1-3 (1974-1987, n=3598). Using similar criteria as described for paper III (if attending >3 surveys, the three most recent were included), these three sub-cohorts resulted in an overall sample of 10799 participants. As some participants were included in multiple sub-cohorts, the overall cohort is not a sum of the total number in the sub-cohorts. As the leisure time SGPALS was not included in Tromsø4 (1994) and were only administrated to those <70 years in Tromsø5 (2001), the sample size for the overall cohort in the reverse analyses is lower than for the main analyses.

2.1.4.1 Additional analyses for paper III and IV

As an additional analysis to paper III and IV, the leisure time and occupational time SGPALS were combined into total physical activity. This was then examined for the joint association of leisure time and occupational time physical activity change with BMI and weight change, using similar analyses as in paper III and IV. With similar inclusion and exclusion criteria, the overall sample comprised 10571 participants, originating from the following sub-cohorts (and only included with their three most recent surveys): Tromsø 5-7 (n=1053), Tromsø 2-4 (n=9040), Tromsø 1-3 (n=478). Similarly, as with main analyses of Paper III and IV, the overall cohort is not a sum of the total number in the sub-cohorts as some participants are included in multiple sub-cohorts.

2.1.5 Paper V

Paper V was a one-step individual participant data meta-analysis of four prospective cohort studies: Tromsø7, The Healthy Ageing Initiative (HAI) 2012-19, the Norwegian National Physical Activity Survey (NNPAS) and the National Health and Nutrition Examination Survey (NHANES) 2003-06.

2.1.5.1 The Tromsø Study 2015-16

The Tromsø Study is previously described (see Paper I). We included both women and men who were ≥ 50 years at baseline. As Paper V used different accelerometry processing than Paper I, and included more confounders than in Paper I, 5822 participants had valid accelerometry data in Tromsø 7 as well as data for all covariates (sex, smoking, education, weight and height, alcohol intake, history of cardiovascular disease, cancer, and diabetes).

2.1.5.2 Healthy Ageing Initiative (HAI) 2012-2019

The HAI study is an ongoing population-based cohort study in Umeå, Sweden. Since 2012, all adults are invited to participate in the study when they turn 70 years. The primary aim of The HAI is to identify risk factors for cardiovascular disease, falls and fractures. The participation rate is currently 70%. The ActiGraph GT3X+ (ActiGraph, LLC, Pensacola, Florida, United States) accelerometers are provided to participants and used on the right hip (5, 6). In total, 4313 participants had valid accelerometry data and information on all covariates (sex, smoking, education, weight and height, alcohol intake, history of cardiovascular disease, cancer, and diabetes), and all participants met the ≥ 50 years inclusion criteria.

2.1.5.3 The Norwegian National Physical Activity Survey (NNPAS) 2008-09

The NNPAS (Norwegian name: Kartlegging av Aktivitetsnivå i Norge, KAN) is an ongoing national representative cohort study aimed at monitoring physical activity levels of Norwegians via two completed surveys (2008-09 and 2014-15) as well as one ongoing data collection (2021-22). Data were extracted from the first survey conducted in 2008-09 (8). Of the 11248 invited participants, 3485 (34%) accepted the invitation. The ActiGraph GT1M (ActiGraph, LLC, Pensacola, Florida, United States) accelerometer was used on the right hip and were sent by mail to participants. The age-span of the participants were 20-85 years (8). In total, 2171 participants were ≥ 50 years, had valid accelerometry data and information on all covariates (sex, smoking, education, weight and height, alcohol intake, history of cardiovascular disease, cancer, and diabetes).

2.1.5.4 The National Health and Nutrition Examination Survey (NHANES) 2003-06

The NHANES is an ongoing national representative survey in the United States with 19 complete surveys since inception in 1959-62. We downloaded data from the 2003-04 and 2005-06 survey (available at <https://www.cdc.gov/nchs/nhanes/>). Participants used the ActiGraph 7164 (ActiGraph, LLC, Pensacola, Florida, United States) accelerometer which was worn on the hip. Of the 4910 who wore an accelerometer, 3142 (64%) participants were ≥ 50 years, provided valid accelerometry data and information on all confounders (sex, smoking, education, weight and height, alcohol intake, history of cardiovascular disease, cancer, and diabetes).

2.2 Ethical consideration

All study cohorts included in the papers of this thesis were conducted according to the Declaration of Helsinki (208). All participants in Tromsø 4–7 (1994-2016) provided written informed consent. Participants in Tromsø 1-3 (1974-1987) provided oral consent at participation, as written informed consent was not required at the time, and they received information regarding data storage and access for future research purposes; use of these data are in the public interest, in accordance with the Personal Data Act in Norway (209). All participants in The HAI study, The NNPAS study, and The NHANES provided written informed consent. The Regional Ethical Review Board in Umeå, Sweden approved the HAI study (Ref.: 07-031M). The REK region South-East B approved the NNPAS study (Reference number: S-08046b). The National Centre for Health Statistics Research Ethics Review Board (available at: <https://www.cdc.gov/nchs/nhanes/irba98.htm>) approved the NHANES. Papers I-V were approved by REC North (Ref.: 2016/1792, update Ref. 14289, Appendix A-D).

2.3 Exposure, outcome, covariates, effect modifiers

In Paper I and II, physical activity was the outcome. In Paper III and IV, physical activity change was the exposure, and BMI change and weight change (only Paper III) the outcomes. In the reverse analyses of paper IV, the exposure was BMI change, while physical activity change was the outcome. Paper I and V used accelerometry-measured physical activity. Paper II used both accelerometry-measured and self-reported physical activity with PAQs. In Paper III and IV, physical activity was measured with a PAQ. In Paper V, accelerometry-measured physical activity and sedentary time was the exposures and mortality the outcome.

Except for Paper II, sex, age, education, smoking and BMI were included as covariates. Height was also included as a covariate in Paper I to reduce the potential influence of height on stride length, which may influence step count. In addition to the covariates included in Paper I (except height), Paper V also included alcohol intake, history of cardiovascular disease, cancer, and diabetes as covariates. In Paper III and IV, the covariates were also examined as effect modifiers.

2.3.1 Accelerometry-measured physical activity

In Paper I, II and V, physical activity was measured with accelerometry.

2.3.1.1 Paper I and II

In Tromsø7, physical activity was measured with the ActiGraph wGT3X-BT (ActiGraph, LLC, Pensacola, United States). The accelerometer was handed out in the clinic to participants and placed on the right hip. Participants were instructed to wear the device for eight consecutive days.

The wGT3X-BT accelerometer weighs 19 grams with dimensions 4.6 cm x 3.3 cm x 1.5 cm. It can be set to sample data at 30-100 Hz, has a memory capacity of 4 gigabyte, corresponding to 180 recording days. If the knot for inserting the cable to a computer is sealed, it is reported to be water resistance at 1 meter depth for 30 minutes. It measures acceleration in three axes, vertical, coronal, and sagittal planes, and can provide outputs in the vertical axis only, or as triaxial vector magnitude (VM, the square root of the sum of squared activity counts). An option for extracting raw acceleration in gravitational force is also available. The ActiGraph accelerometer excludes any acceleration that is considered too low or high to be human movements (210). The accelerometer can be set to sample in two different modes: low-frequency extension mode or normal (default) filter mode. How these filters operate were initially proprietary information (210), but are now openly available (211). The normal filter is reported to include acceleration occurring at 0.25-2.5 Hz (212), while the low frequency extension filter uses a weighting function at 0.75 Hz, with progressively lower weighting below and above 0.75 Hz (212). In all papers involving accelerometry, the normal filter was used.

In Tromsø7, a 24-hour wear protocol was used and set to record at 100 Hz. The participants returned the accelerometer in a pre-paid envelope. The raw acceleration data was thereafter downloaded using the manufacturers software (ActiLife, ActiGraph, LLC, Pensacola, Florida, United States), and further reduced to 10 second acceleration epochs. The 10-second epochs of all axes in addition to the proprietary step count were converted from agd.-files to csv.-files and were further analysed using the Quality Control and Analysis Tool, a software developed in Matlab (The Math Works, Inc., Natick, Massachusetts, United States). The 10-second epochs were summed to 60 seconds, and checked for non-wear time with an algorithm reported by Hecht *et al.* (206); each minute was classified as wear time if two of the three following criteria were met: 1) if VM per minute was >5; 2) Of the following 20 minutes, is at least 1 minute >5 VM per minute; 3) Of the preceding 20 minutes, is at least 1 minute >5 VM per minute.

If only one, or none, of the wear time criteria were met, the minute was classified as non-wear time. Following visual inspection of diagrams for each day of 30 random participants, it appeared that the non-wear time algorithm also excluded sleep, therefore, we also defined non-wear time as sleep. Valid wear time was set to be a minimum of four days with 10 hours of wear time (45, 213)

We used the triaxial VM counts per minute (CPM) and uniaxial (vertical axis) CPM, divided by valid wear days, as total physical activity, which is previously demonstrated as an appropriate estimate of total volume of PAEE against doubly labelled water (~60% explained variance) (214). We classified absolute physical activity intensity in acceleration thresholds according to Sasaki *et al.* (215) for VM CPM, and according to Freedson *et al.* (216) for uniaxial CPM. We classified sedentary time according to Treuth *et al.* (217), which was originally developed for adolescent girls but later adopted for use in adults (218), for uniaxial CPM, and according to Peterson *et al.* (219) for VM CPM. The cut-offs for intensity are presented in Table 2.1

Table 2.1. *The acceleration thresholds to classify physical activity intensity in paper I and II.*

Intensity	METs	Oxygen uptake (ml·kg⁻¹·min⁻¹)	Uniaxial (CPM)	Triaxial (VM CPM)
Sedentary	<1.5	<5.25	<100	<150
Light	1.5-2.9	5.25-10.49	100-1951	150-2689
Moderate	3.0-5.9	10.5-20.9	1951-5724	2690-6166
Vigorous	6.0-8.9	21.0-31.4	5725-9498	6167-9641
Very Vigorous	≥9.0	≥31.5	≥9499	≥9642

METs and oxygen uptake representing absolute intensities are derived from Ainsworth et al. (220). The uniaxial CPM cut-offs are derived from Freedson et al. (216) and Treuth et al. (217). The triaxial VM CPM are derived from Sasaki et al. (215) and Peterson et al. (219). MET=Metabolic equivalent of task, CPM=counts per minute, VM=vector magnitude.

Minutes in different intensities were extracted as minutes per day of valid wear time. Additionally, meeting the lower-limit physical activity guideline of 150 minutes of MVPA per week (31) was defined as those accumulating ≥22 minutes of MVPA per day (150 minutes divided by seven days).

2.3.1.2 Paper V

For the HAI and NNPAS, the individual participant data were sent by encrypted electronic mails with password protection (password sent by text message) from the respective cohort technician or researcher. For the NHANES, all data were downloaded (available at

<https://wwwn.cdc.gov/nchs/nhanes/>). Participants from all cohort studies used ActiGraph accelerometers (ActiGraph, LLC, Pensacola, FL United States) on their hip, but used different generations of the device; AM-7164 (NHANES), GT1M (NNPAS), GT3X+ (HAI), GT3X+-BT (Tromsø7). The AM-7164 has a bimorph piezoelectric cantilever beam acceleration sensor, with one end attached to an electronic circuit board (221). The analogue-electric acceleration is band-pass filtered and digitalized using a 8-bit analogue-digital converter, and expressed as acceleration counts (221). The next generations, GT1M, GT3X+ and GT3X+-BT, uses a dual axis microelectromechanical accelerometer, which detects static (force gravity) and dynamic acceleration. The acceleration is detected with a 12-bit analogue-digital converter, filtered to only include acceleration between 0.25-2.5 Hz (221).

The accelerometers were handed out in the clinic in Tromsø7, HAI and NHANES, while they were sent by mail in the NNPAS, and participants were instructed to wear it on their hip. The HAI, NNPAS and NHANES used a seven-day wear protocol and were instructed to wear the device while being awake and remove it for sleeping and water activities (71, 222-224), while Tromsø7 used a 24-hour wear protocol (also while sleeping but not water activities). Therefore, all data between 00:00 and 06:00 from all study cohorts were removed from further analyses, as also previously applied in the NNPAS (223). As the AM-7164 and GT1M records per 60-seconds epochs from the vertical axis, we reduced raw vertical acceleration units (gravitational force) from the GT3X+ (HAI, sampled at 30 Hz) and wGT3X-BT (Tromsø 7, sampled at 100 Hz) to 60 second epochs using the ActiLife Software (ActiGraph, LLC, Pensacola, FL United States). The data were further analysed using the KineSoft software (KineSoft version 3.3.80, Loughborough, United Kingdom). Non-wear time was defined as 60 consecutive minutes of zero acceleration with a 2-minute spike-allowance (Troiano-algorithm) (71). Wear time was defined as four days of at least 10 hours per day (213).

2.3.2 Self-reported physical activity

In Paper II, physical activity was measured with two PAQs: the SGPALS (39) and the PAFID questionnaire. Sedentary time was measured with the IPAQ sitting question (43). In Paper III, the occupational time SGPALS (39) was used. In Paper IV, the leisure time SGPALS (39) was used.

2.3.2.1 Saltin-Grimby Physical Activity Level Scale

The SGPALS was first presented in 1968 by Saltin and Grimby and was developed by Lindholm, Lundgren and Saltin (39). The SGPALS asks participants to rank their physical activity in four hierarchical and mutual exclusive ranks, for both their occupation and leisure time. The Tromsø Study surveys have included a slightly modified version of the original SGPALS (see supplementary materials of Paper III). The SGPALS, as used in The Tromsø Study surveys, is presented in Table 2.2.

Table 2.2. *The modified SGPALS used in the Tromsø Study surveys.*

Occupational Physical Activity			
Question:			
<i>Tromsø 1-3: Type of work: During the last year, have you had:</i>			
<i>Tromsø 4-6: If you have paid or unpaid work, which statement describes your work best?</i>			
1	2	3	4
<i>Mostly sedentary work? (e.g., office work, watchmaker, light manual work)</i>	<i>Work that requires a lot of walking? (e.g., shop assistant, light industrial work, teaching)</i>	<i>Work that requires a lot of walking and lifting? (e.g., postman, heavy industrial work, construction)</i>	<i>Heavy manual labour? (e.g., forestry, heavy farm work, heavy construction)</i>
Leisure time Physical Activity			
Question:			
<i>Exercise and physical exertion in leisure time. If your activity varies much, for example between summer and winter, then give an average. The question refers only to the last twelve months.</i>			
1	2	3	4
<i>Reading, watching TV, or other sedentary activity?</i>	<i>Walking, cycling, or other forms of exercise at least 4 hours a week? Include walking or cycling to workplace, Sunday stroll/walk etc</i>	<i>Participation in recreational sports, heavy gardening, etc.? (note: duration of activity at least 4 hours a week).</i>	<i>Participation in hard training or sports competitions, regularly several times a week?</i>

SGPALS=Saltin-Grimby Physical Activity Scale.

In Paper II, we combined the occupational and leisure time SGPALS into total physical activity, where participants were classified as inactive, moderately inactive, moderately active, and active according to Wareham *et al.* (225) with some modifications. We also created PAL scores of the different combinations of the occupational and leisure time SGPALS, according to Johansson and Westerberp (226), with some minor modifications; for the five answer alternatives for leisure time, we disregarded the “moderate active leisure time group”. The combinations of the combined occupational and leisure time SGPALS are found in Table 2.3.

Table 2.3. *The combined occupational and leisure time SGPALS.*

Intensity	Light Leisure	Moderate Leisure	Vigorous	Very Vigorous
Light Occupation	Inactive (PAL: 1.4)	Moderately inactive (PAL: 1.5)	Active (PAL: 1.7)	Active (PAL: 1.9)
Moderate Occupation	Moderately inactive (PAL: 1.5)	Moderately active (PAL: 1.6)	Active (PAL: 1.8)	Active (PAL: 2.0)
Heavy Occupation	Moderately active (PAL: 1.6)	Active (PAL: 1.7)	Active (PAL: 1.9)	Active (PAL: 2.2)
Very Heavy Occupation	Active (PAL: 1.7)	Active (PAL: 1.8)	Active (PAL: 2.1)	Active (PAL: 2.3)

SGPALS=Saltin-Grimby Physical Activity Scale. PAL=physical activity level according to Johansson and Westerterp (226).

For Paper III and IV, change in occupational and leisure time physical activity, respectively, was computed as follows; (1) *Persistently Inactive* (reporting rank 1 at examination 1 and 2); (2) *Persistently Active* (rank ≥ 2 at examination 1 and 2); (3) *Active to Inactive* (rank ≥ 2 at examination 1 and rank 1 at examination 2); and (4) *Inactive to Active* (rank 1 at examination 1 and rank ≥ 2 at examination 2). For sensitivity analyses, six groups were created; the groups as described above in addition to *Active but decreasing* (rank 4 or 3 \rightarrow 3 or 2), *Active and increasing* (rank 2 or 3 \rightarrow 3 or 4).

2.3.2.2 The Frequency, Intensity and Duration Questionnaire

The PAFID is a PAQ designed at inception of the HUNT study (Norwegian: Helseundersøkelsen I Nord-Trøndelag) in 1984-86 (204). This PAQ includes three questions about exercise: 1) frequency; 2) intensity; and 3) duration. From these three questions, an index reflecting METs was created by multiplying intensity (METs) by duration (minutes) by frequency (times per week) given the following formula: (intensity x duration) x frequency. We also grouped MET-hours per week into quartiles to assess the ranking ability of the PAFID. The PAFID questionnaire is presented in Table 2.4.

Table 2.4. *The PAFID questionnaire.*

Frequency (days)	Intensity (METs)	Duration (minutes)
<i>How frequently do you exercise? With exercise, we mean walking, cross-country skiing, swimming or other exercise/sports.</i>	<i>On average, how hard is the exercise?</i>	<i>On average, how long do you exercise?</i>
Never (0)	I take it easy without breaking into a sweat or losing my breath (3 METs)	<15 minutes (10 minutes)
Less than once a week (0.5)	I push myself so hard that I break into a sweat and lose my breath (6 METs)	15-29 minutes (22.5 minutes)
Once a week (1)	I push myself to near exhaustion (9 METs)	30-60 minutes (45 minutes)
2-3 times per week (2.5)	N/A	>60 minutes (60 minutes)
Almost every day (5)	N/A	N/A

PAFID= Physical Activity Frequency, Intensity, and Duration. MET=Metabolic Equivalent of Task. Brackets indicate numbers in the formula for calculating MET-hours per week: (intensity x duration) x frequency. N/A = not applicable.

2.3.2.3 The International Physical Activity Questionnaire Sitting question

The IPAQ sitting question (43) was included in Tromsø7, which asked participants the following question: “*During the last seven days, how much time did you usually spend sitting on a week day?*”, with respondents writing their amount of sitting in hours per day. This question was also asked for weekend days. We combined the IPAQ week and weekend sitting hours per day by averaging the two responses.

2.3.3 Body mass index and weight

In Paper, I, II, III and IV, body weight and height were measured, and BMI was calculated as body mass divided by height in metres, squared (kg/m^2). In Paper III and IV, we used fixed height at examination 2 (examination 1 in the reverse analyses of Paper IV) to reduce the influence of possible height loss at follow up. In Paper V, all study cohorts had measured weight, except NNPAS that had self-reported weight and height. When BMI was included as a covariate in Paper I and V, we grouped BMI as normal weight ($<25 \text{ kg/m}^2$), overweight ($25\text{-}29 \text{ kg/m}^2$) and obese ($\geq 30 \text{ kg/m}^2$), as this categorical variable was used to assess the effect modification of BMI. In paper IV, continuous BMI change was used as the exposure in the reverse analysis. In Paper III and IV, continuous baseline BMI (examination 2) was used as a covariate.

2.3.4 Mortality

In Paper V, mortality was the outcome. Mortality was linked with the Norwegian (Tromsø Study and NNPAS) and Swedish (HAI) cause of death registries, and the United States National Death Index (NHANES), through 2020 (Tromsø Study), 2017 (NNPAS), 2019 (HAI) and 2015 (NHANES). All registries are consistently found to provide 100% completeness of registered deaths compared with global vital statistics (227-229).

2.3.5 Covariates

All covariates were retrieved from questionnaires, except for age and sex for all cohorts, and education in the HAI, which were retrieved from population registries. External links to all questionnaires used in the Papers are found in Appendix E. Education was grouped as primary (≤ 12 years), high school (13-15 years), university < 4 years and university ≥ 4 years in Paper I, II, III and IV. In order to harmonize the educational systems of the respective countries (Norway, Sweden and the United States) in Paper V, education was grouped as in Paper I-IV for Tromsø7 and NNPAS, but grouped as (≤ 12 years), high school (13-15 years), university < 3 years and university ≥ 3 years in the HAI, and as (≤ 12 years), high school (13-15 years), university any year in the NHANES. Smoking was grouped as current-, previous-, or never-smoker in all papers. Alcohol was grouped as units per week in Paper V. In Paper V, diseases were self-reported in Tromsø7, NNPAS and NHANES, while they were retrieved from national registries for cancer and cardiovascular disease in the HAI cohort.

2.3.6 Availability of included questionnaire data in this thesis

2.3.7 Estimated cardiorespiratory fitness

Cardiorespiratory fitness was used to estimate the relative intensity that participants in Paper I would perform physical activity, from different absolute intensities. Cardiorespiratory fitness was estimated using a non-exercise prediction model that was based on self-reported physical activity, resting heart rate, age, sex and waist circumference (WC), developed by Nes *et al.* (230). The PAQ used by Nes *et al.* (230) was the PAFID (204). To use this PAQ to estimate cardiorespiratory fitness, Nes *et al.* (230) created a physical activity index from frequency, intensity and duration, with greater weighting applied to intensity than the original index score by Kurtze *et al.* (204). Resting heart rate was measured in a seated position following five minutes rest, where we used the mean of recording 2 and 3 (out of total three recordings). The following formulas were used to estimate cardiorespiratory fitness; men: $100.27 - (0.296 \times \text{age})$

- (0.369 x WC) - (0.155 x resting heart rate) + (0.226 x physical activity-index), women: 74.74 - (0.247 x age) - (0.259 x WC) - (0.114 x resting heart rate) + (0.198 x physical activity index) (230). This prediction is reported to explain 61% of the variance in measured cardiorespiratory fitness using indirect calorimetry in a test to exhaustion (230). As this analysis included resting heart rate and WC, the accelerometry sample in Tromsø7 for this analysis (N=5745) is different than the comparison of accelerometry and the PAFID in Paper II (N=5902).

2.3.8 Statistical analyses

2.3.8.1 Paper I

Analyses of covariance (ANCOVA) were used to examine the association between accelerometry-measured physical activity (VM CPM, uniaxial CPM, minutes in sedentary, light and MVPA from both triaxial and uniaxial acceleration) and sex, 10-year age-groups, BMI groups, and educational level, adjusted for sex, age, BMI, education, smoking and height. Paired sample t-tests examined differences between triaxial and uniaxial physical activity estimates. Independent sample t-tests examined differences in age, weight, height, and BMI between the total Tromsø7 sample (N=20485) and the Tromsø7 accelerometry sample (n=5918). Pearson chi square tests examined differences in distribution of BMI groups, educational level, and smoking habits between those who declined the invitation to wear an accelerometer, and those who accepted the invitation. The Statistical Package for Social Sciences (SPSS, version 25, International Business Machines Corporation, United States) was used to perform the statistical analyses with alpha set to 0.05. The descriptive accelerometry estimates of physical activity are shown as unadjusted mean \pm standard deviation.

2.3.8.2 Paper II

Pearson correlations were used to examine the associations between self-reported physical activity as a continuous scale (SGPALS: PAL score, PAFID: MET-hours per week, IPAQ: hours per day) and accelerometry-measured physical activity (VM CPM, minutes in sedentary, light and MVPA as 10-minute bouts and non-bouts minutes per day). A coefficient of 0.00 to 0.09, 0.10 to 0.39, 0.40 to 0.69 and ≥ 0.70 was considered a negligible, weak, moderate and strong correlation, respectively (231). Analyses of variance (ANOVA) were used to examine the association between self-reported physical activity as categorical ranks (SGPALS: inactive, moderately inactive, moderately active, and active; PAFID: quartiles of MET-hours per week; IPAQ: quartiles of hours per day) and accelerometry-measured physical activity. All analyses

were performed as overall, and stratified by sex, 10-year age groups, BMI groups and education. A Bland-Altman plot (205) was created to examine limits of agreement between accelerometry-measured sedentary time and the IPAQ sitting question. A one-sample t-test was performed to examine whether the mean difference between accelerometry-measured and self-reported sedentary time was different from 0, which was followed up by a linear regression to examine proportional bias in the mean and difference of accelerometry-measured and self-reported sedentary time.

In the additional analyses, Pearson correlations and ANOVAs were used to examine the associations between accelerometry-measured physical activity and leisure time and occupational SGPALS separately. Limits of agreement between accelerometry-measured sedentary time and the IPAQ sitting question were examined by Bland-Altman plots (205) using uniaxial CPM with: 1) the Hecht wear time algorithm (206), and; 2) the Troiano wear time algorithm (71). One-sample t-tests were used to examine whether the mean difference between accelerometry-measured and self-reported sedentary time was different from 0 and linear regressions were used to examine proportional bias in the Bland-Altman plots. The SPSS (version 25, International Business Machines Corporation, Armonk, New York, USA) was used to perform the statistical analyses with alpha set to 0.05.

2.3.8.3 Paper III and IV

Statistical analyses in Paper III and IV were similar. Paired sample t-tests were used to examine whether participants changed BMI and weight from examination 2 to 3. Analyses of covariance examined whether physical activity changes from examination 1 to 2 predicted BMI or weight changes from examination 2 to 3; both overall, and stratified by sex, birth year, smoking, education, and leisure-time (Paper III) or occupational (Paper IV) physical activity change from examination 1 to 2, with adjustment for sex, birth year, smoking, education and BMI or weight at examination 2. We examined interaction effects between occupational (paper III) and leisure (paper IV) time physical activity change and potential effect modifiers (sex, birth year, smoking, education, and leisure time (Paper III) or occupational (Paper IV) physical activity change from examination 1 to 2 in the overall cohort. For sensitivity analyses, we computed occupational (Paper III) and leisure time (Paper IV) physical activity change into six groups: (1) *Persistently Inactive*, (2) *Persistently Active*, (3) *active but decreasing* (rank 4 or 3→3 or 2), (4) *active and increasing* (rank 2 or 3→3 or 4), (5) *Active to Inactive* and (6) *Inactive to Active*. Data are shown as mean and 95% CIs unless otherwise is stated.

For the reverse analyses in Paper IV, multinomial logistic regressions were used to estimate the odds ratio (OR) with 95% CI for changing leisure time physical activity from examination 2 to 3 per unit BMI change from examination 1 to 2, adjusted for sex, birth year, smoking and education at examination 2. *Persistently Active* was set as reference category. The analyses were only performed in the overall sample ($n = 4385$) and were stratified by sex, birth year, smoking, education, and occupational physical activity change. Interaction effects were examined between BMI change and potential effect modifiers (sex, birth year, smoking, education and BMI at examination 2, and occupational physical activity change from examination 1 to 2).

The additional analyses of Paper III and IV, examining whether combined occupational and leisure time physical activity change predicted subsequent BMI and weight change used similar statistical analysis as Paper III and IV: ANCOVA adjusted for sex, age, education, smoking and BMI/weight at examination 2. The SPSS (version 26, International Business Machines Corporation, United States) was used for the statistical analyses with alpha set to 0.05.

2.3.8.4 Paper V

To avoid influence of extreme values in the accelerometry data in Paper V, values outside the 1st and 99th percentile of their distribution were winsorized to their respective 1st and 99th percentile values. First, restricted cubic splines Cox regressions were used with mutual adjustment for physical activity (light physical activity and MVPA) and sedentary time, according to previous studies (35), which were also adjusted for sex, education, BMI, smoking, alcohol intake, study cohort, history of cardiovascular disease, cancer, diabetes, and age (in years) as timescale (232). As NHANES does not provide information on attendance or death date (only follow-up time to censoring, death, or study end), we set the attendance date to 01.01.2004 (wave 2003-04) and 01.01.2006 (wave 2005-06), and calculated death date, emigration or censoring by addition of follow-up time. Participants' study entry was set two years after attendance (left truncation) and followed to death, censoring (emigration), or study end, whichever came first. We found no two-way interactions between covariates and physical activity measures or sedentary time in the multivariable models (all $p > 0.07$), whereas we observed interactions between all physical activity variables and sedentary time in continuous forms ($p < 0.001$). To examine effect modification of MVPA in associations between sedentary time and mortality risk, we split MVPA by lower-limit WHO-guidelines (22 MVPA min·day⁻¹

¹). Due to no international recommendations quantifying restrictions of sedentary time (31), we examined effect modification by sedentary time in association between light- and total physical activity, and MVPA, and mortality by separate analyses split by full-sample median sedentary time into “low” (<10.5 hours·day⁻¹) and “high” (≥10.5 hours·day⁻¹) sedentary participants. Knots in cubic splines were placed at the 5th, 50th and 95th percentiles of the distributions and within effect-modifier strata (*e.g.*, dose-response association for MVPA and knot placements estimated separately within low and high sedentary time) in the effect modification models. Wald tests confirmed departure from linearity in all models (all $p < 0.001$). Changing knot locations or increasing knot numbers did not change interpretations of the spline slopes.

The joint associations of MVPA and sedentary time (both in continuous form) on mortality risk were modelled using fractional polynomials (due to non-linear associations in spline models) to identify the best fit Cox regression (determined by Akaike Information Criterion). The best fitting model included $\log(\text{MVPA})$ and “sedentary time raised to power of 3 (sedentary time³)” and “ $\log(\text{sedentary time}) \times \text{sedentary time}^3$ ”. This model was different from the model including linear continuous interaction of “MVPA \times sedentary time” and their two-way cross products (likelihood-ratio= $p < 0.001$). As light physical activity and sedentary time were highly correlated ($r = -0.96$) and total physical activity included sedentary time (<100 CPM), we did not examine the combined association of light- or total physical activity with sedentary time.

We also applied these sensitivity analyses: 1) restricting 5 years follow-up after study attendance; 2) median split sedentary time by Norwegian and Swedish cohorts (Tromsø, HAI and NNPAS) and the NHANES; and 3) calibrated individual-level summary data in the NHANES (CPM \times 0.92, light physical activity (min·day⁻¹) \times 0.88, and sedentary time (hours·day⁻¹) \times 1.02) (233).

Schoenfeld’s residuals tests confirmed no violated proportional hazards for all covariates (all $p \geq 0.08$), except education in low sedentary participants ($p = 0.02$). However, considering all Schoenfeld’s residuals tests performed for all covariates, we suspect this to be a type-2 error. As the log-log survival plot of education displayed reasonable parallel lines (Figure 2.1), indicating no violated proportional hazards, we performed analyses without stratified baseline hazards for education in low sedentary participants. Statistical analyses were performed using Stata version 17.0 (StataCorp LLC, Texas, United States) with alpha set to 0.05.

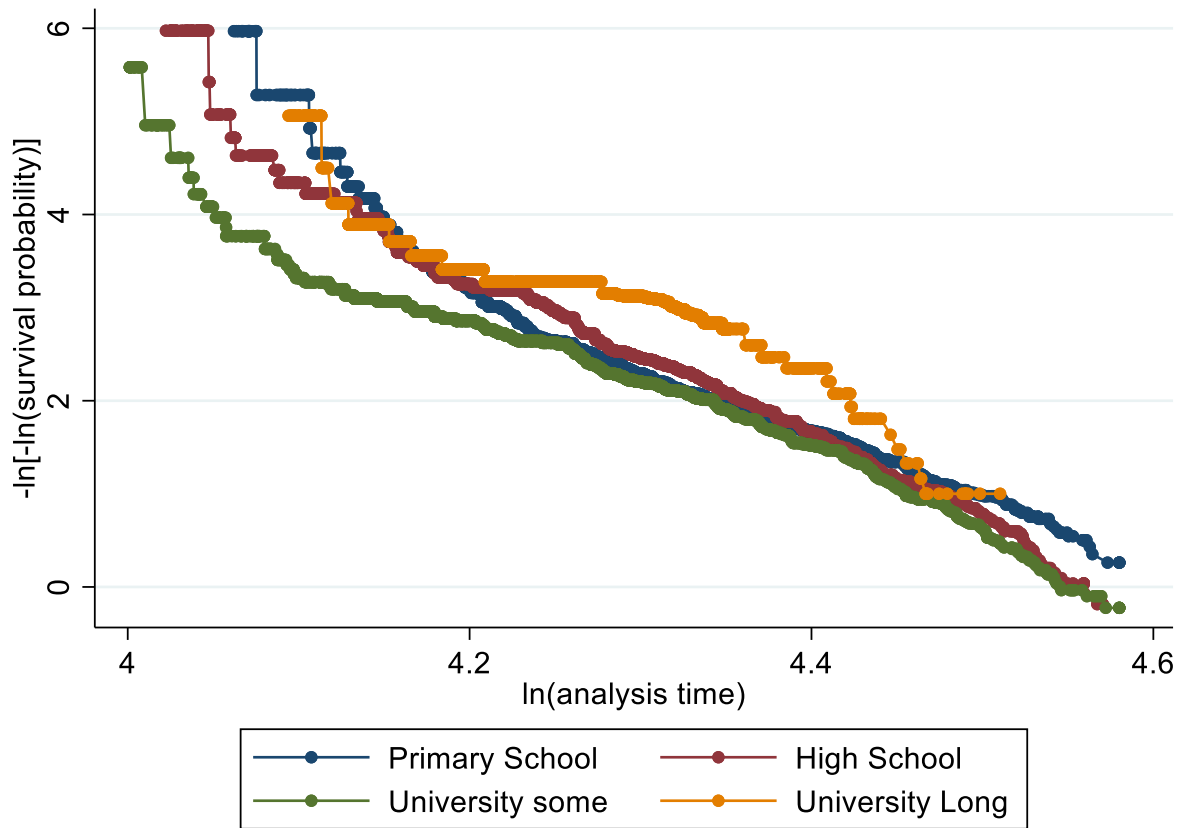


Figure 2.1. Log-log survival plot of education in low sedentary participants (<10.5 hours·day⁻¹). Adjusted for MVPA, alcohol, BMI, cohort, smoking, sex, CVD, cancer, diabetes and age (timescale). The Schoenfeld's residuals test indicated a violated proportional hazard at $p=0.02$. MVPA=moderate and vigorous physical activity, BMI=body mass index, CVD=cardiovascular disease.

3 Results

3.1 Paper I

When examining prevalence estimates of physical activity using triaxial data, 22% (95%CI: 21-23%) met the 2010 WHO guidelines of 150 minutes of MVPA per week in at least 10-minute continuous bouts. When counting every minute of MVPA according to 2020 WHO guidelines, 70 % (95%CI: 69-71%) met the guidelines. There were no sex differences in total physical activity or in sedentary time, but women accumulated more light physical activity compared with men ($p<0.001$) and men more MVPA than women ($p<0.001$). Physical activity was lower by 10-year age groups (all $p<0.0001$), higher by higher educational level, and lower by higher BMI groups (all $p<0.0001$). Although statistically different in some stratified analyses (p -range=0.001-0.02), sedentary time were generally stable across age groups, educational level, and BMI groups.

Triaxial data displayed higher physical activity- and lower sedentary estimates, than uniaxial data. These differences were most profound in sedentary time and light physical activity, where approximately 100 less sedentary minutes and 90 more light physical activity minutes were observed in triaxial compared with uniaxial data. There were approximately 10 more minutes of non-bouted and 2 more minutes of 10-minute bouted MVPA in triaxial than uniaxial data. In uniaxial data, 18% (95%CI: 17-18%) met the 2010 WHO guidelines, and 55% (95%CI: 53-56%) met the 2020 WHO guidelines.

3.1.1 Additional analysis paper I: what relative intensity participants in paper I would be performing different absolute intensity of physical activity in METs.

Table 3.1 presents the distribution of the corresponding estimated relative intensity for absolute light, moderate, vigorous, and very vigorous intensity. Figure 3.1 displays the association between estimated cardiorespiratory fitness and percentage of relative intensity at moderate absolute intensity (3.0 METs/10.5 ml·kg⁻¹·min⁻¹) for the accelerometer sample. If performing physical activity at light absolute intensity (1.5 METs/5.25 ml·kg⁻¹·min⁻¹), it would correspond to a mean relative intensity of 16-17% of estimated maximal oxygen uptake, with the upper limit for the least fit at 67%. The corresponding mean relative intensity for absolute moderate (3.0 METs/10.5 ml·kg⁻¹·min⁻¹), vigorous (6 METs/21 ml·kg⁻¹·min⁻¹) and very vigorous (9 METs/31.5 ml·kg⁻¹·min⁻¹) intensity were 32-34%, 64-68% and 96-102% of maximal oxygen

uptake. The least fit would be performing 134%, 267% and 401% of maximal oxygen uptake at absolute moderate, vigorous, and very vigorous absolute intensity, respectively.

Table 3.1. Relative intensity of estimated cardiorespiratory fitness at different absolute intensity. The Tromsø Study 2015-16.

Absolute physical activity intensity	Light	Moderate	Vigorous	Very Vigorous
METs (ml·kg ⁻¹ ·min ⁻¹)	1.5 (5.25)	3 (10.5)	6 (21)	9 (31.5)
Relative physical activity intensity				
<i>Tromsø7 Total sample (N=20298)</i>				
Mean (%)	16.0	31.9	63.8	95.8
95%CI (%)	15.9-16.1	31.7-32.1	63.4-64.3	95.1-96.4
<i>Distribution</i>				
25 th percentile (%)	17.9	35.7	71.4	107.7
Median (%)	15.3	30.7	61.4	92.1
75 th percentile (%)	13.4	26.8	53.5	80.2
Min-max (%)	8.3-66.8	16.6-133.6	33.2-267.3	49.8-400.9
<i>Tromsø 7Accelerometry sample (N=5745)</i>				
Mean (%)	16.9	33.8	67.7	101.5
95%CI (%)	16.8-17.0	33.6-34.0	67.3-68.1	100.9-102.1
<i>Distribution</i>				
25 th percentile (%)	19.0	37.9	75.8	113.7
Median (%)	16.4	32.7	65.4	98.2
75 th percentile (%)	14.2	28.4	56.9	85.3
Min-max (%)	8.9-66.8	17.9-133.6	35.7-267.3	53.5-400.9

Data is shown as mean, CI, 25th, median, 75th and minimum and maximum of percentage of estimated cardiorespiratory fitness. CI=confidence interval.

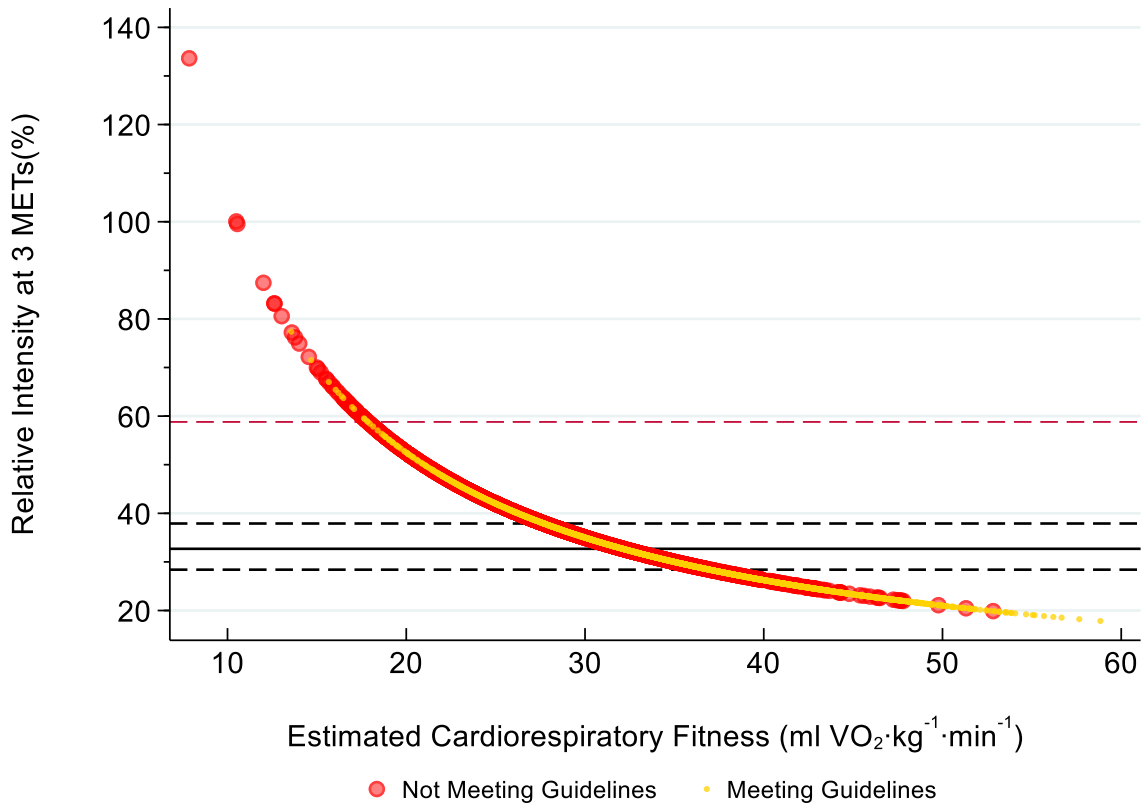


Figure 3.1. Scatter plot of estimated cardiorespiratory fitness and relative intensity at absolute moderate intensity for the Tromsø7 accelerometry sample.

Red and yellow dots are those not meeting and meeting current lower-limit physical activity guidelines of 150 minutes per week of MVPA, respectively. Solid horizontal line is the median (30.7%), and dashed lines are the 25th (35.7%) and 75th (26.8%) percentile of the distribution of relative intensity. The red dashed line represents the 1th (58.8%) percentile of the distribution. MET=metabolic equivalent of tasks, VO₂=oxygen uptake, MVPA=moderate and vigorous physical activity.

3.2 Paper II

There were weak correlations between PAL scores from the SGPALS and accelerometry-measured physical activity (range $r=0.16-0.32$). Accelerometry-measured physical activity was higher by higher SGPALS rank (all $p_{\text{trend}} < 0.001$), where steps per day and non-bouted and 10-minute bouted MVPA doubled from rank 1 to rank 4 (steps·day⁻¹: rank 1-4: 4900-8291, non-bouted MVPA: 23-53 min·day⁻¹, bouted MVPA: 4-17.6 min·day⁻¹).

MET-hours per week from the PAFID showed weak to moderate correlations with total physical activity (VM CPM, $r=0.34$), non-bouted MVPA ($r=0.39$), bouted MVPA ($r=0.44$) and steps per day ($r=0.43$) but correlated negligibly with light physical activity ($r=0.06$).

Accelerometry-measured physical activity was higher by higher quartiles of MET-hours per week (all $p_{\text{trend}} < 0.001$), where steps per day and non-bouted and bouted MVPA were doubled from quartile 1 to 4 (steps·day⁻¹: quartile 1-4: 5207-8559, non-bouted MVPA: 25-55 min·day⁻¹, bouted MVPA: 4-24 min·day⁻¹).

There were weak correlations between accelerometry-measured and self-reported sedentary hours in the IPAQ (weekdays: $r=0.22$, weekend days: $r=0.15$, combined: $r=0.22$). From quartile 1 to 4 of self-reported sedentary hours, there was a one-hour difference in accelerometry-measured sedentary time (9-10 hours·day⁻¹).

3.2.1 Additional analyses paper II: the separate associations between occupational and leisure time SGPALS and accelerometry-measured physical activity

The associations between the leisure time SGPALS and accelerometry-measured physical activity are presented in Table 3.2. The leisure time SGPALS correlated weakly with all accelerometry measures (VM CPM: $r=0.27$, $p < 0.001$, steps per day: $r=0.31$, $p < 0.001$, light physical activity: $r=0.13$, $p < 0.001$, MVPA: $r=0.27$, $p < 0.001$). There were differences in all accelerometry estimates between the leisure time SGPALS ranks (all $p < 0.001$, Table 4.3).

Table 3.2. The associations between leisure time SGPALS and accelerometry estimates.

	Leisure time SGPALS ranks				
	Light (n=745)	Moderate (n=3610)	Hard (n=1384)	Very (n=119)	Hard
VM CPM* α	423.8 \pm 5.9	535.3 \pm 2.8	591.8 \pm 4.8	677.0 \pm 18.6	
Steps per day* α	4895.5 \pm 84.0	7001.8 \pm 46.1	7934.6 \pm 79.7	9424.0 \pm 317.2	
Light (min·day ⁻¹)* α	369.2 \pm 3.5	404.7 \pm 1.5	412.2 \pm 2.2	418.3 \pm 6.5	
MVPA (min·day ⁻¹)* α	24.2 \pm 0.9	40.6 \pm 0.5	51.0 \pm 0.8	63.1 \pm 3.2	

Data are shown as mean \pm standard error of the mean. *Significant differences between SGPALS ranks, $p < 0.001$. α Significant trend by increasing SGPALS rank, $p < 0.001$. SGPALS=Saltin-Grimby Physical Activity Level Scale, VM CPM=vector magnitude counts per minute, MVPA=moderate and vigorous physical activity.

The associations between the occupational SGPALS and accelerometry-measured physical activity are presented in Table 3.3. The occupational SGPALS showed negligible correlations with MVPA ($r=0.08$, $p < 0.001$) and steps per day ($r=0.08$, $p < 0.001$) and weak correlations with light physical activity ($r=0.27$, $p < 0.001$) and VM CPM ($r=0.19$, $p < 0.001$). There were differences in all accelerometry estimates between the occupational SGPALS ranks (all $p < 0.001$, Table 4.3).

Table 3.3. The associations between occupational SGPALS and accelerometry estimates.

	Occupational SGPALS ranks			
	Light (n=2279)	Moderate (n=1027)	Heavy (n=664)	Very Heavy (n=110)
VM CPM* α	529.0 \pm 3.5	582.1 \pm 5.3	617.5 \pm 7.1	610.4 \pm 20.9
Steps per day* α	7190.7 \pm 60.7	7732.0 \pm 88.8	7886.2 \pm 109.6	7325.8 \pm 266.9
Light (min·day ⁻¹)* α	386.3 \pm 1.7	432.2 \pm 2.8	446.3 \pm 3.4	440.0 \pm 8.4
MVPA (min·day ⁻¹)* α	43.2 \pm 0.6	45.3 \pm 0.9	49.6 \pm 1.3	51.7 \pm 3.7

Data are shown as mean \pm standard error of the mean. *Significant differences between SGPALS ranks, $p < 0.001$. α Significant trend by increasing SGPALS rank, $p < 0.001$. SGPALS=Saltin-Grimby Physical Activity Level Scale, VM CPM=vector magnitude counts per minute, MVPA=moderate and vigorous physical activity.

The Bland Altman plot of the difference and mean of triaxial accelerometry measured sedentary time and self-reported sedentary time is illustrated in Figure 3.2. The mean difference between triaxial accelerometry- and self-reported sedentary time was different from 0 ($p < 0.001$), where the difference decreased by -0.75 hours (95% CI: -0.80 to -0.72, $p < 0.001$) for every mean hour increase in accelerometry-measured and self-reported sedentary time.

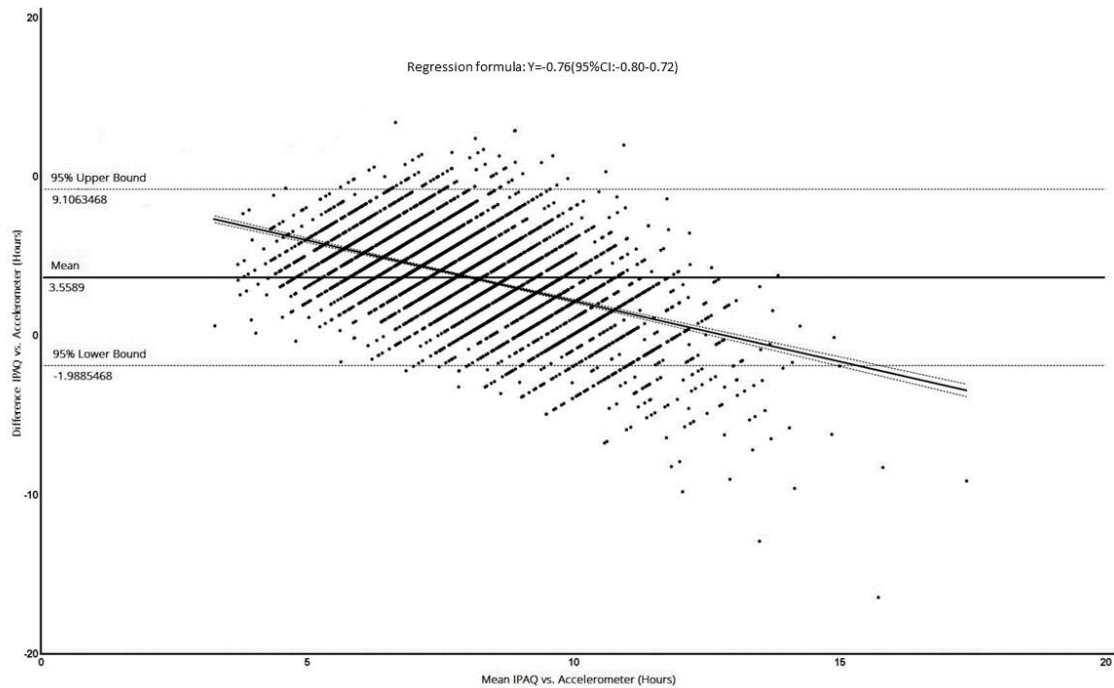


Figure 3.2. Bland-Altman plot of triaxial accelerometry measured sedentary time versus self-reported sedentary time.

Accelerometry sedentary time derived from Paterson *et al.* (219) at <150 vector magnitude counts per minute. Non-wear time algorithm derived from Hecht *et al.* (206). The trend line represents the regression of the unstandardized beta-coefficient ($B = -0.76$) with 95%CI (-0.80 to -0.72). Data are shown in hours per day. IPAQ=International Physical Activity Questionnaire. This figure is also found under supplementary materials in paper II.

The two additional Bland Altman plots of differences and means between uniaxial accelerometry-measured and self-reported sedentary time are illustrated in Figure 3.3 and 3.4, using the Hecht *et al.* (206) and Troiano *et al.* (71) non-wear time algorithm, respectively. Both mean differences between uniaxial accelerometry and self-reported sedentary time were different from 0 (both $p < 0.001$). For every mean hour increase in accelerometry-measured and self-reported sedentary time, the difference decreased by -0.80 hours (95%CI: -0.84 to -0.75, $p < 0.001$) when using the Hecht algorithm (206) and by -1.04 (95%CI: -1.07 to -1.00, $p < 0.001$) when using the Troiano algorithm (71).

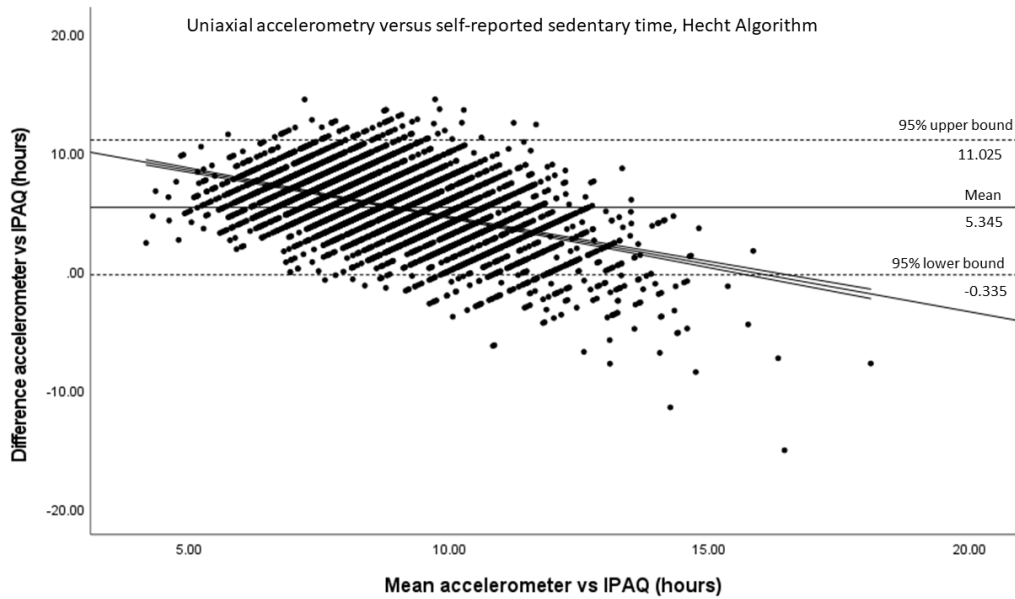


Figure 3.3. Bland-Altman plot of uniaxial accelerometry measured sedentary time versus self-reported sedentary time, using the Hecht et al. (217) wear time algorithm. Accelerometry-measured sedentary time is derived from Treuth et al. at <100 counts per minute. Data are shown in hours per day. The trend line represents the regression of the unstandardized beta-coefficient ($B=-0.80$) with 95%CI (-0.84 to -0.75). IPAQ=International Physical Activity Questionnaire, CI=confidence interval.

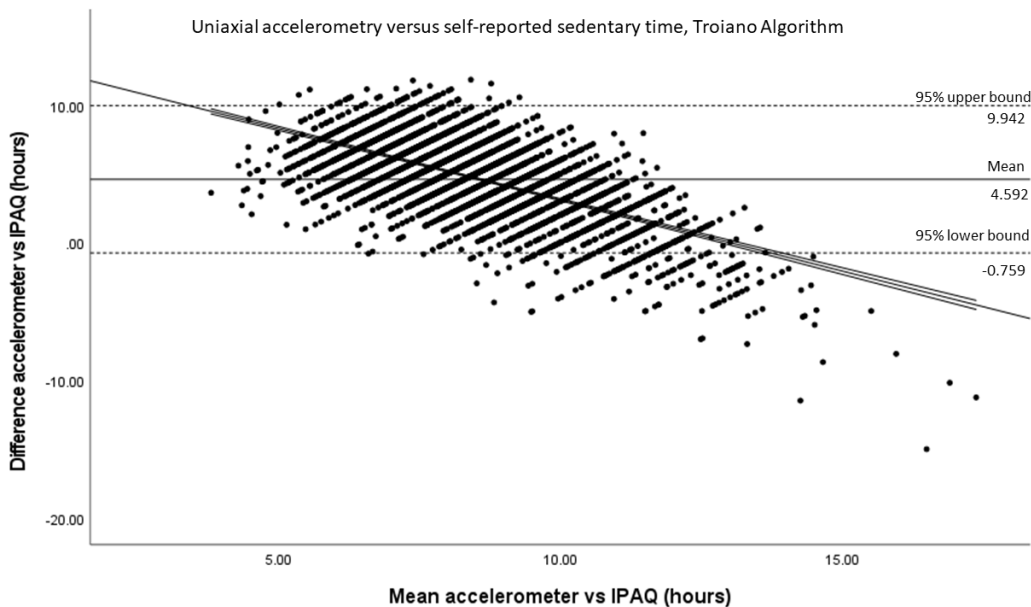


Figure 3.4. Bland-Altman plot of uniaxial accelerometry measured sedentary time versus self-reported sedentary time, using the Troiano et al. (71) wear time algorithm. Accelerometry-measured sedentary time is derived from Treuth et al. (217) at <100 counts per minute. Data are shown in hours per day. The trend line represents the regression of the unstandardized beta-coefficient ($B=-1.04$) with 95%CI (-1.07 to -1.00). IPAQ=International Physical Activity Questionnaire, CI=confidence interval.

3.3 Paper III

In the overall cohort, BMI increased by $0.84 \text{ kg}\cdot\text{m}^{-2}$ (95%CI 0.82 to $0.89 \text{ kg}\cdot\text{m}^{-2}$) from examination 2 to 3. Following adjustments for sex, birth year, smoking, education and BMI at examination 2, there were no difference in BMI increase between the occupational physical activity change groups (Persistently Inactive: $0.81 \text{ kg}\cdot\text{m}^{-2}$, 95%CI 0.75 to $0.87 \text{ kg}\cdot\text{m}^{-2}$; Persistently Active: $0.87 \text{ kg}\cdot\text{m}^{-2}$, 95%CI 0.82 to $0.92 \text{ kg}\cdot\text{m}^{-2}$; Active to Inactive: $0.81 \text{ kg}\cdot\text{m}^{-2}$, 95%CI 0.67 to $0.94 \text{ kg}\cdot\text{m}^{-2}$; Inactive to Active: $0.91 \text{ kg}\cdot\text{m}^{-2}$, 95%CI 0.81 to $1.01 \text{ kg}\cdot\text{m}^{-2}$; $p=0.25$).

In cohort-specific analyses, there were higher BMI increase in the earliest cohorts (Tromsø 1-3, 1974-87, BMI change: $0.49 \text{ kg}\cdot\text{m}^{-2}$, 95%CI: $0.44\text{-}0.54 \text{ kg}\cdot\text{m}^{-2}$; Tromsø 2-4, 1979-95, change BMI: $1.13 \text{ kg}\cdot\text{m}^{-2}$, 95%CI: $1.09\text{-}1.17 \text{ kg}\cdot\text{m}^{-2}$; Tromsø 3-5, 1987-2001, BMI change: $0.95 \text{ kg}\cdot\text{m}^{-2}$, 95%CI: $0.90\text{-}1.01 \text{ kg}\cdot\text{m}^{-2}$) than in the newer cohorts (Tromsø 4-6, 1994-2008, BMI change: $0.12 \text{ kg}/\text{m}^2$, 95%CI: $0.04\text{-}0.20 \text{ kg}/\text{m}^2$, Tromsø 5-7, 2001-2016, BMI change: $0.21 \text{ kg}/\text{m}^2$, 95%CI: $0.09\text{-}0.33 \text{ kg}/\text{m}^2$). There were no differences in BMI increase between occupational physical activity change groups in cohort-specific analyses.

3.4 Paper IV

In the overall cohort, BMI increased with $0.86 \text{ kg}/\text{m}^2$ (95% CI: $0.82\text{-}0.90 \text{ kg}/\text{m}^2$) from examination 2 to 3. With adjustment for sex, birth year, education, smoking and BMI at examination 2, there was no association between leisure time physical activity change from examination 1 to 2 and BMI change from examination 2 to 3 (Persistently Inactive: $0.89 \text{ kg}/\text{m}^2$ (95% CI: $0.77\text{-}1.00 \text{ kg}/\text{m}^2$), Persistently Active: $0.85 \text{ kg}/\text{m}^2$ (95% CI: $0.81\text{-}0.89 \text{ kg}/\text{m}^2$), Active to Inactive: $0.90 \text{ kg}/\text{m}^2$ (95% CI: $0.79\text{-}1.00 \text{ kg}/\text{m}^2$), Inactive to Active $0.85 \text{ kg}/\text{m}^2$ (95% CI: $0.75\text{-}0.95 \text{ kg}/\text{m}^2$), $p=0.84$).

In the reverse analysis, increasing BMI was associated with Persistently Inactive (OR: 1.17, 95% CI: $1.08\text{-}1.27$, $p < 0.001$) and changing from Active to Inactive (OR: 1.16, 95% CI: $1.07\text{-}1.25$, $p < 0.001$) compared with being Persistently Active. We observed interactions of sex, birth year, smoking, education, and occupational physical activity change in the association between BMI change and subsequent leisure time physical activity change (all $p < 0.001$). Men were more likely to be Persistently Inactive than Persistently Active per BMI-unit increase, while this was not observed in women. Those in higher birth year strata (1940–49, ≥ 1950) were

more likely to be Persistently Inactive or changing from Active to Inactive with increasing BMI, which was not observed in those born ≤ 1939 , and those being obese showed no association between BMI change and subsequent leisure time physical activity change.

3.4.1 Additional analysis paper III and IV: the association between combined occupational and leisure time physical activity change and subsequent BMI and weight change.

To complement the domain-specific analyses of paper III and IV, occupational and leisure time physical activity were combined into total physical activity, as described in paper II. The results are presented in Table 3.4. These additional analyses confirm the results observed in paper III and IV. There was no association between changes in total physical activity and subsequent changes in BMI or weight. In stratified analyses, an association between physical activity change and subsequent BMI and weight change was observed in men, those born before 1929, smokers, and those with primary school as highest education, where those who were persistently active gained more BMI and weight than those being persistently inactive, or those changing from active to inactive, or from inactive to active.

Table 3.4. BMI and weight change by total physical activity change. The Tromsø Study 1-7.

Tromsø 1-7 (1974 to 2015-16)	Change total physical activity examination 1 to 2					P _{equality}
	Total	Persistently inactive	Persistently Active	Active to inactive	Inactive to active	
	Outcome change examination 2 to 3					
<i>Total (n)</i>	10571	2540	5235	1014	1782	
BMI (kg/m ²)	Mean	0.94	1.04	0.97	1.00	0.15
	95% CI	0.87 to 1.01	0.99 to 1.08	0.86 to 1.08	0.91 to 1.08	
Weight (kg)	Mean	2.66	2.98	2.80	2.85	0.09
	95% CI	2.46 to 2.87	2.84 to 3.12	2.48 to 3.12	2.61 to 3.09	
Sex						
<i>Women (n)</i>	5060	1307	2335	564	864	
BMI (kg/m ²)	Mean	1.31	1.31	1.29	1.29	0.99
	95% CI	1.20 to 1.42	1.23 to 1.39	1.13 to 1.46	1.15 to 1.42	
Weight (kg)	Mean	3.54	3.52	3.50	3.45	0.98
	95% CI	3.25 to 2.84	3.30 to 3.74	3.05 to 3.95	3.09 to 3.81	
<i>Men (n)</i>	5511	1233	2900	450	928	
BMI (kg/m ²)	Mean	0.59	0.78	0.69	0.73	0.008
	95% CI	0.50 to 0.68	0.72 to 0.83	0.55 to 0.84	0.63 to 0.83	
Weight (kg)	Mean	1.82	2.46	2.22	2.29	0.004
	95% CI	1.54 to 2.11	2.28 to 2.64	1.76 to 2.68	1.97 to 2.61	
Birth year						
≤ 1929 (n)	682	171	317	64	130	
BMI (kg/m ²)	Mean	-0.18	0.33	0.05	0.09	0.015
	95% CI	-0.43 to 0.07	0.15 to 0.51	-0.35 to 0.44	-0.19 to 0.37	
Weight (kg)	Mean	-0.53	1.03	0.11	0.23	0.016
	95% CI	-1.30 to 0.24	0.47 to 1.58	-1.10 to 1.33	-0.62 to 1.08	
1930-1939 (n)	2813	658	1458	234	463	
BMI (kg/m ²)	Mean	0.68	0.79	0.67	0.74	0.50
	95% CI	0.54 to 0.81	0.70 to 0.88	0.44 to 0.90	0.58 to 0.90	

Weight (kg)	Mean	1.90	2.21	1.94	2.05	0.57
	95% CI	1.51 to 2.29	1.96 to 2.47	1.30 to 2.58	1.59 to 2.50	
<i>1940-1949 (n)</i>		4043	1016	1978	357	692
BMI (kg/m ²)	Mean	1.10	1.12	1.08	1.08	0.96
	95% CI	0.99 to 1.21	1.04 to 1.20	0.89 to 1.27	0.94 to 1.22	
Weight (kg)	Mean	3.12	3.20	3.12	3.09	0.96
	95% CI	2.79 to 3.45	2.97 to 3.43	2.57 to 3.66	2.69 to 3.48	
<i>1950-1959 (n)</i>		2793	619	1376	329	469
BMI (kg/m ²)	Mean	1.25	1.36	1.38	1.33	0.57
	95% CI	1.11 to 1.38	1.26 to 1.45	1.18 to 1.56	1.17 to 1.49	
Weight (kg)	Mean	3.61	3.98	3.96	3.88	0.52
	95% CI	3.20 to 4.02	3.71 to 4.25	3.40 to 4.51	3.42 to 4.34	
<i>≥1960 (n)</i>		240	76	106	30	28
BMI (kg/m ²)	Mean	0.85	0.60	0.94	1.29	0.63
	95% CI	0.26 to 1.44	0.10 to 1.09	0.01 to 1.86	0.32 to 2.26	
Weight (kg)	Mean	2.36	1.69	2.75	3.72	0.57
	95% CI	0.78 to 3.94	0.35 to 3.03	0.26 to 5.25	1.10 to 6.34	
Smoking						
<i>Smoker (n)</i>		4441	1075	2149	428	789
BMI (kg/m ²)	Mean	0.98	1.14	0.93	1.01	0.042
	95% CI	0.87 to 1.10	1.06 to 1.22	0.75 to 1.11	0.88 to 1.14	
Weight (kg)	Mean	2.81	3.29	2.68	2.87	0.027
	95% CI	2.48 to 3.13	3.06 to 3.52	2.17 to 3.19	2.49 to 3.24	
<i>Previous (n)</i>		1242	355	564	125	198
BMI (kg/m ²)	Mean	0.48	0.66	0.51	0.72	0.39
	95% CI	0.29 to 0.68	0.50 to 0.81	0.18 to 0.83	0.46 to 0.98	
Weight (kg)	Mean	1.36	1.87	1.54	2.19	0.31
	95% CI	0.79 to 1.93	1.42 to 2.32	0.58 to 2.49	1.43 to 2.95	
<i>Never smoker (n)</i>		4888	1110	2522	461	795
BMI (kg/m ²)	Mean	1.03	1.04	1.13	1.05	0.69
	95% CI	0.93 to 1.13	0.97 to 1.10	0.98 to 1.29	0.93 to 1.17	
Weight (kg)	Mean	2.93	2.97	3.25	2.99	0.66
	95% CI	2.63 to 3.21	2.78 to 3.16	2.81 to 3.70	2.65 to 3.33	
Education						
<i>Primary school (n)</i>		4595	796	2665	397	737
BMI (kg/m ²)	Mean	0.85	0.99	0.78	0.86	0.048
	95% CI	0.73 to 0.98	0.92 to 1.06	0.60 to 0.96	0.73 to 0.99	
Weight (kg)	Mean	2.44	2.78	2.20	2.38	0.06
	95% CI	2.07 to 2.80	2.58 to 2.98	1.69 to 2.72	2.00 to 2.76	
<i>High School (n)</i>		3241	911	1460	323	547
BMI (kg/m ²)	Mean	0.98	1.11	1.07	1.08	0.42
	95% CI	0.87 to 1.10	1.02 to 1.21	0.87 to 1.27	0.93 to 1.23	
Weight (kg)	Mean	2.78	3.23	3.06	3.10	0.26
	95% CI	2.44 to 3.12	2.96 to 3.50	2.49 to 3.63	2.66 to 3.53	
<i>University <4 years (n)</i>		1505	425	649	148	283
BMI (kg/m ²)	Mean	1.03	1.03	1.24	1.16	0.48
	95% CI	0.86 to 1.20	0.90 to 1.17	0.95 to 1.53	0.95 to 1.37	
Weight (kg)	Mean	2.97	3.07	3.69	3.47	0.37
	95% CI	2.47 to 3.48	2.66 to 3.47	2.83 to 4.54	2.85 to 4.08	
<i>University >4 years (n)</i>		1230	408	461	146	215
BMI (kg/m ²)	Mean	0.92	0.97	1.10	1.07	0.54
	95% CI	0.77 to 1.07	0.83 to 1.11	0.85 to 1.36	0.86 to 1.28	
Weight (kg)	Mean	2.69	2.93	3.25	3.15	0.52
	95% CI	2.23 to 3.14	2.51 to 3.36	2.49 to 4.01	2.53 to 3.78	

Data are adjusted for sex, birth year, smoking, education and BMI or weight at examination 2, and shown as adjusted mean and 95% CI. CI=confidence interval, BMI=body mass index, P_{equality}=main effect of groups.

3.5 Paper V

In analyses with mutual adjustment of physical activity and sedentary time, higher physical activity of all intensities was associated with lower risk of mortality in a curvilinear fashion. For example, with 0 minutes per day of MVPA as reference, 10 minutes per day of MVPA was associated with 27% lower risk of mortality (HR: 0.73, 95% CI: 0.65-0.82) and 100 minutes per day of MVPA was associated with 63% lower risk (HR: 0.33, 95% CI: 0.19-0.57). Using 8 hours per day of sedentary time as reference, accumulating over 12 hours of sedentary time per day was associated with higher risk of mortality (HR: 1.53, 95% CI: 1.27-1.84).

In analysis split into those accumulating <10.5 and ≥ 10.5 hours·day⁻¹ of sedentary time, with 0 minutes of MVPA as reference, 10 minutes per day of MVPA was associated with 15% (HR:0.85, 0.74-0.96) and 35% (HR:0.65, 0.53-0.79) lower mortality among those accumulating <10.5 and ≥ 10.5 hours per day of sedentary time, respectively. Maximal risk reduction was observed at 113 (HR: 0.37, 95%CI: 0.19-0.73) and 90 minutes per day of MVPA (HR: 0.36, 95%CI: 0.18-0.75) in low and high sedentary participants, respectively.

In analysis split by meeting physical activity guidelines, with 8 hours per day of sedentary time as reference, sedentary time was not associated with mortality for participants who met the guidelines. Among participants who did not meet the guidelines, there was a curvilinear association between sedentary time and mortality, where greater than 12 hours per day of sedentary time was associated with 38% higher risk of mortality (HR:1.38, 95%CI: 1.10-1.74).

Joint associations combining MVPA and sedentary time confirmed results in split analyses, indicating that MVPA was associated with mortality irrespective of the amount of sedentary time. Conversely, the association between sedentary time and mortality was largely influenced by the amount of MVPA. For example, even small amounts of MVPA ameliorated the higher risk of mortality associated with high sedentary time; using 0 minutes per day of MVPA and 8 hours per day of sedentary time as reference, 10 minutes of MVPA was associated with 32% (HR: 0.68, 95% CI: 0.49-0.95) lower mortality risk at 6 sedentary hours per day, 55% (HR: 0.45, 95% CI: 0.31-0.65) at 10 hours per day, and 28% (HR:0.72, 95% CI:0.65-0.81) lower risk at 13 hours per day. At 0 minutes per day of MVPA, being sedentary for 6 hours per day was associated with 56% higher risk of mortality (HR: 1.56, 95% CI: 1.01-2.39), while over 8 hours

per day of sedentary time were not associated with mortality even at 13 hours per day of sedentary time (HR: 1.35, 95%CI: 0.81-2.24).

Light physical activity was curvilinearly associated with lower mortality risk but only in highly sedentary participants. Compared with 183 minutes per day as reference, 15 more minutes of light physical activity were associated with 11% (HR:0.89, 95%CI:0.85-0.95) lower mortality risk, and maximal risk reduction was observed at 330 minutes per day (HR:0.61, 95%CI:0.43-0.86). Total physical activity was inversely and curvilinearly associated with mortality risk in both low and high sedentary participants. The lowest mortality risk (HR:0.17, 95%CI:0.08-32) in those with low sedentary time was observed at 690 counts per minute, and in those with high sedentary time at 450 counts per minute (HR:0.33, 95%CI:0.20-54).

4 Discussion

4.1 Physical activity levels, weight gain and mortality

The following discussion presents additional reflections and perspectives on study results described in this thesis, beyond that of the peer-reviewed publications.

4.1.1 Measurements of physical activity: Paper I and II

As a secondary aim of Paper I, we compared accelerometry estimates of physical activity between triaxial and uniaxial accelerometry. Although comparisons between uniaxial and triaxial acceleration measures have been published previously (53), a novel finding in our comparisons was that prevalence of meeting physical activity guidelines differed by 20 percentage points between uniaxial and triaxial accelerations. These findings advanced our knowledge on how uniaxial and triaxial data may cause different prevalence estimates.

In Paper II, we created MET-values from the PAFID questionnaire and PAL scores from the SGPALS, which allowed us to examine the validity of continuous variables from the PAQs. We also used the original SGPALS ranks and categorized MET-hours per week into quartiles in the PAFID to examine the validity properties of these PAQs if processed as crude hierarchical groups. We observed positive associations between accelerometry-measured physical activity and ranks of the SGPALS and quartiles of MET-hours per week of the PAFID. These observations are consistent with previous studies examining the criterion validity of these PAQs against accelerometry (204, 234, 235). Additionally, the SGPALS (234, 236, 237) and the PAFID questionnaire (204, 238) were also associated with cardiorespiratory fitness, and the SGPALS has also been validated against doubly labelled water (226). The broad conclusion of Paper II was that it may be optimal to process PAQs into crude groups in order to provide meaningful results, although information content may be lost when categorizing continuous variables (239).

In Paper II, we also processed self-reported sedentary time with the IPAQ as continuous sedentary hours per day and into quartiles of self-reported sedentary hours. Although there were large differences in self-reported sedentary hours between the quartiles, there was only ~1 hour difference in accelerometry-measured sedentary time between quartile 1 and 4 of self-reported sedentary time in the IPAQ. In the sensitivity analysis of Paper II, the Bland Altman plot demonstrated negative proportional bias with higher mean sedentary time of self-reported and

accelerometry-measured sedentary time Moreover, the magnitude of the correlations ($r \sim 0.20$) between the IPAQ sitting question and accelerometry-measured sedentary time in Paper II can be considered weak. This suggests that regardless of how self-reported sedentary time from the IPAQ is processed, it poorly reflects accelerometry-measured sedentary time.

As diversity in populations may influence the validity of measurement tools across different populations (*i.e.*, time, place and person (240)), it should not be assumed that previously reported validity of these PAQs (40, 43, 204) would be similar in other cohorts. For example, although the correlation coefficients observed between accelerometry-measured and self-reported sedentary behaviour from the IPAQ in Paper II are consistent with previous research (231, 241, 242), these correlations seem to vary across countries ($r=0.07-0.49$) (43), which may illustrate demographic differences in validity of this PAQ.

As previous validation studies of these PAQs recruited participants solely for their validity studies (40, 43, 204), Paper II was designed within a large cohort study with assumed high representativeness. This may assist researchers who investigate both previous and future studies, as interpretation of data can have public health impact.

Previous validity studies of the SGPALS compared criterion measures of the leisure time and occupational SGPALS separately (40), except two studies that examined the combined total physical activity (225, 226). However, the two studies that examined the combined leisure time and occupational SGPALS by energy expenditure as the criterion used heart rate monitoring (225) and doubly labelled water (226). In contrast, we examined the validity of the combined total SGPALS with accelerometry as the criterion, which has not, to my knowledge, been previously done. Although we might expect similar results regarding ranking capability as we also observed in Paper II, we can now relate accelerometry estimates distributed among the different ranks of the total SGPALS, which can be used to approximate how much physical activity each rank represents.

Similarly, although ranking capability of the PAFID was previously demonstrated (204), the previous study used another accelerometer brand (204) than in Paper II. Similarly, Paper II provides a resource for researchers when interpreting studies using the PAFID, as it can be related to accelerometry estimates from the ActiGraph, which is the most frequently used accelerometer in published literature (50).

As accelerometry-measured total physical activity includes both occupational and leisure time physical activity, we deemed it inappropriate to include separate analysis of the leisure time and occupational SGPALS in the peer-reviewed publication. However, as previous studies compared criterion accelerometry to the leisure time and occupational SGPALS separately (40), Paper II was supplemented with additional analyses to examine these associations. There were positive associations between both volume and intensity measures of physical activity and higher SGPALS ranks for leisure time and occupational physical activity separately. This is also consistent with previous validation studies of this PAQ for leisure time physical activity, however, not for occupational time physical activity (234, 243). As our study includes a larger sample size and was designed within a large cohort study with assumed high representativeness, this may explain the inconsistent finding.

4.1.2 Physical activity and weight gain: Paper I-IV

In Paper I, those who were classified as normal weight spent more time in MVPA compared with those who were classified as overweight and obese. These observations are consistent with previous cross-sectional studies of device-measured physical activity (75, 78, 223). However, cross-sectional designs cannot examine the direction in the association (107), *i.e.*, it is as likely that weight gain precedes physical activity as *vice versa*. The direction of associations between physical activity and weight/BMI gain were examined in longitudinal analyses in Paper III and IV. Here, we modelled physical activity change from one examination to the next, and then regressed these changes on weight and BMI changes from the second examination to a third examination. In Paper III and IV, we did not observe an association between physical activity changes and subsequent weight and BMI changes. However, we observed that BMI changes predicted subsequent leisure time physical activity declines in Paper IV, with 15% higher odds of changing from active to inactive with every increasing unit of BMI. This indicates that it is more likely that weight gain precedes physical activity declines at population level.

The obesity epidemic is a large public health concern in western high-income countries. Although it remains debated whether physical activity level contributes to the rising population weight gain (107), the results of Paper III and IV strengthen the hypothesis that weight gain may precede physical activity changes at population level. These findings support an alternative aetiology for the obesity epidemic, and can be considered as an important contribution to, and reference for, relevant policy revision.

Compared with the previous study that used physical work exertion and dichotomized BMI (244), Paper III used occupational physical activity as the exposure and continuous BMI and weight data, which preserved information and statistical power (239). A literature search prior to designing Paper III revealed a lack of published papers that have used similar analytical approaches (244); thus, we designed the study in an effort to extend previous knowledge. Moreover, the study by Dobson *et al.* (244) also embedded their physical work exertion in many other work exposures, while Paper III solely targeted occupational physical activity, potentially lowering chances of the table 2 fallacy (245).

Further, we also advanced the knowledge base by examining BMI and weight changes over several decades, including prior to and during the rise in the obesity epidemic (~1990) (79). This enabled us to examine a potential cohort effect by birth year strata. Here, we observed a cohort effect of weight gain where those born after 1950 gained more weight than those born before, a finding that is previously observed in Tromsø Study data (246). However, there appeared to be no cohort effect in the association between occupational (Paper III) or leisure time (Paper IV) physical activity change and subsequent BMI or weight change.

Many studies included in the recent systematic review examining whether physical activity can prevent population weight gain had 1-2 years of follow-up time (106). In Paper III and IV, the examinations were ~6 years apart. As population weight gain has gradually increased over time (79), this enabled us to study these associations with similar timeframes.

One previous study used a similar analytical approach (124) as Paper IV. However, they did not examine a potential reverse association examining whether BMI gain is associated with physical activity change (124). Thus, to my knowledge, Paper IV is the first to address a potential reverse association with this analytical approach. Moreover, we also examined potential effect modifications in the reverse analyses of Paper IV, where all potential effect modifiers displayed significant interactions. However, there seemed to only be small magnitude differences in the associations for strata analyses, suggesting that these effect modifications may be of low public health relevance. Nevertheless, this warrants future research.

Paper III and IV were supplemented with an additional analyses examining the combined leisure and occupational SGPALS change, and the association with BMI and weight change,

using the same analytical approach. These additional analyses further strengthen the findings of Paper III and IV, as there was no association between total physical activity change and subsequent BMI and weight gain. It should be noted that in some stratified analysis, there were significant associations at alpha set to 0.05; however, as there were 75 ANCOVAs performed in Paper III, IV and the accompanied additional analyses, it is likely that these associations were type-2 errors. For example, with Bonferroni corrections, 75 statistical tests suggest associations should be at alpha <0.0007, of which all p<0.05-associations of the additional analyses were higher than p<0.0007.

A previous study estimated that increasing PAEE with ~100 kcals per day would be sufficient to prevent weight gain at the population level (84), indicating that equivalent decreases would result in weight gain. This ~100 kcals per day is similar to the estimated lower energy expenditure deriving from declines in occupational physical activity in the United States (100). Most occupational physical activities in The Tromsø Study surveys changed from standing and walking to sitting (104), which is consistent with other cohorts (100, 108, 247). The energy expenditure difference of sitting versus standing is estimated to be 54 kcals over 6 hours (*i.e.*, 72 kcals over 8 hours) (248), which is half a chocolate bar or an apple.

These small PAEE differences between ranks of the occupational SGPALS were also illustrated in the additional analyses of Paper II. Although the additional analyses in Paper II were likely mutually influenced by leisure time and occupational physical activity of the accelerometry assessment, there were ~7 minutes difference in MVPA per day and ~200 steps per day between the lowest and highest rank of the occupational SGPALS. Such small differences have also been observed previously (234). Thus, decreasing occupational physical activity between ranks of the SGPALS, as observed in Paper III, is likely associated with low actual differences in physical activity levels, *i.e.*, low differences in PAEE. Consequently, although higher intensity occupational physical activity may be perceived as more exhaustive than lower intensity, the small difference in PAEE between occupational SGPALS ranks likely explains why we observed no differences in subsequent weight and BMI change in Paper III.

It may be easier to achieve energy balance at high energy turnover (high energy expenditure), as highly active individuals may experience hunger induced from physical activity, while being inactive would result in lower energy expenditure without sufficient regulation of energy intake (83). Heavy manual labour workers are estimated to work at ~30-35 % of maximal oxygen

uptake over an eight hour work day (249). Such a PAEE volume may be sufficient to compensate the increased energy intake of 500 kcal per day observed in high-income countries (250, 251). However, heavy manual workers only represented a fraction of The Tromsø Study sample; ~8% in 1979-80, ~2% in 2015-16 (104). Examining whether heavy manual workers have higher protection of weight gain from their occupational physical activity may be a future research target.

In Paper I, the difference between normal weight, overweight and obese corresponded to a ~5 minutes' difference in MVPA per day and ~1000 steps per day by every higher BMI category. The additional analysis of Paper II indicated that leisure time physical activity is largely reflected in accelerometry-measured physical activity; one rank lower leisure time SGPALS was associated ~10 minutes less MVPA per day or ~1000 less steps per day. Similar large differences between accelerometry and the leisure time SGPALS are previously observed (234, 235). Considering that there were smaller differences in accelerometry estimates between occupational SGPALS ranks than between leisure time SGPALS ranks, increasing weight has potentially greater consequences for leisure time physical activity than for occupational physical activity. Additionally, as occupational physical activity involves limited choices due to set work tasks, reverse causation between occupational physical activity change and BMI change is unlikely. This highlights the importance of identifying the aetiology causes for the obesity epidemic, and to implement public health initiatives aimed at preventing population weight gain, as this likely negatively influences leisure time physical activity levels.

Examining the physical activity volume change is crucial in the association with BMI and weight change (107). The SGPALS' four change groups have limited physical activity volume information. An alternative to examine volume change is to create greater number of categorical groups (107). Our results were unchanged in the six-group sensitivity analysis; however, this approach only provides an indication of volume change. Consequently, although the leisure time SGPALS is consistently found to be associated with many health indicators, diseases, and higher criterion measures (such as accelerometry and cardiorespiratory fitness (40)), low physical activity volume information in this PAQ may have limited the ability to examine the association with weight changes. Nevertheless, despite this limitation, we observed 15% higher odds of changing from active to inactive with every increasing unit of BMI, suggesting this finding has public health relevance.

The impact of Paper III was demonstrated by an invited commentary to Paper III by Biswas (252), discussing whether occupational physical activity has a role in prevention of population weight gain, and it was also named editor's choice of the March 2021 (78th) issue of Occupational and Environmental Medicine. Paper III and IV was also recently cited in a text book chapter on obesity and diabetes (253), potentially influencing education on obesity and the role of physical activity.

4.1.3 Physical activity, sedentary time, and mortality: Paper V

Paper V addresses the potential causal associations between physical activity, sedentary time, and mortality, a question that is commonly debated in physical activity epidemiology (254). Although previous studies using individual participant data meta-analysis of multiple cohorts examined the same research question (191, 193, 194, 201) as Paper V, they used a two-step approach that merges harmonized study-level data in meta-analytic procedures (196, 198). Paper V used a one-step approach that allowed for more advanced interaction and effect modification analysis (196, 198).

Findings from Paper V suggest that performing MVPA according to the lower-limit WHO guidelines of 150 minutes per week (31) eliminates any risk of mortality associated with high sedentary time. Previous studies examining a potential effect modification of physical activity in the association between sedentary time indicated that MVPA equivalent to ~40-60 minutes per day eliminates the association between sedentary time and mortality (191, 193, 194, 201), which is a higher MVPA volume than observed in Paper V.

Further, higher MVPA was associated with lower mortality risk irrespective of sedentary time, although sedentary time modified the association where those accumulating higher sedentary time displayed a greater magnitude in inverse association than those accumulating less sedentary time. These findings were consistent in the joint analysis of MVPA and sedentary time, where even some minutes of MVPA were associated with a substantial lower mortality risk across the sedentary time spectrum. Previous studies examining effect modification of sedentary time in the association between physical activity and mortality suggest that sedentary time attenuates this association to a greater extent than in Paper V, for those performing some amounts of MVPA (191, 193, 194, 201).

The lowest mortality risk in Paper V was observed for those with the highest total physical activity volume. As a higher proportion of PAEE derives from light physical activity at population level (255), this may suggest that total physical activity volume is more important than intensity in lowering mortality risk. We observed lower mortality risk with higher light physical activity, but only in those who were highly sedentary. In studies using compositional analysis, reallocating sedentary time with light physical activity is associated with lower risk of mortality (194, 256-258). Thus, it is likely that light physical activity is also beneficial for longevity (194, 256-259).

However, during waking hours, although sedentary time is inversely proportional to physical activity, this is mainly light physical activity, which in Paper V was evident with a negative Pearson correlation at -0.96 between light physical activity and sedentary time. Consequently, as those being less sedentary are already accumulating high volumes of light physical activity, this likely explains why we observed no association between light physical activity and mortality in these individuals, as the effect from light physical activity is already maximized due to the existing high volume of light physical activity.

A recent study reported that with similar PAEE, the lowest mortality risk was observed in those with largest proportion of PAEE deriving from MVPA, and additionally, similar lower risk was observed if having dissimilar PAEE, but similar MVPA proportion of PAEE (260). Similarly, another study displayed that even though some participants with high volume of light physical activity accumulated similar total physical activity volumes as most of those with a larger proportion from MVPA, individuals with the highest MVPA also had the highest total physical activity and the lowest risk of mortality (261). Finally, one study reported that those reporting vigorous physical activity had lower mortality risk than those primarily reporting moderate intensity (262). Consequently, even though we observed lowest mortality risk among those accumulating highest total physical activity, and the highest proportion is probably from light physical activity, it is likely that the lowest mortality risk is among individuals who perform a fair proportion of total physical activity in at least moderate absolute intensity.

The considerable association magnitudes observed in Paper V highlights the potential of increasing physical activity levels for longevity. Indeed, evidence supporting the potential benefit of physical activity for increasing longevity is growing. Population attributable fractions indicate that 9% of all deaths could be avoided if all were sufficiently active (2), and a recent

study using NHANES data indicated that a modest 10-minute increase of physical activity would prevent ~100000 deaths annually in United States (263). It is unlikely that a single study, such as Paper V, would result in a dramatic policy or guideline change, but such research does shed in-depth light on the roles of physical activity and sedentary time on mortality. This finding somewhat conflicts with the recent 2020 WHO guidelines suggesting that individuals should aim for 300 minutes of MVPA per week, if accumulating high amounts of sedentary time (31). Thus, further research should be undertaken to better evidence optimal population guidelines.

4.1.4 Physical activity levels, weight gain and mortality: Papers I-V

Paper I involved a descriptive analysis of physical activity levels, and such descriptive data are always applicable to public health (240). Especially as risk factors for disease may change over time (240) and may also be different between regions, countries and counties, it remains imperative that risk factors for disease are constantly updated.

In paper I, higher age was associated with lower physical activity. These observations are consistent with previous studies (71-75, 223, 264). In the literature, there is no biological explanation for why older individuals perform less physical activity of higher intensity than younger individuals. However, it likely that the ageing process reduce the body's capacity to perform physical activity as older age is associated with difficulties in walking, pain, physical complaints (75, 265-267), and lower cardiorespiratory fitness (268-271).

Although older age is associated with lower cardiorespiratory fitness (268-271), increasing physical activity levels will result in improvements, maintenance or prevention of steep declines in cardiorespiratory fitness (272-275). Consequently, increasing physical activity levels, or maintaining high physical activity levels, may prevent, or at least delay, the onset of morbidity, which may have substantial impact on public health.

Increased body fat is associated with lower cardiorespiratory fitness (276). Notably, fat mass does not directly diminish cardiorespiratory fitness, but it seems rather that the submaximal aerobic work capacity is lower due to the excess body fat (277). Consequently, excess fat mass may result in a higher relative effort when engaging in equivalent absolute physical activity level, compared with individuals of similar weight but proportionally greater lean mass. This was demonstrated in an experimental study of overfeeding with 4 MJ (1000 kilocalories) per

day over eight weeks, where free-living walking distances decreased due to lower walking velocity (*i.e.*, movement limitation) in both normal weight and obese individuals following overfeeding (278). However, although obese individuals perform lower absolute physical activity levels than normal weight individuals, a higher weight results in more expended energy due to the excess weight, resulting in similar absolute PAEE (279). Therefore, both maintenance of normal weight and high cardiorespiratory fitness may be of importance for maintaining high physical activity levels.

In Paper V, we observed large magnitude of lower mortality risk from some minutes of MVPA. For example, there was over 20% risk difference between 0 and 10 minutes of MVPA per day, and over 40% risk difference between 0 and 20 minutes of MVPA per day. Ten minutes of MVPA corresponded to one lower rank in the leisure time SGPALS in Paper II, while the MVPA difference between rank 1 and 2 of the combined SGPALS was 20 minutes (and an average 10-minute difference between all ranks). In Paper IV, every unit increase in BMI was associated with 15 % higher odds of changing from active to inactive in the SGAPLS, which is changing from rank 2 to 1, but can also be changing from rank 4 or 3 to 1. Consequently, increasing weight may have severe consequences for public health, as it decreases physical activity levels (Paper IV), which is associated with higher risk of mortality (Paper V). This highlights the need to identify and implement public health measures to prevent population weight gain, as it influences physical activity levels, which in turn influence risk of mortality.

As an additional analysis of Paper I, cardiorespiratory fitness was estimated to examine at what relative intensity participants in Tromsø7 would perform their respective absolute physical activity intensity. For example, the mean relative intensity corresponding to 3 METs was 30.7 % of estimated maximal oxygen uptake in the total sample, which was slightly higher in the Tromsø7 accelerometry sample (33.8 %). These medians were also around the 25th and 75th percentile of the distributions in such a large sample. This means that for the majority of the population, performing absolute moderate intensity corresponding to physical activity guidelines (*i.e.*, ≥ 3 METs) (31) can be achieved at a relatively low intensity, and increasing the volume of absolute moderate intensity will likely lower their risk of mortality. This also means that for 10 % of the population, between the 10th and 1th percentile, a relatively higher intensity must be exerted to accumulate minutes corresponding to the guidelines. However, it can still be perceived as achievable for many, as ~40-60% of maximal oxygen uptake is usually defined as low to moderate relative intensity (273), such as jogging or running on a flat surface.

It is only for the lowest fit, the remaining 1% of the population, that performing absolute moderate intensity may be unachievable. However, the greatest health effects associated with physical activity are observed for these individuals, as reported in Paper V. Therefore, a simple take-home message for these individuals would be: “*some physical activity is better than none*”(31), meaning that their relative low or moderate intensity may still be beneficial for their health, regardless if it is below or above the absolute threshold of the specified guidelines.

To sum up, these points emphasise: 1) the importance of public health initiatives to increase population levels of physical activity, 2) prevent population weight gain to avoid declines in physical activity, 3) that only some additional minutes of physical activity lowers the risk of mortality, and 4) increasing physical activity levels is achievable for the vast majority of the population.

4.2 Causality

Causal inference is, according to Morris (165), how the “ways of living” across different groups is related to diseases, or according to Rothman (280); “how nature works” (280). In Paper III and IV, we examined the longitudinal association between physical activity and weight change. In Paper V, we examined the longitudinal association between physical activity, sedentary time, and mortality. It is thus natural to infer causation on these associations.

4.2.1 Rothman’s causes

Rothman’s causes (281) illustrate that multiple causes may act upon the sufficient cause. For changing weight, the necessary cause is energy imbalance (83-85). However, what causes energy imbalance may be one of the insufficient causes, or all, or some of them. For example, a small decrease in energy expenditure and a small increase in energy intake may together result in weight gain, while they alone may be of insufficient magnitude to cause weight change, as homeostasis regulates small changes in energy expenditure and intake (*e.g.*, increasing energy expenditure or increasing hunger to eat more energy), as illustrated by Levine *et al.* (175) and mentioned previously (see 2.3.1 Sedentary behaviour and mortality).

Rothman uses “synergy” (190) or biological interaction (282), where the joints effects of each cause may exceed the strength of each individual cause, i.e., they can be interdependent. The magnitude of each insufficient cause may be different among different individuals, and also

different in time (281). For example, some life events (e.g., getting married, death of spouse, having a baby, changing work environment) may cause eating more (or less) or perform more (or less) physical activity, and consequently, causes changes in energy balance. In Paper III and IV, physical activity appeared not to contribute to weight gain at population level but indeed, very high volumes of physical activity will likely prevent weight gain at individual level, where high energy turnover induces hunger (83). For example, few elite endurance athletes are obese (15-18).

In regard to physical activity, obesity and mortality, one study examined a joint association between physical activity and adiposity, showing that high adiposity and low physical activity level was associated with higher risk of mortality (283). In comparison, those with low adiposity and high physical activity levels, and those with high adiposity and high physical activity levels had a lower risk of mortality (283). Likewise, this is also demonstrated in a joint association between physical activity and diet quality, where those eating a low-quality diet and performing low physical activity levels had higher risk of mortality than those eating a high-quality diet and performing high levels of physical activity, and those eating a high-quality diet and performing lower levels of physical activity (284). However, the sufficient cause for mortality is likely not physical activity, adiposity, or diet, but they are all associated with diseases such as diabetes, which is associated with cardiovascular disease (285, 286). Alternatively, physical activity, adiposity and diet are also associated with cancer (287-290), which may be a sufficient cause for premature mortality. This supports that there is a causal association between physical activity, obesity, diet and mortality but they act on combined effects, or as Rothman coined, 'synergy effects' (281).

4.2.2 Hill's criteria for causality

Hill's criteria for causality, presented in 1965, was one of the first epidemiological frameworks for causal inference (291) and may also be the most used. It includes nine criteria: 1) Strength, 2) Consistency, 3) Specificity, 4) Temporality, 5) Biological Gradient, 6) Plausibility, 7) Coherence, 8) Experiment 9) Analogy (291). I will use Hill's criteria (291) as a framework for my causal inference on the associations observed in Paper V.

4.2.2.1 Strength of the association

The magnitude of the association between exposure and outcome is Hill's top criteria for causality (291). Simply put, an association is likely causal if there is a great magnitude. We observed a great magnitude for the inverse association between higher physical activity and

lower risk of mortality. While for sedentary time, the magnitude appeared to be small, and depended largely on the amount of physical activity. Hill's strength criteria support a causal association between physical activity and mortality but not between sedentary time and mortality.

4.2.2.2 Consistency

Consistency is whether an association is observed more than once (291). For example, whether an association is observed in multiple populations and by different research groups. Our findings are consistent with previous research regarding physical activity and mortality, and regarding sedentary time and mortality (35, 191-194), supporting that the association between physical activity and mortality, and between sedentary and mortality, are both causal.

4.2.2.3 Specificity

Whether the association we observe is solely due to our tested exposure, or whether other factors also influence this association (*i.e.*, confounding bias), is of large concern in epidemiology (240). For the association between physical activity and sedentary time, with mortality, we adjusted for potential confounding sources, suggesting that this association is specific. However, diet quality was unadjusted. Moreover, another case for a specific association is that MVPA was associated with mortality irrespective of the amount of sedentary time, while the association between sedentary time and mortality appeared to depend largely on the amount of MVPA. Consequently, physical activity appears to have a greater specific association with mortality, than that of sedentary time.

4.2.2.4 Temporality

There is always a chance of reverse causation in observational research; the cause cannot precede the exposure (291). This is best exemplified by the well-known phrase, of what comes first: the chicken or the egg, or in Norway, the hen or the egg (or by Hill: the cart or the horse (291)). That death occurs prior to physical activity is dubious, however, in this case, reverse causation bias represents that within the time frame from baseline measurements of physical activity and sedentary time, prior deleterious episodes may have caused development of disease, or risk factors for disease, that can explain lower physical activity levels and higher sedentary time prior to death. In the sensitivity analysis in Paper V, we restricted the follow-up time to those having more than 5 years, where we observed attenuated effects, albeit still great in magnitude. For the association between sedentary time and mortality, previous research has shown that if excluding those with less than 5 years follow-up time, the association disappeared

(292, 293), indicating that sedentary time is largely influenced by reverse causation bias, where many deaths associated with sedentary time occur in a short time frame. However, this was unchanged in the sedentary time-mortality association in Paper V. Consequently, the temporality criterion favours a causal association between sedentary time and mortality but indicates presence of reverse causation bias in the association between physical activity and mortality.

4.2.2.5 Biological gradient

This is the dose-response association; if there is higher risk of disease by higher amount of exposure, “*then we should look most carefully for such evidence*” (291). In Paper V, we observed dose-response associations for both physical activity and sedentary time, with mortality, suggesting that both associations are causal. However, when examined jointly, higher MVPA was associated with lower risk of mortality irrespective of sedentary time, while the association between sedentary time and mortality was largely influenced by MVPA levels, thus suggesting that there is a greater biological gradient in the association between physical activity and mortality than the association between sedentary time and mortality.

4.2.2.6 Plausibility

Plausibility is whether the observation we observe is plausible (291). Physical activity improves, maintains, and prevents steep declines in cardiorespiratory fitness (273-275). Cardiorespiratory fitness is consistently found to be associated with lower risk of mortality (275, 294-297), *i.e.*, it is likely that the causal association between physical activity and mortality is mediated by an increase, maintenance, or prevention of decline in cardiorespiratory fitness. This hypothesis was recently tested in a mediation analysis showing that cardiorespiratory fitness mediates the association between physical activity and mortality, although some of the effect was also mediated by diabetes and hypertension (298). Cardiorespiratory fitness displays greater magnitude for lower mortality risk than physical activity (299), which could indicate that physical activity needs to be of sufficient intensity to improve or maintain cardiorespiratory fitness (299). What manifests as sufficient intensity for improving cardiorespiratory fitness depends on the individual’s heritability, *i.e.*, their genetic response from physical activity (272, 300), and initial fitness level.

However, a recent twin-pair study showed similar risk of mortality in twins of discordant cardiorespiratory fitness levels (301), indicating that the association between cardiorespiratory fitness and mortality may not be causal. This highlights one of Hills notions that that biological

plausibility is limited to our current knowledge (291). Hence, we may not know the full extent of the association between physical activity and mortality.

In regard to the association between sedentary time and mortality, a study in rodents observed downregulation of lipoprotein lipase activity, which was not sufficiently upregulated following later activity (177). This association however, was not observed when replicated in an experiment in humans (302). Another proposed mechanism is low shear stress on blood vessels in those who are sedentary for prolonged time, due to reduced blood flow (303). However, following 10 minutes of light intensity walking, the reduced blood flow returned to baseline values (303). A low intensity step volume is suggested to be 60 steps per minute ($1.8 \text{ km}\cdot\text{h}^{-1}$), which is about 2 METs (304). This is 600 steps over 10 minutes, which is a lower step volume than those living with disease or conditions (304). Therefore, those being ill and not walking 10 minutes per day of light intensity are likely suffering from diseases due to other reasons than their sedentary time.

4.2.2.7 Coherence

Coherence is whether results are consistent with what we know about the exposure and outcome, if other likely outcomes show an association with the exposure, and/or that there is coherent findings between observational and experimental studies (291), *i.e.*, that the association aligns with what is currently known. There are coherent findings between Paper V and other studies examining physical activity and other outcomes, such as cardiovascular disease, cardiovascular risk factors such as blood pressure, biomarkers, and also for metabolic disorders such as diabetes (274, 305, 306), which are suggested pathways for why physical activity may prevent premature mortality (274). For sedentary time, there are also coherent findings for lower sedentary time being associated with lower risk of cardiovascular disease and diabetes (188).

4.2.2.8 Experiment

As Hill said, we can “*occasionally appeal to experimental, or semi-experimental, evidence.*” (291). This is a criteria for causality that is missing for the association between physical activity and mortality (254). To my knowledge, the only trial that examined the association between physical activity and mortality in a population free from known disease (307) reported similar mortality rates between the group instructed to adhere to physical activity guidelines and the group who were provided structured exercise. As far as I know, there is no experimental study examining an association between sedentary time and mortality. Thus, “*the strongest support*

for the causation hypothesis” (291) is not confirmed for neither physical activity nor sedentary time and mortality.

4.2.2.9 Analogy

Analogy is whether we can observe an association for something similar to our examined exposure (291). An analogy for physical activity is hard to come by, however, sedentary time may be similar to bedrest. Bedrest has severe influence on physiological outputs (308) and disease outcomes (309). However, as Saltin *et al.* (310) illustrated in 1968, the deleterious physiological effects following bedrest returned to baseline values following three weeks of physical activity, ameliorating the detrimental effect of past sedentary time (*i.e.*, bedrest). This conforms with findings in Paper V, both that those with high sedentary time accumulated lower overall physical activity, and that one minute of MVPA displayed lower risk of mortality at any given amount of sedentary time in the joint associations. Consequently, it is pertinent to ask whether sedentary time is simply the reverse of the coin for physical inactivity (176).

4.2.2.10 Are the associations between physical activity, sedentary time, and mortality causal?

As many of Hill's criteria are met for a causal association between physical activity and mortality, it can be concluded that this relationship is likely causal. However, as there is no evidence of both observational studies and randomized controlled trials showing consistent findings (254), we can also conclude that it is not causal.

“What I do not believe - and this has been suggested - is that we can usefully lay down some hard-and-fast rules of evidence that must be obeyed before we accept cause and effect”

Sir Austin Bradford Hill (291)

4.3 Bias

Paper II was mainly focused on bias associated with self-reported physical activity, but all papers of this thesis is likely influenced by different kind of bias. One can broadly classify bias in information bias and selection bias (240).

4.3.1 Information bias

Information bias is measurement error, which relates to validity and reliability (240). Measurement error depends on the participant being measured, the measurement/test, the measurement equipment, and the data processing of the measurement.

4.3.1.1 Differential misclassification

Differential misclassification is systematic measurement error, and can be caused by how a measurement tool is calibrated, brands of the measurement tool and how the measurement protocol is designed (240).

In Paper V, we included four cohort studies that all used different generations of the ActiGraph accelerometer. Previous studies have identified that ActiGraph generations record acceleration differently (233, 311). Therefore, we performed sensitivity analysis where we calibrated the NHANES acceleration data to the newer generation ActiGraphs using the reported correction factors of a study that had a similar data recording protocol (233) as in Paper V. Interestingly, the differences between the device versions did not seem to have large influence on the associations with mortality. However, we calibrated these on study level, *i.e.*, the summary mean CPM and mean minutes of intensity of each individual data in the dataset, and *not* each CPM and intensity-minute over the measurement period for every individual, as done in the

study by Ried-Larsen *et al.* (233). Thus, the accelerometry estimates of Paper V could be influenced by differential misclassification.

4.3.1.2 Non-differential misclassification and regression dilution bias

Measurements can also be non-differential, meaning that there is no systematic error but random error, and participants may be both measured higher or lower than the “true value” (240). Random measurement error causes regression dilution bias (312). For example, the previous evidence of physical activity and mortality is primarily based on self-reported data (2, 188, 189, 313, 314) that are prone to measurement error, and for the most, non-differential misclassification (36, 315-317). This likely underestimates the association magnitudes between physical activity and health outcomes. For example, the meta-analysis by Ekelund *et al.* (35) of accelerometry-measured physical activity reported mortality risks twice as great in magnitude compared with self-reported physical activity (173, 259, 313).

In epidemiology, it is a commonly held view that non-differential misclassification in different directions cancel each other out so they do not influence the results (240). In Paper I, 70% of the study sample were determined sufficiently active by meeting the current lower-limit WHO guidelines (31). This prevalence estimate using accelerometry is similar to the estimate using self-reported physical activity in the national estimate from 2014-15 (67%) and the global prevalence estimate (70%) (64). The similar prevalence estimate between accelerometry and self-report can be explained by the nature of random measurement error; if the same sample underwent another measurement, then random measurement error will classify some new individuals as sufficiently active, while some others will now be classified as inactive at the second measurement, resulting in similar prevalence estimates at both measurement occasions (240). This will likely happen regardless of measuring with accelerometry or with PAQs, as both are influenced by random measurement error. However, there are some nuances to this picture, as the IPAQ asks about continuous 10-minute bouts of physical activity, and when employing such strict criteria on accelerometry estimates, the number of sufficiently active participants dropped to 22% in Paper I, and to 32% in the national estimate (67).

However, even though non-differential misclassification is commonly believed to cancel each other out, this is only true in prevalence estimates and may cause large bias in associative studies (240). In Paper V, as we harmonized our data to match older accelerometry devices, we only extracted the vertical acceleration axis. In Paper I, triaxial accelerometry recorded more

physical activity of higher intensity than uniaxial data, which may have caused regression dilution bias in Paper V. However, whether uniaxial or triaxial data best reflect actual physical activity levels is unknown. Therefore, it is unknown whether uniaxial compared with triaxial accelerometry under- or over-estimates actual physical activity levels. Consequently, it is unknown whether uniaxial or triaxial accelerometry causes the greatest regression dilution bias.

When comparing accelerometry estimates of PAEE, MVPA and total CPM (total physical activity) with PAEE estimated from doubly labelled water, both PAEE, MVPA and total CPM from accelerometry shows a correlation coefficient at $r \sim 0.5$, and $\sim 50\%$ explained variance in the correlation with PAEE from doubly labelled water (44, 57). Consequently, PAEE, MVPA and total CPM from accelerometry are equally inaccurate, or accurate, in accounting for variance in PAEE (44). The remaining variance is lost when using acceleration cut-offs derived from treadmill calibrations when performing accelerometry recordings during free-living. This remaining unexplained variance in PAEE is likely other types of physical activity, such as cycling (318), swimming, cross-country skiing, and/or resistance exercise (13). Moreover, although hip-worn accelerometry show high correlation with energy expenditure during walking and running (215, 216, 319, 320), acceleration plateaus at $10 \text{ km}\cdot\text{h}^{-1}$ while running, simply due to biomechanics of running; no increased hip movement at running speeds over $10 \text{ km}\cdot\text{h}^{-1}$ (319).

In Paper II, the criterion validity of PAQs were compared against accelerometry-measured physical activity. A criterion measure can be what is considered the ‘gold standard’ within a field but can also be the criterion validity against a chosen criterion. As there is no gold standard for measuring physical activity (321), the criterion in Paper II is not a gold standard criterion, but a criterion with assumed higher precision (44, 57, 58). We did not address concurrent validity of the SGPALS and the PAFID, as these two PAQs ask about usual physical activity levels (over the past year in the SGPALS (39), and over no specific period for the PAFID questionnaire (204)). The IPAQ comparison with accelerometry in Paper II was not a perfect concurrent measurement, as the IPAQ short form sitting question asks about sitting time over the past week, which was compared against seven-day accelerometry recordings in the following week after the participants answered the IPAQ.

According to the findings of Paper II, the validity of the IPAQ sitting question seems to be inaccurate in estimating sitting time, or at least sedentary time. Intuitively, this may not be

surprising, as remembering how much time one spends sitting is challenging. The results of the IPAQ sitting question were inconsistent with a large multicentre study that examined the validity of the IPAQ, with Spearman's correlation ranging from 0.50 to 0.94, with the exception for two centres that had correlations of 0.18 and 0.35 against accelerometry (43). Reasons for these inconsistent findings are likely attributable to regression dilution bias, as there are random measurement errors both in PAQs and accelerometry. Other explanations can be time, place and person (240), especially if cultural differences (*i.e.*, place) are present when answering PAQs (36), or alternatively, the IPAQ sitting question appeared invalid for measuring sedentary time in a population in northern Norway (*i.e.*, person) in 2015-16 (*i.e.*, time).

Regression dilution bias will influence results differently depending on whether the random measurement bias is in the exposure or outcome variable. If the random error is in the exposure variable, then the regression line slope will move towards the null. If the random error is in the outcome variable, then the regression line slope remains unchanged while the standard error of the mean will increase the CI (312). In Paper III and IV, self-reported physical activity is imprecise in measuring physical activity, while BMI is highly precise in measuring the product of weight and height. Therefore, that there is no association between physical activity and BMI may be influenced by regression dilution, as the exposure is diluted by measurement error (107).

In Paper IV, the analyses were also reversed, examining BMI change as the exposure and physical activity change as the outcome. We observed a 15% higher odds ratio when changing from active to inactive, with every increasing unit of BMI. Here, as the exposure is precise while the outcome is imprecise, the association is likely more valid, as the standard error of the mean increased the CI with a point estimate that would be similar if using a measurement tool with less measurement error (107), such as accelerometry. Thus, it is likely that weight gain results in physical activity declines at population level (107), a finding that has been reproduced multiple times (109, 115, 118, 138, 142, 146, 152), while it is less clear if physical activity declines result in weight gain due to regression dilution bias, as most studies used PAQs (107).

4.3.1.3 Response bias

Response bias relates to the effort or motivation of participants to provide accurate results (240), such as adhering to the protocol of a test or using time to accurately answer questionnaires. Tromsø7 is a comprehensive cohort study, and as such, answering all included questionnaires

and examinations in the first visit required an estimated time of 1.5 hours. Thus, many of the included variables in this thesis may, to some degree, be influenced by response bias. Response bias could also influence the participants' motivation to adhere to the protocol for the accelerometry recording (322). However, over 80% of the participants that wore an accelerometer in Tromsø 7 had ≥ 4 days of valid accelerometry wear time in Paper I, which can indicate low influence of response bias.

Response bias may also operate in the opposite direction, *i.e.*, that it increases the effort of participants during measurements. The Hawthorne effect was first mentioned in studies examining the effect of illumination on work productivity in the Hawthorne plant in Chicago, Illinois, United States (323, 324). It was concluded from these studies that people who were being observed, were found to work harder (324). In epidemiology and medicine, this can be related to the placebo effect (324), where people may feel better if they believe strongly in an intervention, such as physical activity, and so they will put more effort into it, and thus experience greater effects.

In physical activity epidemiology, the Hawthorne effect is often named reactivity (46). For example, if participants wear a physical activity tracker/monitor, they may want to show the researcher that they are active, while they normally are less active when not wearing a monitor (46). Thus, response bias can also be social desirability bias. Papers I, II and V are likely influenced by reactivity of the accelerometry recordings, and it is challenging to know the extent of, and how to account for, this bias in analyses. As we adjusted all accelerometry estimates to 16 hours per day in Paper V, we potentially attenuated response bias in Paper V, albeit participants may still perform higher levels than usual.

4.3.1.4 Investigator bias

Investigator bias is related to the researcher, or research technician. There are subjective choices made by a researcher when using accelerometry, which may cause investigator bias (45, 210, 213). Usually, standard operating procedures are chosen by researchers when using accelerometry prior to performing accelerometry recordings. The choices in standard operating procedures include body placement (usual places are lower-back, hip, wrist (210) or thigh (325)), 24-hour or waken-day wear time protocols, and sampling frequency (210). Following the recordings, accelerometry data processing may influence estimates, such as choice of epoch length and wear-time detection algorithms, and calibration of intensity (210).

In Paper I and II, a 24-hour wear time protocol was used and the wear time algorithm by Hecht *et al.* (206) was applied. The wear time algorithm by Hecht *et al.* (206) was calibrated using the RT3 accelerometer (Stayhealthy, Monrovia, California, United States) in chronic obstructive pulmonary disease patients. These choices were outside the range of my decisions in our employed software; Quality Control and Assessment Tool developed in Matlab (The MathWorks, Inc., Natick, Massachusetts, USA). A recent study by Shaheen *et al.* (326) with the same dataset from Tromsø7 as in Paper I and II, used raw accelerometry and a dataset with confirmed wear time from a sub-sample of Tromsø7 with electrocardiogram recordings and evaluated the non-wear time performance of the Troiano *et al.* (71), Choi *et al.* (327) and Hecht *et al.* (206) algorithms. On overall performance, Choi *et al.* (327) was the most appropriate of the count based algorithms, followed by the Troiano *et al.* (71), and the Hecht *et al.* (206) was placed last. However, the Hecht *et al.* (206) algorithm captured similar amount of wear time as the more commonly used Troiano *et al.* (71) algorithm (326). Consequently, although being first validated in diseased patients, the Hecht *et al.* (206) algorithm appears appropriate to use on a larger population-based sample.

A 24-hour wear time protocol was used in Tromsø7 to include a potential of measuring sleep. However, there are few available sleep-detection algorithms, and they are usually not performing well in differentiating between non-wear time and sleep (210). As described in Paper I, the wear time algorithm by Hecht *et al.* (206) appeared to classify non-wear time during night time. Therefore, we determined all non-wear time as both sleep and non-wear time. This most likely caused misclassification bias. All non-wear time algorithms are faced with misclassification bias, especially in classifying non-wear time from sedentary time (*e.g.*, in uniaxial, at <100 cpm (217)), but higher intensity accelerations are most likely activity, as the wear-time algorithms are concerned with consecutive zero acceleration.

For Paper II, additional analyses were performed to compare the IPAQ and accelerometry-measured sedentary time using Bland-Altman plots (205) with different wear time algorithms and between using triaxial and uniaxial acceleration. Regardless of wear time algorithm, or if using triaxial or uniaxial acceleration output, the Bland-Altman plot displayed large discrepancies and negative proportional bias as the mean sedentary time between accelerometry-measured and self-reported sedentary time increased, albeit the mean difference was greatest in uniaxial acceleration using the Hecht *et al.* (206) algorithm.

In Paper V, all accelerometry data were processed using another software (Kinesoft, Loughborough, United Kingdom) than in Paper I and II to harmonize all accelerometry measurements in the cohorts. Here, the wear time algorithm by Troiano *et al.* (71) was used for harmonization purposes, as not all data had triaxial acceleration. We also used a cut-off for MVPA as the average of four calibration studies of young adults (216, 319, 320, 328) (the Troiano wear time algorithm (71)), which is potentially more justifiable than solely using a single calibration study as in Paper I and II (215).

It is previously demonstrated that interpolated intensity-specific accelerometry thresholds corresponding to 3 METs vary depending on cardiorespiratory fitness level (329). As higher cardiorespiratory fitness is inversely associated with age (268, 269), the absolute intensity-thresholds for accelerometry-measured physical activity calibrated in younger adults in Paper I, II (215) and V (71) may not reflect intensities of older adults, given as relative intensity. However, the WHO physical activity guidelines are concerned with absolute intensity (31), and as there is no consensus of intensity-splits in accelerometry-measured physical activity (210), we chose commonly used thresholds (71, 223).

In Paper I, II and V, although we measured sedentary time as previously done (35), it is in reality a measurement of low acceleration, *i.e.*, lower ambulant movement. Sedentary behaviour is defined as “*any waking behaviour characterized by an energy expenditure ≤ 1.5 metabolic equivalents of tasks while sitting, reclining or in lying posture*” (8). Thus, hip worn accelerometers likely also detect standing still. Nevertheless, our finding of low accuracy in the IPAQ sitting question in Paper II are likely still applicable, as the findings in Paper II are consistent with a validity study comparing thigh-worn accelerometry with self-reported sedentary time with a modified IPAQ sitting question (330). Similarly, our findings of effect modification of physical activity in the association between sedentary time and mortality and *vice versa* in Paper V is also still applicable; it is likely that it is total physical activity volume (sum of frequency, duration and intensity), and not posture *per se*, that influences mortality risk (*i.e.*, sedentary time is the reverse of the coin for physical inactivity) (35, 182), which was also evident in Paper V in the stratified analysis for light- and total physical activity.

As one does not perform physical activity 24 hours a day, 7 days a week, physical activity varies across time, and for some, it can be volatile (331). Additionally, in a physical activity

bout, intensity can also vary. In physical activity epidemiology, one usually wants to measure habitual physical activity, as this is a feasible variable for examining associations with health outcomes (213, 332). As measuring physical activity deals with both inter- and intra-individual variability, this leads to non-differential misclassification bias caused by investigator bias, as one must choose the recording days (332). How many days the physical activity measurement requires depend on the chosen tool (e.g., recall questionnaire, diary, heart rate, device) (332).

It is challenging to determine habitual physical activity when using accelerometry, as it is unknown how many days of recording is sufficient to measure habitual physical activity (332). Determining number of recording days for valid habitual physical activity is usually a compromise between having a reliable measure and including sufficient sample sizes, as strict criteria on recording days results in loss of sample size (210). Normally, physical activity epidemiology uses an intraclass correlation of 0.8 for acceptable reliability in measurements, *i.e.*, sufficient consistency to determine habitual physical activity (332).

In general, strict inclusion criteria on recording days provides higher reliability in measurements, however, four days appears sufficient to produce acceptable reliability of total physical activity given as acceleration counts and in light intensity and MVPA (45, 213, 332), and sedentary time (333). Therefore, we used four days of valid wear time of the days that had ≥ 10 hours per day. However, it is previously recommended that if using a 24-hour wear protocol, numbers of valid days should be higher than if using waking time wear protocols (210). However, 80% of the participants in Tromsø 7 had seven days of valid wear time in Paper I, indicating that the accelerometry estimates of physical activity in Paper I and II were sufficiently reliable to determine habitual physical activity level.

In Paper III and IV, we adjusted for baseline weight at the second examination since unadjusted weight may overestimate the association magnitude on weight change (334). Some have suggested that adjusting for baseline values when examining the effect of the exposure on outcome change from baseline to follow-up in observational studies may lead to biased interpretations (334, 335). In observational studies, differential misclassification is expected in many cases (335). Thus, adjusting baseline outcome values is similar to examining the effect of exposure on outcome change, given that all had the same baseline value of the outcome, which may answer another research question than if asking whether different exposures cause

different changes in the outcome (*i.e.*, not adjusting the baseline values) (335). This is known as Lord's paradox (336).

In Lord's paradox, two statisticians examine whether male or female students gained more weight following eating at a university dining hall over two semesters (336). One statistician does not adjust for baseline weight and concludes no difference in weight gain between male and female students, while the other statistician adjusts for baseline weight and concludes that the males gained more weight than the females (336). The paradox lies in that both statisticians provide correct conclusions (336), which complicates the choice of adjusting baseline values of the change outcome of interest in observational studies.

In Paper IV, persistently active and those changing from inactive to active from the first to the second examination had lower baseline BMI at the second examination than those who remained persistently inactive, displaying differential misclassification of baseline BMI values. However, as these differences in Paper IV were within 0.5 of mean BMI units (kg/m^2), it is questionable how much it would influence the results. Nevertheless, displaying and adjusting these baseline values is a type of bias, termed "the horse-racing effect" (337), where one peeks halfway through the race, prior to placing the bet on the horse leading the race (that has less distance left and thus higher chance of winning the race).

In observational research on exposure and weight change, low or high baseline weight will have different potential of change, which may cause a spurious association as it conditions the analysis on baseline weight that may be low or high due to other unobserved causes for weight change prior to baseline. In other words, adjusting baseline values of the outcome change may open a backdoor path to a collider (334), if the collider (*i.e.*, unmeasured cause) is also associated with the exposure. If there is no association between the exposure and the unmeasured cause, then the association can be underestimated, and adjusting baseline may either way cause bias (334).

Adjusting baseline values is usually of greater concern if the outcome measurement includes random measurement error, *i.e.*, non-differential misclassification (334). As non-differential misclassification at baseline and follow up are random, they are independent. Since measurement error at baseline negatively influence change from baseline to follow-up, measurement error at baseline and in the change variable is negatively correlated (334). This

causes regression to the mean (334). However, as measured weight is assumed to be accurate with limited non-differential misclassification (107), adjusting baseline weight will likely not overestimate the association between physical activity and weight change. Rather, it will likely provide a more accurate exposure effect of physical activity as unadjusted baseline weight may overestimate the effect of physical activity on weight change (107) but Lord's paradox (336) still applies where underestimation is plausible (334), as described above. However, in the reverse analyses of Paper IV, self-reported physical activity is influenced by non-differential misclassification (36), both in the outcome change and baseline physical activity. Then, adjusting for the baseline value would then overestimate the association magnitude (334). For this reason, we did not adjust for baseline physical activity levels at the second examination (baseline) when examining the association between weight change as the exposure and physical activity change as the outcome in the reverse analyses in Paper IV.

4.3.1.5 Social desirability bias

In behaviour science, social desirability bias is likely prevalent, but the extent of such bias is challenging to interpret (240). It is common to report more of a behaviour that is perceived socially accepted by the participant, whereas reporting a behaviour that is socially unacceptable may be underreported. For example, the amount of daily cigarette smoking is underreported, while the amount of physical activity is overreported.

In Paper III and IV, we used the SGPALS to measure physical activity. As this is self-reported, it is likely influenced by social desirability bias, as indicated by Paper II. The main finding of Paper II was that the criterion validity of the PAQs against accelerometry seems to depend on how the two PAQs are processed, as grouped ranking or as a continuous variable. This can have implications for future studies and may also be counterintuitive; grouping a continuous variable leads to loss of information and statistical power (239). However, given the consistent observed imprecision of PAQs (36), grouping continuous PAQ scores may lead to important findings that can have relevant public health impact although some information is lost.

4.3.1.6 Confounding bias

Confounding bias occurs when a third variable influence both the exposure and the outcome, and is one of the greatest concerns in epidemiology, as epidemiology mostly deals with observational studies (240). All papers in this thesis are observational and are likely influenced by residual confounding, except the observed values of the measurements in Paper II, as these

compared two instruments intended to measure the same construct without adjustments for covariates.

In Paper I, III, IV and V, we adjusted for likely confounders *a priori* based on previous literature. These *a priori* adjustments are almost uniformly reported in most studies in physical activity epidemiology, mostly according to the correlates of physical activity (76).

However, in Paper III and IV, we did not adjust for energy intake, as it is only available in Tromsø 4 (1994) and Tromsø 7 (2015-16). Energy intake influences energy balance, and this may have caused residual confounding. Nevertheless, energy intake variables estimated from food frequency questionnaires (as in Tromsø 4 and 7) are consistently found to produce great random measurement errors (338), which suggests that energy intake from a food frequency questionnaire is not likely to influence the analysis. For this reason, epidemiologists rarely calculate energy balance and instead infer weight change as energy balance (83, 339). Thus, one could look at Paper III and IV as examining the association between physical activity change and energy balance, *i.e.*, the role of physical activity in energy balance at population level.

In Paper V, we did not adjust for diet quality as this was unavailable due to processing capacity in some cohorts. Diet quality is associated with mortality (284), which may have caused residual confounding in paper V. Nevertheless, as argued in Paper V, other variables could act as proxy measures, such as education, smoking and disease, which are variables that are associated with diet quality (340, 341).

Further, physical inactivity is previously found to display similar lower risk of mortality as socio-economic status (342). Consequently, it might be that the lower risk of mortality is confounded by other factors associated with high socio-economic status, such as diet quality, alcohol intake, obesity, or diabetes (254, 300). Although we adjusted for alcohol intake, BMI and diabetes in Paper V, statistical adjustment in observational data can only adjust estimates, not control for confounding.

Finally, previous studies have demonstrated a similar risk of mortality among twin pairs with discordant physical activity level (343) but due to low number of twins (monozygotic: n=32, dizygotic: n=134), this study was underpowered. Although the study involved more twin-pairs,

there were few twins with discordant physical activity levels (343), highlighting that genetic predisposition may influence physical activity, as observed previously (344).

Although this is likely causing collider bias, this could also be confounding bias due to genetic predisposition (254, 300) that is not associated with participation.

4.3.1.7 Reverse causation bias

In Paper IV, we examined whether the association between physical activity change and BMI change could be reversed, *i.e.*, whether BMI change causes physical activity change and not *vice versa*. In the main analysis, we observed no association between physical activity change and BMI change, while we observed a reversed association. Thus, considering bias associated with self-reported physical activity as described above, the findings in the reverse analysis of Paper IV may be caused by reverse causation bias. However, it is also likely that the association is bidirectional, meaning that physical activity and weight are mutually associated in both directions (107). Bidirectional associations are observed in children and adolescents in a mendelian randomization study (152), and in secondary analysis in a sample from a randomized controlled trial in adults (153).

In Paper V, there is also a risk of reverse causation bias. Naturally, death cannot precede physical activity levels, however, reverse causation bias when examining the association between physical activity and mortality is whether morbidity from health conditions or diseases influences physical activity levels, and therefore, whether an association between higher physical activity and mortality is confounded by morbidity. For this reason, we excluded the first two years of follow-up time to avoid the potential of reverse causation bias. Additionally, we also performed sensitivity analysis by excluding those with <5 years of follow-up time, to examine whether this influenced the association. In the sensitivity analysis, we observed that excluding those with <5 years follow-up time attenuated the association between physical activity and mortality, however, the association between sedentary time and mortality was unchanged. This is consistent with a recent study by Tarp *et al.* (292) regarding the association between physical activity and mortality (292). However, our observation of no changed association between sedentary time and mortality is inconsistent with Tarp *et al.* (292), which indicated that many deaths associated with sedentary time occurred within short time frames. To further elucidate the potential of reverse causation bias from sedentary time, Tarp *et al.* (292) warranted larger cohorts of device-measured sedentary time in older adults. In Paper V,

we used a large sample with mostly older adults. Nevertheless, although excluding years of follow-up potentially attenuates reverse causation bias, it does not eliminate such bias (345).

4.3.2 Selection bias and representativeness

Selection bias occurs when the sample from the base population is unevenly selected, meaning that the findings may not be generalizable to the target population we want to infer causation or description (240). Consequently, selection bias addresses external validity; whether our selected sample is representative of the target population (240). Selection bias includes non-response bias, attrition bias and collider bias.

Rothman *et al.* (280) argue that descriptive epidemiology is not science, meaning that it does not increase our understanding of how nature works. However, one may also argue the opposite, as one would like to know if a prevalence estimate declines or inclines over time, which is nature working its course over time. In Paper III and IV, the broad research question was whether physical activity declines can be one of the aetiology causes for the obesity epidemic. As the obesity epidemic is a consequence of weight gain in the population, having a representative sample of the base population is vital to answer this question. For example, the working mechanism for weight gain is known (energy imbalance (83)), however, what is causing the energy imbalance in the population is less clear and much debated in the literature (107). As such, one of the strengths in Paper III and IV is that the Tromsø Study samples display high participation of invited participants, supporting that the included sample is representative of the base population and thus suitable to answer this research question.

In Paper V, one could argue that the included cohorts are not representative beyond Scandinavia and North America. However, an association between physical activity and mortality is observed across continents (313), suggesting that the potential causal association between physical activity and mortality is universal.

However, in all studies of this thesis, there is a possibility that the results are influenced by selection bias. Those being fit and positive towards physical activity may be more likely to participate in the studies, normally coined as self-selection into study (240) or non-response bias, but also sometimes referred to as the healthy exerciser bias (254). Here, those who are genetically predisposed to be fit are also those able to perform physical activity, which can influence estimates in Paper I by displaying higher physical activity estimates than the physical

activity levels of the base population. This could, in turn, influence the validity of results in Paper II, since the observed criterion validity may only apply for those being fit and healthy and not the base population. Finally, it could cause no association in Paper III and IV as we adjusted baseline values of the outcome as described above (see 5.3.1.4 Investigator bias), or it could cause spurious associations in Paper IV, due to collider bias.

Collider bias is when study participation is associated with both the exposure and outcome, (346-348), where the values of the two variables are conditioned upon study participation, *i.e.*, opening a backdoor path to a collider in directed analytic graphs (346). In Paper I, we observed that those who declined the invitation to wear an accelerometer were more likely to be women, older and less educated than those who accepted the invitation. Women, older individuals, and those in lower educational groups were found to accumulate less physical activity than men, younger individuals, and those with higher education.

Usually, this can be controlled for by adjusting for these variables, as done in Paper V. However, this will only be sufficient if these variables are representative of the base population (346). The response rate in Tromsø7 was 65% of all invited participants, and of the total attending sample who were invited to an extended examination, 63% attended (which is 65% of those invited to the first examination). As both the exposure (education) and outcome (physical activity) are associated with participation in Paper I, controlling for these variables are equivalent to conditioning your analysis on participation that may lead to spurious associations due to conditioned collider bias (346-348), if including unrepresentative samples in your analysis. Thus, uneven distribution of sex, education and age from the base population may have caused collider bias in Paper I, II and V.

For these reasons, the great magnitude in the inverse association between physical activity and mortality in Paper V, which is also observed by others (35, 260), could be influenced by collider bias. Nevertheless, to what extent collider bias causes spurious results is challenging to predict, and may differ depending on each specific cohort (349). Consequently, it is difficult to determine if collider bias is evident in Paper I, II and V of this thesis.

4.3.3 Observational design

Almost all evidence examining an association between physical activity and mortality are based on observational studies (254), which can be influenced by the different biases of relevant

concern in epidemiology. To avoid most of these biases, suggested solutions include co-twin studies of discordant physical activity levels, randomized controlled trials, mendelian randomization, and individual participant data meta-analysis (350).

One twin-study by Karvinen *et al.* (343) found no association between physical activity and mortality in monozygotic twins, however, due to low number of twins (monozygotic: n=32, dizygotic: n=134), this study was underpowered.

Randomized controlled trials may be optimal for examining causal association in many circumstances, as randomization controls for confounding bias (351). In cardiac patients, a Cochrane review of randomized controlled trials (352), and a meta-analysis of randomized controlled trials (353), suggests that exercise rehabilitation lowers mortality risk more than usual care (not involving exercise), however, as these are diseased groups, other biases are applicable (see 5.3.1.6 Confounding bias and 5.3.2 Selection bias).

To my knowledge, the Generation 100 study by Stensvold *et al.* (307) is the only randomized controlled trial that has examined the association between physical activity and mortality in individuals free from disease (*i.e.*, outside clinical care). This study reported similar death rates between those performing structured exercise and those asked to adhere to physical activity guidelines (307). Although the aim of the study was to compare structured aerobic exercise of moderate and high relative intensity (>70% of maximal heart rate) with physical activity levels equivalent to the WHO guidelines in absolute intensity (≥ 3 METs) (307), observing different mortality rates between groups could serve as evidence for lower mortality risk with higher physical activity levels in terms of volume or intensity.

To my knowledge, there is no mendelian randomization study examining a causal association between physical activity and mortality. This may partly be due to the limited number of identified genetic variants associated with physical activity (350).

Paper V addressed this question using a one-step individual participant data meta-analysis, supporting a causal association between physical activity and mortality, which contradicts the twin-study of Karvinen *et al.* (343) and the recent trial by Stensvold *et al.* (307). However, in some circumstances, there may not be an ideal study design to examine a causal association and one must infer causation of the available observational data (354).

5 Conclusions

Thirty percent of all adults are insufficiently active. As low physical activity levels associate with a substantial higher risk of mortality, physical inactivity is a large public health threat. However, even some minutes of physical activity, at any intensity, will likely lower the risk of mortality, and this is also irrespective of the amount of sedentary time. Moreover, although sedentary time is associated with higher risk of mortality, meeting current lower-limit physical activity guidelines ameliorates the mortality risk from high sedentary time. Individual participant data meta-analysis allows for merging large cohort studies, which increases sample size and statistical power and may allow for firmer interpretations. Findings from this thesis strengthens the hypothesis that physical activity is causally associated with mortality; however, future research is needed to postulate a causal association with high certainty.

Validated PAQs provide a translation to higher criterion measures of physical activity. Crude self-reported physical activity groups provided clearer patterns of higher device-measured physical activity by higher grouped ranking, while continuous scales of the PAQs showed small correlation magnitudes with device-measured physical activity. Processing PAQs in crude groups may attenuate biases associated with self-reported physical activity albeit this comes at the expense of detail level in the PAQs. When using crude change groups of PAQs, neither occupational nor leisure time physical activity declines seem to contribute to population weight gain when regressing physical activity changes on BMI or weight changes in prospective designs. It is more likely that population weight gain leads to physical activity declines, however, a bidirectional association cannot be ruled out. This emphasizes that one should look for other major aetiological causes driving the obesity epidemic in order to inform policy.

This thesis highlights the public health gain of increasing population levels of physical activity, and of preventing population weight gain to avoid physical activity declines.

6 References

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Paper I

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RESEARCH ARTICLE

Physical activity levels in adults and elderly from triaxial and uniaxial accelerometry. The Tromsø Study

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Abstract

Introduction

Surveillance of physical activity at the population level increases the knowledge on levels and trends of physical activity, which may support public health initiatives to promote physical activity. Physical activity assessed by accelerometry is challenged by varying data processing procedures, which influences the outcome. We aimed to describe the levels and prevalence estimates of physical activity, and to examine how triaxial and uniaxial accelerometry data influences these estimates, in a large population-based cohort of Norwegian adults.

Methods

This cross-sectional study included 5918 women and men aged 40–84 years who participated in the seventh wave of the Tromsø Study (2015–16). The participants wore an Acti-Graph wGT3X-BT accelerometer attached to the hip for 24 hours per day over seven consecutive days. Accelerometry variables were expressed as volume (counts·minute⁻¹ and steps·day⁻¹) and as minutes per day in sedentary, light physical activity and moderate and vigorous physical activity (MVPA).

Results

From triaxial accelerometry data, 22% (95% confidence interval (CI): 21–23%) of the participants fulfilled the current global recommendations for physical activity (≥150 minutes of MVPA per week in ≥10-minute bouts), while 70% (95% CI: 69–71%) accumulated ≥150

publication of datasets with the potential of reverse identification of de-identified sensitive participant information. The data can however be made available from the Tromsø Study upon application to the Tromsø Study Data and Publication Committee. Contact information: The Tromsø Study, Department of Community Medicine, Faculty of Health Sciences, UiT The Arctic University of Norway; e-mail: tromsous@uit.no.

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minutes of non-bouted MVPA per week. When analysing uniaxial data, 18% fulfilled the current recommendations (i.e. 20% difference compared with triaxial data), and 55% (95% CI: 53–56%) accumulated ≥ 150 minutes of non-bouted MVPA per week. We observed approximately 100 less minutes of sedentary time and 90 minutes more of light physical activity from triaxial data compared with uniaxial data ($p < 0.001$).

Conclusion

The prevalence estimates of sufficiently active adults and elderly are more than three times higher (22% vs. 70%) when comparing triaxial bouts and non-bouted MVPA. Physical activity estimates are highly dependent on accelerometry data processing criteria and on different definitions of physical activity recommendations, which may influence prevalence estimates and tracking of physical activity patterns over time.

Introduction

Physical inactivity is the fourth-leading cause for premature mortality globally, and the health benefits of physical activity are undisputable [1–3]. Thus, surveillance of physical activity at the population level is crucial in order to track levels and trends of physical activity, which may support public health initiatives to promote physical activity [4].

Traditionally, physical activity is assessed using self-report methods, which are susceptible to recall and social desirability bias [5]. Over the last two decades, the use of objective approaches to measure bodily movements, such as accelerometers, have progressively increased and may complement self-reported measures in large scale population-based studies [6–9]. However, accelerometry measured physical activity levels vary across different populations, socioeconomic status, sex and body composition [10–15]. Although these differences may be true, inherent variations in device technology and data processing procedures influence the outcome [7] and may hamper the comparability between studies.

Additionally, more recent accelerometers measure acceleration in three axes (vertical, coronal and sagittal) [7], whereas older models that are used in many observational studies measured acceleration in the axial (vertical) plane only [6]. Triaxial accelerometers are expected to record a wider range of movement and activities than uniaxial accelerometers [16]. In laboratory studies, measures of standardized activities from uniaxial and triaxial accelerometry differs in adolescents [17], but are similar in adults [18]. However, in free-living studies of adults, triaxial accelerometry data detected more minutes in higher intensity physical activity [8] and a larger volume of sporting activities than uniaxial accelerometry data [19]. To our knowledge, no study has compared triaxial and uniaxial accelerometry data from the GT3X ActiGraph accelerometer in a large population-based sample during free-living conditions. Thus, considering the potential differences in triaxial and uniaxial data, comparisons of prevalence estimates in a large population sample are warranted.

The current global recommendations for physical activity suggests at least 150 minutes of moderate and vigorous physical activity (MVPA) per week in at least 10-minute bouts [20]. Recently, new recommendations in the United States have omitted the bout length requirement [21]. When comparing prevalence estimates of bouts and non-bouted MVPA from uniaxial accelerometry, the proportions fulfilling the recommendations vary largely (1%–70%)

[10, 22, 23]. Although similar discrepancies may be expected from triaxial accelerometry, the proportional differences are unknown.

The aim of this study was to describe the levels and prevalence of physical activity in a large population-based cohort stratified by age, sex, body mass index (BMI) and educational level; and to compare potential differences in these estimates between triaxial and uniaxial accelerometry data.

Materials and methods

Design

The Tromsø Study is an ongoing population-based cohort study in the municipality of Tromsø, Norway. The study invites participants from previous surveys as well as random samples in repeated surveys (Tromsø 1: 1974, Tromsø 2: 1979–80, Tromsø 3: 1986–7, Tromsø 4: 1994–95, Tromsø 5: 2001, Tromsø 6: 2007–08, Tromsø 7: 2015–16). The data collection consists of questionnaires and interviews, biological sampling and clinical examinations. The detailed design of the Tromsø Study is described elsewhere [24]. The present study includes participants from the seventh survey conducted in 2015–16.

In Tromsø 7, all inhabitants of Tromsø municipality aged 40 years and older ($N = 32591$) were invited to the first visit, of which 21083 (65%) attended. Of all invited participants to Tromsø 7, a sub-sample was invited back for a second visit that included more extensive examinations. This sub-sample ($n = 13304$) included 20% of the inhabitants 40–59 years ($n = 4,008$) and 50% of the inhabitants 60–84 years ($n = 6,142$) randomly drawn from the total sample. In addition, previous participants in selected clinical examinations in Tromsø 6 not already included in the random sample were added ($n = 3,154$). Of the 8346 attending the second visit, due to logistical reasons, 6778 were invited to wear an accelerometer, of which 6333 (93%) accepted. Participants without valid accelerometry data due to lost accelerometers ($n = 6$), returned accelerometers with technical error ($n = 37$) or with invalid wear time data ($n = 165$) were excluded. Accordingly, 6125 participants provided valid wear time of four days of at least 10 hours. Of these, 167 and 65 participants did not report their educational level and smoking habits, respectively, and 24 did not undergo weight and/or height measurement. With some failing to report two or more potential covariates, we ended up with a sample of 5918 participants aged 40–84 years with valid data on accelerometry measured physical activity and potential confounders, which are included in our analyses.

All participants gave written informed consent. Tromsø 7 and this present study were approved by the Regional Ethics Committee for Medical Research (REC North ref. 2014/940 and 2016/758410, respectively) and the Norwegian Data Protection Authority.

Data collection

Height and weight were measured in light clothing without shoes. BMI was calculated as weight divided by the square of height ($\text{kg}\cdot\text{m}^{-2}$) and defined as normal- and underweight ($<25 \text{ kg}\cdot\text{m}^{-2}$), overweight ($25\text{--}29.9 \text{ kg}\cdot\text{m}^{-2}$) or obese ($\geq 30 \text{ kg}\cdot\text{m}^{-2}$), respectively. Information on educational level was collected from questionnaires and categorized in four groups; 1) primary school, 2) high school diploma, 3) University education <4 years and 4) University education ≥ 4 years.

Physical activity and sedentary behaviour were measured with an ActiGraph wGT3X-BT accelerometer (ActiGraph, LLC, Pensacola, United States), firmware versions 1.2.0- to 1.8.0. Trained technicians instructed each participant on how to wear the accelerometer before attaching the accelerometer to their right hip using an elastic band. Participants were instructed to wear the accelerometer for 24 hours a day for eight consecutive days and nights

(the rest of the day following the visit in the clinic and seven more days), perform their daily activities as usual, and only to remove the accelerometer during water-based activities (e.g. showering or swimming) and contact sports. The participants returned the accelerometer by mail in a pre-paid envelope. The ActiLife software (ActiGraph, LLC, Pensacola, United States) was used for initialisation and downloading the data. The accelerometer was initialized for raw data mode with a sampling frequency of 100 hertz and were set to start recording at 00:00 the day following the visit in the clinic.

Accelerometry data processing

When reducing the raw acceleration files to epochs, the normal (default) filter in the ActiLife software was applied, which is proprietary to the manufacturer [7, 25]. The epochs were aggregated to 10 seconds. The .agd-files (epoch files) were further converted to .csv-files using the ActiLife software, which were thereafter analysed using the Quality Control & Analysis Tool (QCAT), a custom-made software for processing of accelerometry data developed in Matlab (The MathWorks, Inc., Natick, Massachusetts, USA). The acceleration units are expressed in triaxial vector magnitude (VM) (the square root of the sum of squared activity counts) counts per minute (CPM), and as uniaxial CPM for data from the axial plane (vertical axis) only. The step count of the accelerometer was derived from the axial plane, based on a proprietary algorithm developed by the manufacturer.

The 10-second epoch data was summed to 1 minute, where each minute was classified as wear time if either its value was ≥ 5 VM CPM and there were at least 2 minutes ≥ 5 VM CPM on the proceeding or following 20-minute time span, or if its value did not exceed 5 VM CPM, but both on the preceding, and on the following 20-minute, there were 2 or more minutes of ≥ 5 VM CPM. Otherwise the acceleration was considered to be noise and classified as non-wear time [26]. Recordings containing at least four days with a minimum of 10 hours wear time each, were included in the analyses [7, 27]. All files flagged with invalid wear time data were visually inspected to confirm that the participants did not have valid wear time data (≤ 10 hours and ≤ 4 days). By visual inspection of diagrams from 30 random participants, the non-wear time algorithm appears to exclude sleep, which is thus defined as non-wear time in our analyses.

The triaxial VM CPM cut-points for different intensities were determined according to Peterson et al. [28] for sedentary behaviour and Sasaki et al. [29] for MVPA as follows: sedentary behaviour: < 150 , light physical activity: 150–2689, and MVPA: ≥ 2690 VM CPM. Intensity-specific cut-points for the axial plane were < 100 CPM for sedentary behaviour, a cut-point originally determined for adolescents girls [30] but also later adopted for adults [31]. For light physical activity and MVPA, the uniaxial CPM cut-points were set between 100 and 1951 CPM and ≥ 1952 CPM, respectively [32]. The study by Peterson et al. [28] suggest that 100 uniaxial CPM are equivalent to 150 triaxial VM CPM. The studies by Sasaki et al. [29] and Freedson et al. [32] validated the respective cut-points using similar protocols that are matched in locomotion speeds on the treadmill and the movements should thus be biomechanically equivalent, resulting in comparable triaxial and uniaxial intensity specific cut-points for walking and running.

The following variables were extracted for our analyses: days of wear time, mean wear time per valid day of wear time, mean uniaxial CPM, mean triaxial VM CPM, mean steps per day, time ($\text{min} \cdot \text{day}^{-1}$) spent in sedentary-, light-, moderate and vigorous intensity physical activity, and the percentage meeting the World Health Organisation (WHO)'s recommended levels of physical activity (i.e. ≥ 150 min of MVPA per week in ≥ 10 -minute bouts) [20]. Participants who accumulated ≥ 22 mean minutes of MVPA per day in at least 10-minute bouts (i.e. 150

minutes per week divided by seven days) were considered meeting the recommendations. This criteria of 150 min of MVPA per week was also assessed in accumulated non-bouted MVPA [21]. We assumed that triaxial VM CPM would capture more movements than uniaxial CPM. Thus, physical activity estimates are primarily derived from triaxial VM CPM, which are compared to uniaxial CPM.

Availability of data and materials

The full variable list for accelerometry estimates of physical activity data in the Tromsø Study is available at NESSTAR WebView tool [33]. The data that support the findings of this study are available from the Tromsø Study but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. The data can however be made available from the Tromsø Study upon application to the Data and Publication Committee of the Tromsø Study [34]. The Matlab code for the QCAT software for the current study can be made available upon reasonable request to the corresponding author, however, the accelerometry data processing of epoch data was carried out in the QCAT software as described above. The QCAT software is under development and is planned to be made publicly available as an open source software in the future.

Statistical analysis

All data were confirmed to be normally distributed by visual inspection of the residuals when performing univariate analyses of covariance (ANCOVA) to assess associations between physical activity measures and age (10-year age groups), sex, BMI and educational level, with mutual adjustment for each other (e.g. when analysing physical activity by BMI, these analyses are adjusted for sex, age, and education etc.) in addition to adjustment for smoking and height. Paired samples t-tests was performed to check for differences between triaxial and uniaxial results, without adjustments for covariates. Independent sample t-tests was performed to assess for differences in age, weight, height and BMI between the total sample and the accelerometer sample, in addition to assess for sex differences in descriptive variables, in both the total and the accelerometer sample. Finally, we performed Pearson's chi square tests to assess differences in the distribution of BMI groups, educational level and smoking habits among those who were invited but declined to wear an accelerometer and those who were invited and accepted the invitation. The descriptive physical activity estimates are presented as unadjusted mean \pm standard deviation (SD) unless otherwise is stated. The Statistical Package for Social Sciences (Version 25, International Business Machines Corporation, United States) was used to perform all statistical analysis.

Results

Overall and sex specific participant characteristics of the total Tromsø 7 sample with valid data on covariates (BMI, education and smoking, $N = 20485$) are presented in [Table 1](#). Overall and sex specific participant characteristics of the accelerometry sample ($N = 5918$) are presented in [Table 2](#). There were no differences in BMI between the total sample and the accelerometry sample ($p = 0.054$), while age, height and weight differed between the total sample and the accelerometry sample ($p < 0.001$). In the accelerometry sample, women had lower BMI, height and weight than men (all $p < 0.001$). Age distribution varied, where the age group 60–69 years consisted of 42% of the sample. The majority of the sample was overweight, as 45.3% ($n = 2681$) and 22.6% ($n = 1337$) were classified as overweight and obese, respectively.

Table 1. Participant characteristics. The Tromsø Study total sample 2015–16.

	Women	Men	Total
N	10753 (52.5%)	9732 (47.5%)	20485
Age (years)	57.0 ± 11.3	57.2 ± 11.2	57.1 ± 11.3
Height (cm)*	164.3 ± 6.5	177.8 ± 6.7	170.7 ± 9.4
Weight (kg)*	72.6 ± 13.9	88.1 ± 14.2	80.0 ± 16.0
BMI (kg·m ⁻²)*	26.9 ± 4.9	27.8 ± 4.0	27.3 ± 4.5
<25	4329 (64.9%)	2337 (35.1%)	6666 (32.5%)
25–29.9	3997 (44.6%)	4958 (55.4%)	8955 (43.7%)
>30	2427 (49.9%)	2437 (50.1%)	4864 (23.7%)
Educational level			
Primary school	2567 (54.4%)	2149 (45.6%)	4716 (23%)
High school	2735 (48.0%)	2963(52.0%)	5698 (27.8%)
University <4 yrs	1897 (47.8%)	2070 (52.2%)	3967 (19.4%)
University ≥4 yrs	3554 (58.2%)	2550 (41.8%)	6104 (29.8%)
Smoking			
Daily	1558 (54.8%)	1288 (45.2%)	2849 (13.9%)
Previous	4706 (52.0%)	4340 (48.0%)	9046 (44.2%)
Never	4489 (52.2%)	4104 (47.8%)	8593 (41.9%)

BMI = body mass index. Data are shown as mean ± standard deviation or n (%). The presented relative (%) prevalence is horizontal between women and men, while in the total column vertical between groups of BMI, educational level and smoking. *Significant difference between women and men (p<0.001)

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Overall physical activity levels

On average, the participants wore the accelerometer for 6.8 (SD: 0.5) days, and 58 (1%), 151 (3%), 860 (15%) and 4849 (81%) participants provided four, five, six and seven days of ≥10 hours of wear time, respectively. Mean wear time per day was 17.3 (SD: 1.8) hours. The

Table 2. Participant characteristics. The Tromsø Study accelerometry sample 2015–16.

	Women	Men	Total
N	3172 (53.6%)	2746 (46.4%)	5918
Age (years)	63.4 ± 10.2	63.4 ± 10.1	63.3 ± 10.2
Height (cm)*	163.6 ± 6.3	176.9 ± 6.7	169.8 ± 9.3
Weight (kg)*	71.7 ± 12.9	86.9 ± 13.7	78.8 ± 15.3
BMI (kg·m ⁻²)*	26.8 ± 4.7	27.8 ± 3.9	27.2 ± 4.4
<25	1218 (64.1%)	682 (35.9%)	1900 (32.1%)
25–29.9	1270 (47.4%)	1411 (52.6%)	2681 (45.3%)
>30	684 (51.2%)	653 (48.8%)	1337 (22.6%)
Educational level			
Primary school	1008 (58.2%)	724 (41.8%)	1732 (29.2%)
High school	838 (50.1%)	834 (49.9%)	1672 (28.3%)
University <4 yrs	515 (46.4%)	594 (53.6%)	1109 (18.7%)
University ≥4 yrs	811 (57.7%)	594 (42.3%)	1405 (23.7%)
Smoking			
Daily	396 (56.4%)	306 (43.6%)	702 (12%)
Previous	1498 (47%)	1405 (51%)	2903 (49%)
Never	1278 (40%)	1035 (37%)	2313 (39%)

BMI = body mass index. Data are shown as mean ± SD or n (%). The presented relative (%) prevalence is horizontal between women and men, while in the total column vertical between groups of BMI, educational level and smoking. *Significant difference between women and men (p<0.001)

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Table 3. Volume measures and intensity specific minutes per day by sex. The Tromsø Study accelerometry sample 2015–16.

	Women (n = 3172)	Men (n = 2746)	Total (n = 5918)
Wear time per day (hr)	17.2±1.7	17.3±1.9	17.3±1.8
Uniaxial counts per minute	249.4±103.9*	264.5±119.9	256.4±111.87
Vector magnitude counts per minute	539.5±168.5	530.4±187.3	535.3±177.5
Steps per day	6999.9±2940.1	6932.7±2924.5	6968.7±2932.8
Sedentary behaviour uniaxial (min·day ⁻¹)	687.8±93.7	704.8±104.5	695.7±99.2
Sedentary behaviour triaxial (min·day ⁻¹)	574.4±94.2	604.7±103.4	588.5±99.7
Light physical activity uniaxial (min·day ⁻¹)	318.2±78.3	300.2±81.6	309.9±80.4
Light physical activity triaxial (min·day ⁻¹)	417.5±86.1*	384.2±86.9	402.0±88.1
MVPA uniaxial			
With 10-min bouts (min·day ⁻¹)	11.2±14.9	11.6±16.2	11.3±15.5
Without 10-min bouts (min·day ⁻¹)	28.0±22.3*	31.8±25.7	29.8±24.0
MVPA triaxial			
With 10-min bouts (min·day ⁻¹)	13.2±16.2	13.7±18.3	13.4±17.2
Without 10-min bouts (min·day ⁻¹)	38.4±27.6*	44.0±32.3	41.0±30.0

Data are shown as unadjusted mean ± SD. The presented P_{equality} derives from the ANCOVA and is adjusted for educational level, body mass index, height, age and smoking. MVPA = moderate and vigorous physical activity. *significant difference between women and men ($p < 0.05$).

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participants accumulated a mean of 535 (SD: 2.3) VM CPM and 6968.7 (SD: 2932.8) steps per day. From triaxial accelerometry data, time spent in sedentary behaviour and light physical activity was 9.8 (SD: 1.7) and 6.7 (SD: 1.5) hours per day, respectively. The participants accumulated 41 (SD: 30) and 13 (SD: 17.2) minutes per day of non-bouted MVPA and bouted MVPA, respectively (Table 3).

Physical activity levels by age, sex, BMI and educational level

There were no sex differences in volume estimates (VM CPM and steps per day) or in time spent sedentary (Table 3). Women accumulated more minutes of light physical activity than men ($p < 0.001$) and men accumulated more minutes of non-bouted MVPA than women ($p < 0.001$), while women and men accumulated an equal amount of bouted MVPA ($p = 0.08$) (Table 3). In total, 22% (95% C.I.: 21–23%) fulfilled the recommended levels of physical activity (determined as ≥ 22 minutes MVPA per day in ≥ 10 -minute bouts), compared with 70% (95% CI: 69–71%) in accumulated non-bouted MVPA (Fig 1).

All physical activity measures were inversely associated with age ($p < 0.001$), except for time spent in sedentary behaviour ($p = 0.01$) (Table 4).

Steps per day and VM CPM were inversely associated with BMI ($p < 0.001$) (Table 5). Sedentary time was positively associated with BMI ($p = 0.02$), while light physical activity, accumulated non-bouted MVPA and bouted MVPA were inversely associated with BMI ($p < 0.001$) (Table 5).

Finally, VM CPM, steps per day and sedentary behaviour were not associated with educational level ($p > 0.06$). There were differences in light physical activity between educational levels ($p = 0.003$), and bouted MVPA were positively associated with educational level ($p = 0.02$). There were no differences in accumulated non-bouted MVPA between educational levels ($p = 0.59$) (Table 6).

Triaxial versus uniaxial data processing

There were differences between all triaxial and uniaxial accelerometry estimates of physical activity (all $p < 0.05$) (Table 3, 4, 5 and 6). Data from triaxial accelerometry data resulted in

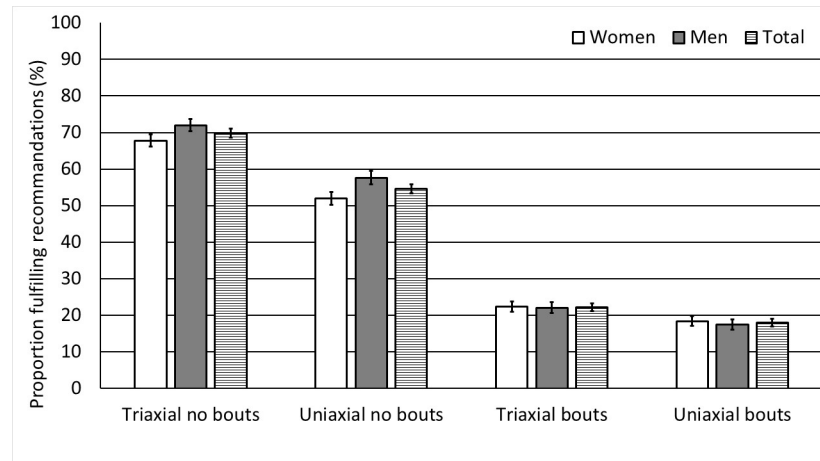


Fig 1. The proportion of women (n = 3172) and men (n = 2746) separately, and in total (n = 5918), fulfilling the WHO's recommendations for physical activity of 150 minutes of MVPA per week, in both accumulated non-bouted and bouted MVPA and from triaxial and uniaxial data. Data is shown as percentage and error bars are 95% C.I.

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~110 less minutes spent sedentary and ~90 more minutes spent in light physical activity compared with data from uniaxial accelerometry ($p < 0.001$). A larger proportion of participants (22%, 95% C.I.: 21–23%) fulfilled the current physical activity recommendations when using triaxial data compared with analyses from uniaxial accelerometry (18%, 95% C.I.: 17–19%). For accumulated non-bouted MVPA, the corresponding prevalence estimates were 70% (95% C.I.: 69–71%) and 55% (95% C.I.: 53–56%) from tri- and uniaxial accelerometry, respectively (Fig 1).

Additionally, comparisons of tri- and uniaxial accelerometry resulted in different associations with age, sex, BMI and education; Women accumulated more minutes in light intensity physical activity than men from triaxial data ($p < 0.001$), which was not observed from uniaxial data ($p = 0.10$) (Table 3). Sedentary time was positively associated with BMI from triaxial data ($p = 0.02$), but not from uniaxial data ($p = 0.06$) (Table 5). There was a difference in light physical activity between BMI groups from triaxial data ($p < 0.001$), but not from uniaxial data ($p = 0.06$) (Table 5).

Dropout analysis

There were no differences in distribution of smoking habits ($p = 0.45$) and BMI groups ($p = 0.62$) between participants who accepted and participants who declined the invitation to wear an accelerometer. A larger proportion of women than men declined the invitation to wear an accelerometer ($p = 0.04$), and participants who declined were older and had lower education than those who accepted the invitation ($p < 0.001$).

Discussion

In this population-based study of Norwegian adults and elderly, 22% fulfilled the current global recommendation for physical activity, however, when counting all accumulated non-bouted MVPA, the proportion increased three-fold, to 70%. Physical activity levels were inversely associated with older age and men accumulated more minutes of non-bouted MVPA than women. Those with lower BMI and higher education accumulated more minutes in MVPA. Furthermore, our results suggest higher prevalence estimates of sufficiently active

Table 4. Volume measures and intensity specific minutes per day by age groups. The Tromsø Study accelerometry sample 2015–16.

	40–49 years (n = 759)	50–59 years (n = 986)	60–69 years (n = 2501)	70–79 years (n = 1437)	≥80 years (n = 235)	P _{equality}
Wear time per day (hr)	17.4±1.5	17.6±1.6	17.4±1.7	16.8±1.9	16.2±2.2	<0.001
Uniaxial counts per minute	301.8±117.3	289.5±106.3	261.7±107.3	214.6±101.9	170.6±88.6	<0.001
Vector magnitude counts per minute	609.3±179.3	578.9±166.6	542.5±172.4	475.5±167.4	402.1±142.6	<0.001
Steps per day	8135.4±2814.0	7964.6±2756.8	7198.7±2831.5	5681.4±2631.6	4449.9±2448.7	<0.001
Sedentary behaviour uniaxial (min·day ⁻¹)	686.3±95.3	699.0±95.5	698.0±99.6	694.4±100.5	695.8±112.4	0.009
Sedentary behaviour triaxial (min·day ⁻¹)	579.5±96.1	593.3±96.0	593.0±99.5	584.5±101.8	573.3±111.4	0.01
Light physical activity uniaxial (min·day ⁻¹)	322.5±75.3	320.3±75.7	315.5±79.4	294.1±82.7	262.0±80.0	<0.001
Light physical activity triaxial (min·day ⁻¹)	409.8±83.3	408.4±83.6	405.7±87.3	391.6±93.3	376.7±87.0	<0.001
MVPA uniaxial						
With 10 min bouts (min·day ⁻¹)	12.6±15.1	13.8±15.7	12.3±16.2	8.1±14.2	5.4±11.8	<0.001
Without 10 min bouts (min·day ⁻¹)	37.1±24.0	36.6±23.4	31.1±24.1	21.4±21.5	14.0±18.4	<0.001
MVPA triaxial						
With 10 min bouts (min·day ⁻¹)	15.1±16.5	16.1±17.0	14.5±18.0	10.0±16.1	6.5±13.0	<0.001
Without 10 min bouts (min·day ⁻¹)	52.7±29.1	49.5±28.7	42.7±29.8	29.9±27.3	18.4±22.0	<0.001

Data are shown as unadjusted mean ± SD. The presented P_{equality} derives from the ANCOVA and is adjusted for body mass index, sex, educational level, smoking and height. MVPA = moderate and vigorous physical activity.

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participants from triaxial accelerometry data than from uniaxial accelerometry data, and we observed differences in all measures from tri- and uniaxial data, which was consistent across age, sex, BMI, and education.

Our prevalence estimates of physical activity based on accelerometry suggest that 1 out of 5 are fulfilling the current recommendations of ≥150 minutes per week of MVPA, which is

Table 5. Volume measures and intensity specific minutes per day by BMI. The Tromsø Study accelerometry sample 2015–16.

	Normal weight (n = 1900)	Overweight (n = 2681)	Obese (n = 1337)	P _{equality}
Wear time per day (hr)	17.5±1.7	17.2±1.8	17.0±1.9	<0.001
Uniaxial counts per minute	279.7±119.2	256.6±109.7	222.8±95.9	<0.001
Vector magnitude counts per minute	579.1±183.0	533.5±171.9	472.9±162.6	<0.001
Steps per day	7857.7±3132.5	6929.1±2768.9	5784.7±2497.5	<0.001
Sedentary behaviour uniaxial (min·day ⁻¹)	698.2±101.4	692.4±96.4	699.0±100.7	0.06
Sedentary behaviour triaxial (min·day ⁻¹)	575.4±101.3	587.3±96.4	609.3±100.7	0.02
Light physical activity uniaxial (min·day ⁻¹)	314.7±81.0	312.0±79.8	298.7±79.7	0.06
Light physical activity triaxial (min·day ⁻¹)	422.1±87.1	402.0±85.1	373.6±87.5	<0.001
MVPA uniaxial				
With 10-min bouts (min·day ⁻¹)	15.6±18.0	10.8±14.8	6.2±10.9	<0.001
Without 10-min bouts (min·day ⁻¹)	35.7±25.6	29.5±23.4	21.9±20.2	<0.001
MVPA triaxial				
With 10-min bouts (min·day ⁻¹)	17.8±19.4	13.1±16.7	7.9±12.8	<0.001
Without 10-min bouts (min·day ⁻¹)	47.0±31.4	40.8±29.6	32.9±26.7	<0.001

Data are shown as unadjusted mean ± SD. The presented P_{equality} derives from the ANCOVA and is adjusted for age, sex, educational level, smoking and height. BMI = body mass index, MVPA = moderate and vigorous physical activity.

<https://doi.org/10.1371/journal.pone.0225670.t005>

Table 6. Volume measures and intensity specific minutes per day by education. The Tromsø Study accelerometry sample 2015–16.

	Primary School (n = 1732)	High School (n = 1672)	University <4 years (n = 1109)	University ≥4 years (n = 1405)	P _{equality}
Wear time per day (hours)	17.0±1.9	17.3±1.8	17.3±1.9	17.4±1.7	0.26
Uniaxial counts per minute	230.2±107.1	251.2±108.8	264.9±107.6	288.1±115.9	0.18
Vector magnitude counts per minute	505.4±178.5	533.3±178.7	538.6±171.9	571.9±172.5	0.58
Steps per day	6128.4±2803.5	6906.1±2819.9	7154.9±2828.9	7931.5±2991.6	0.07
Sedentary behaviour uniaxial (min·day ⁻¹)	686.6±101.2	695.7±98.5	701.8±102.1	702.1±94.3	0.06
Sedentary behaviour triaxial (min·day ⁻¹)	578.9±100.2	588.3±100.8	596.9±102.0	593.9±95.1	0.10
Light physical activity uniaxial (min·day ⁻¹)	311.3±85.8	316.4±81.4	304.7±76.5	304.4±74.3	0.002
Light physical activity triaxial (min·day ⁻¹)	404.9±94.0	407.8±87.5	394.3±85.6	397.8±82.2	0.003
MVPA uniaxial					
With 10-min bouts (min·day ⁻¹)	7.9±13.5	9.8±13.9	12.4±15.1	16.5±18.3	0.02
Without 10-min bouts (min·day ⁻¹)	23.1±22.4	28.1±22.7	32.0±22.7	38.2±25.6	0.06
MVPA triaxial					
With 10-min bouts (min·day ⁻¹)	9.6±15.6	11.9±15.6	14.7±16.6	18.9±19.7	0.02
Without 10-min bouts (min·day ⁻¹)	33.8±29.8	40.2±29.8	43.1±28.3	49.3±29.6	0.59

Data are shown as unadjusted mean ± SD. The presented P_{equality} derives from the ANCOVA and is adjusted for sex, age, body mass index, smoking and height. MVPA = moderate and vigorous physical activity.

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substantially lower than the global estimate from self-reported physical activity in western high-income countries (~63%) [35]. As self-reported physical activity is prone to recall and social desirability bias, self-report may overestimate the true physical activity level [36], which may indicate that more accurate estimates can be derived from device-based assessments (e.g. accelerometry) [37]. Thus, understanding how different measurements tools may influence the prevalence estimates is important to inform public health recommendations and policies.

The WHO's physical activity recommendations for health are primarily based on self-reported physical activity [20]. Recently, based on data from both self-report and accelerometry, the revised United States recommendations for physical activity omitted the requirement that MVPA should be performed in at least 10-minute bouts [21]. Although the domain or type of MVPA is unknown, non-bouted MVPA may represent more sporadic activities and small bursts of movements, which may include transportation, stair climbing or house work, compared to bouted MVPA, which may be more planned and structured activities [38]. It is likely that individuals report activities when responding to self-report instruments that will not be detected as continuous ≥10 minutes by an accelerometer (e.g. playing intermittent sports, walking with stops to cross a road or to rest for some minutes). Thus, when using a stringent ≥10 minute criteria for fulfilling the recommendation, physical activity assessed by accelerometry may lead to an underestimation of the true prevalence.

Our data showed that the proportion fulfilling the recommended levels is highly dependent on whether MVPA is measured as bouted or accumulated non-bouted time; we observed a three-fold increase from 22% in bouted MVPA to 70% in accumulated non-bouted MVPA. Such patterns are also observed in previous studies from uniaxial accelerometry [10, 22, 39]. Moreover, when non-bouted MVPA is measured, our prevalence estimate is closer to the global estimate from self-reported physical activity [35], suggesting that such sporadic physical activity is also included in accelerometry when measuring non-bouted MVPA. Thus, understanding how different definitions of sufficiently active individuals may influence the prevalence estimates is important to inform public health recommendations and policies.

Furthermore, a recent meta-analysis showed maximal risk reduction in all-cause mortality at 24 minutes per day of accelerometry measured MVPA [40], which is similar to our chosen threshold for fulfilling the recommendations of 150 minute per week. The 24 minutes of MVPA for maximal risk reduction is also a substantially lower volume than what have previously been estimated from self-reported methods [41], indicating that the magnitude of the association between MVPA and mortality is in fact underestimated by self-reported methods. Accelerometry has been successfully implemented in surveillance systems and large cohorts [10, 22, 23, 42] and will likely be used in combination with self-reported physical activity in future large-scale studies. Thus, future studies that elucidates how different measurement tools influences the association with health outcomes is warranted.

Our prevalence estimates are similar to previous studies in Norwegian adults [14, 43], but higher than comparable estimates in Germany [42], Sweden [44], Portugal [10], the United States [11] and the United Kingdom [15, 22]. The observation of lower physical activity levels with higher age seems consistent across all studies measuring physical activity by accelerometry [10, 11, 14, 15, 22, 39, 42]. In previous studies, low levels of physical activity in older age are associated with disabilities such as difficulties in walking, pain and physical complaints [42, 45], indicating that the ageing process may influence physical activity levels. However, associations with disabilities disappear when controlling for morbidity confounders [45]. To date, there is no biological explanation for the consistent observed declines in physical activity levels with age, hence, encouraging older individuals to maintain or increase their physical activity levels may stimulate to healthy ageing and may thus have considerable impact on public health.

We found that men spent more time in accumulated non-bouted MVPA than women, whereas no sex differences were observed in bouts MVPA. In previous studies, male participants in studies from Norway [14, 43], the United States [11], Portugal [10], Germany [42] and the United Kingdom [15] accumulated more minutes of MVPA than female participants, whereas Swedish [39] and Chinese [13] women and men accumulated an equal amount of MVPA. The differences between the present study and the abovementioned studies may be due to different data processing protocols, thus, comparisons should be done with caution.

The inverse association between objectively assessed physical activity and BMI observed in the present study is consistent with previous studies [13, 14, 42]. Although a recent systematic review suggest that physical activity can prevent weight gain at the population level [46], methodological issues challenge this interpretation [47]. Basically, it is equally likely that lower levels of physical activity result in high BMI as *vice versa*, however, the direction in the association cannot be determined from cross-sectional designs [48].

Furthermore, our study demonstrated a positive association between bouts MVPA and educational level, which is consistent with studies from other high-income countries [13, 14, 49, 50]. Suggested reasons for lower MVPA in low education groups may include low perceived control, family responsibilities, poor perceived health, and financial and housing problems [51], as well as lack of knowledge of health benefits, attitudes and motivation towards physical activity [49]. Additionally, higher education is also associated with sedentary occupations [52], which may be compensated by an increased engagement in higher intensity leisure time physical activity [49]. In contrast, individuals with lower education are more likely to possess jobs including standing and/or walking, usually of light intensity physical activity [53, 54]. It is previously demonstrated that less sitting time at work may be associated with higher sitting time during leisure time [55]. Hence, those with lower education may be exposed to a more exhaustive working environment resulting in less leisure time physical activity of higher intensity due to the necessity of rest [53, 55, 56].

However, there were no differences in accumulated non-bouted MVPA between educational levels. As bouted MVPA may be planned and structured compared to non-bouted MVPA that may be more sporadic [38], this may also explain why non-bouted MVPA did not differ between educational levels: non-bouted MVPA may be performed during work hours to a larger extent in those with lower education as they may possess jobs including standing and sporadic walking that may reach accelerations corresponding to MVPA, which is in contrast to those with higher education that may have more sedentary occupations [52] and engage in more planned bouted MVPA during leisure time [52, 55].

Triaxial data resulted in more minutes of MVPA and less time spent sedentary than uniaxial data, which is consistent with previous studies in older women [8] and middle-aged adults [42]. Accordingly, the proportion meeting the current recommendations using uniaxial accelerometry data (18%) is approximately 20% lower compared with triaxial accelerometry data (22%). Moreover, this proportion is even larger when assessing non-bouted MVPA (triaxial: 70% vs. uniaxial: 55%). This corroborates previous observations suggesting triaxial accelerometry may capture more movement compared with uniaxial accelerometry [16], which may even be more pronounced in non-bouted MVPA compared with bouted MVPA.

In addition, our analyses suggested differences by sex and education levels when assessing uniaxial and triaxial accelerometry. When triaxial and uniaxial data are compared in laboratory settings, only small and typically non-significant differences are observed [18, 57]. This is possibly explained by the distinct activities performed in the laboratory studies, such as walking and running on a treadmill that have no unique medio-lateral and anterior-posterior accelerations in the hip, resulting in movements in the vertical axis being almost perfectly correlated with total 3-dimensional measurement of the similar movement, whereas behaviours during free-living conditions involve larger variation in movements, and thereby also more unique medio-lateral and anterior-posterior movements in the hip [18]. Additionally, this may explain why men accumulated more uniaxial CPM; as men may perform more walking and running than women, such differences may disappear when also analysing medio-lateral and anterior-posterior hip movements from triaxial accelerometry, which may be performed more by women. Nevertheless, the findings from the present study confirms earlier anticipations that triaxial accelerometry provide higher estimates of physical activity [16]. Thus, this illustrates that comparisons between different accelerometry processing methods should be done with caution and that tracking of physical activity across time is sensitive to accelerometry data collection and processing.

Limitations

There are some limitations to this study. First, the intensity specific count-based cut-points in this study are based on laboratory studies using the relationship between acceleration and oxygen uptake during walking and running, which is then inter- or extrapolated to CPM for the respective intensities [29, 32]. Thus, the chosen cut-points are not calibrated to reflect the caloric intensity of activities that are biomechanically different from walking and running. For example, cycling at moderate intensity may be classified as light physical activity. However, according to the present study, triaxial accelerations seem to express a wider range of movements than uniaxial accelerations resulting in higher estimates of physical activity.

Further, this study included participants aged 40 years and older, whereas the validity studies for the intensity specific cut-points included participants with a mean age of ~25 years [29, 32]. As cardiorespiratory fitness decreases with increasing age [58–60], the employed cut-points in this study may be inappropriate for the older participants as the intensity specific thresholds are absolute. However, our study sample is suggested to represent the entire adult

population [24] and therefore, intensity-specific cut-points validated in young adults was considered the most appropriate.

A non-wear criteria of 20 minutes of consecutive 0 CPM seems to result in the lowest misclassification of wear and non-wear time [61]. However, this non-wear algorithm will exclude slightly more participants from final analyses compared with 60 minutes of consecutive 0 CPM [61]. The chosen algorithm for non-wear time in our study classified ~7 hours per day as non-wear time and only excluded 2.6% participants, in contrast to the study by Peeters et al. [61] where ~6% were excluded following the 20 minutes of consecutive 0 CPM algorithm. However, as no non-wear time algorithm is perfect, some misclassification of wear/non-wear time is inevitable within each trace of included participants. Considering the 24-hour protocol employed in the present study where 30% of the day was classified as non-wear time, it is likely that the method used may have removed too much true sedentary time which would inflate overall volume of activity estimates but not light physical activity and MVPA estimates directly. Moreover, our non-wear algorithm for excluding sleep has not been validated and may misclassify sedentary time.

The present study may be prone to accelerometer reactivity [62]. Some studies have observed higher physical activity levels on day one of recording compared with the following days [62], however, this is not consistent [63–66]. As it seems difficult to control for potential reactivity considering the need for information on the study's purpose, potential reactivity is likely and has to be an acceptable limitation when employing accelerometry to measure individuals' daily physical activity levels and patterns.

Finally, selection bias may have affected our prevalence estimates [67]. A larger proportion of older participants and participants with lower education declined the invitation to wear an accelerometer. However, there were no differences in the distribution of smoking habits and BMI between those who declined and accepted the invitation. Moreover, the acceptance rate to the first visit in Tromsø 7 (65%), and especially the high acceptance rate for wearing the accelerometer (93% out of the 8346 attending the second visit) suggests a fair representativeness in the population. Additionally, the participants accepting to wear an accelerometer seem evenly distributed between educational levels (Table 1), suggesting an even distribution between social classes. Nevertheless, a non-respondent bias due to the most frail and unfit not participating cannot be ruled out.

Strengths

This study included a large sample of adults and elderly, allowing us to assess the prevalence of physical activity in a large heterogeneous sample. Moreover, our population-based study can be considered to have a high acceptance rate (65%), with an even higher acceptance for wearing an accelerometer (93%). Finally, although no gold standard for measuring free living physical activity exists [68], we assessed the prevalence of physical activity using accelerometry, which is more accurate than self-reported methods when compared against the doubly labelled water technique [69, 70].

Conclusion

The prevalence estimates of sufficiently active adults and elderly are more than three times higher (22% vs. 70%) when comparing triaxial bouted and non-bouted MVPA. Physical activity estimates are highly dependent on accelerometry data processing criteria and on different definitions of physical activity recommendations, which may influence prevalence estimates and tracking of physical activity patterns over time.

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Paper II

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Criterion validity of two physical activity and one sedentary time questionnaire against accelerometry in a large cohort of adults and older adults

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ABSTRACT

Objectives We compared the ability of physical activity and sitting time questionnaires (PAQ) for ranking individuals versus continuous volume calculations (physical activity level (PAL), metabolic equivalents of task (MET), sitting hours) against accelerometry measured physical activity as our criterion.

Methods Participants in a cohort from the Tromsø Study completed three questionnaires; (1) The Saltin-Grimby Physical Activity Level Scale (SGPALS) (n=4040); (2) The Physical Activity Frequency, Intensity and Duration (PAFID) questionnaire (n=5902) calculated as MET-hours-week⁻¹ and (3) The International Physical Activity questionnaire (IPAQ) short-form sitting question (n=4896). We validated the questionnaires against the following accelerometry (Actigraph wGT3X-BT) estimates: vector magnitude counts per minute, steps-day⁻¹, time (minutes-day⁻¹) in sedentary behaviour, light physical activity, moderate and vigorous physical activity (MVPA) non-bouted and ≥10 min bouted MVPA.

Results Ranking of physical activity according to the SGPALS and quartiles (Q) of MET-hours-week⁻¹ from the PAFID were both positively associated with accelerometry estimates of physical activity (p<0.001) but correlations with accelerometry estimates were weak (SGPALS (PAL): r=0.11 to 0.26, p<0.001) and weak-to-moderate (PAFID: r=0.39 to 0.44, p<0.01). There was 1 hour of accelerometry measured sedentary time from Q1 to Q4 in the IPAQ sitting question (p<0.001) and also weak correlations (r=0.22, p<0.01).

Conclusion Ranking of physical activity levels measured with PAQs appears to have higher validity than energy expenditure calculations. Self-reported sedentary time poorly reflects accelerometry measured sedentary time. These two PAQs can be used for ranking individuals into different physical activity categories supporting previous studies using these instruments when assessing associations with health outcomes.

INTRODUCTION

Physical activity surveillance at population level may support public health initiatives and allow researchers to track physical activity levels and patterns over time.¹ Physical activity

Summary box

What are the new findings

- Ranking of the two included physical activity questionnaires reduces information content but may be the optimal way of processing self-reported physical activity.
- Volume calculations (physical activity level, metabolic equivalents of task hours) allow the biases associated with self-reported physical activity to be more pronounced.
- Self-reported sitting time shows low validity and does not reflect accelerometry measured sedentary time.

is traditionally measured using self-reported methods such as questionnaires.² However, the validity of physical activity questionnaires (PAQ) is threatened by recall and social desirability bias, resulting in imprecise assessments.^{3–6} Nevertheless, PAQs have over the years led to valuable knowledge on the effect of physical activity on health outcomes and mortality.^{7–14}

Validation of PAQs is crucial to guide researchers when interpreting associations between self-reported physical activity and health outcomes. Moreover, PAQs may inherit different measurement properties. For example, one of the first developed PAQs, by Saltin and Grimby¹⁵ named ‘Saltin-Grimby Physical Activity Level Scale’ (SGPALS),^{16 17} ranks individuals by physical activity levels. A more recent PAQ, the Physical Activity Frequency, Intensity and Duration (PAFID) questionnaire,¹⁸ allows the answers to be summed up as total physical activity volume (ie, energy expenditure, metabolic equivalents of task (MET)-hours per week). Finally, sedentary behaviour has been suggested as a risk factor for disease and mortality, which is also commonly assessed by PAQs,^{19 20} such as the International Physical

Activity Questionnaire (IPAQ) short-form sitting question.²¹ Both PAQs (SGPALS,^{16 22–26} PAFID^{18 27}) and the IPAQ short-form sitting question²¹ have previously been validated, however, the studies that compare these questionnaires against accelerometry are characterised by small sample sizes.^{18 21 23} As population samples are heterogeneous and consequently result in heterogeneous findings, validation studies based on small samples may have limited representability. Furthermore, considering that already established longitudinal population cohorts have implemented PAQs from inception allowing for long follow-up time (SGPALS: >45 years,^{28–30} PAFID: >35 years³¹), validation of PAQs and sitting questionnaires against accelerometry measured physical activity and sitting time from large heterogeneous samples will allow researchers to more accurately interpret results from longitudinal cohort studies where only questionnaires are the physical activity and sedentary time measure.

Moreover, although PAQs can inherit different measurement properties, the methods for processing the PAQs can result in similar expressions (eg, ranking of the SGPALS can be summarised as volume,²⁵ volume calculations can be grouped as quartiles), and thus the processing of questionnaires may also influence the validity differently.

We aimed to assess the validity of two PAQs inheriting different measurement properties; ranking of physical activity levels (SGPALS), volume calculations (PAFID) and one sedentary time questionnaire (IPAQ sitting short-form), by using accelerometry as our criterion, in a large heterogeneous sample of adults and older adults. Additionally, we aimed to assess how ranking and volume calculations of the PAQs reflects accelerometry measured physical activity and sedentary time.

METHODS

Design

We used participants from the seventh wave of the population-based cohort study named The Tromsø Study, which is conducted in Tromsø, Northern Norway. The study includes seven waves of data collection (Tromsø 1: 1974, Tromsø 2: 1979 to 1980, Tromsø 3: 1986 to 1987, Tromsø 4: 1994 to 1995, Tromsø 5: 2001, Tromsø 6: 2007 to 2008, Tromsø 7: 2015 to 2016) (details described elsewhere³²).

Participants

All inhabitants in Tromsø municipality aged 40 years and older were invited to Tromsø 7. A total of 21 083 (65% of 32 591 invited participants) participants attended a first visit including questionnaires, biological sampling and clinical examinations. A random selection of 8346 participants attended a second visit at a later time point (>7 days), where 6778 participants were invited to wear an accelerometer, of which 6332 (93%) participants accepted. Of those who provided valid accelerometry data, 4040 participants completed both the leisure time and occupational time SGPALS; 5902 participants

completed the PAFID questionnaire, and 5186 and 5088 participants completed the sitting question from the IPAQ short-form for week and weekend, respectively, where 4896 completed both.

All participants gave written informed consent.

Patient and public involvement

The Tromsø study advisory board includes patient (University hospital of Northern Norway) and public (eg, Norwegian Health Association, Tromsø municipality) representatives. Some participants are invited as ambassadors when data collection is ongoing, where they actively contribute to recruitment of participants. We have together with the Norwegian Health Association provided individual feedback on levels of physical activity to participants in Tromsø 7. There was no public involvement when designing this study.

Data collection

Height and weight were measured in light clothing without shoes. Body mass index (BMI) was calculated (kg/m^2) and defined as normal and underweight ($<25 \text{ kg}/\text{m}^2$), overweight (25 to $29.9 \text{ kg}/\text{m}^2$) and obese ($\geq 30 \text{ kg}/\text{m}^2$). Educational level was collected from questionnaires and categorised in; (1) primary school, (2) high school diploma, (3) university education <4 years and (4) university education ≥ 4 years.

The physical activity and sitting questionnaires

The Saltin-Grimby physical activity level scale

The SGPALS asks participants to rank their leisure time and occupational time physical activity level separately, choosing one of four options. Based on the idea of the original questionnaire by Saltin and Grimby¹⁵, the SGPALS used in Tromsø 7 is a slight modification of Saltin and Grimby¹⁵ according to Rödger *et al.*¹⁷ The SGPALS is presented in online supplementary table 1.

We computed the SGPALS as combined leisure time and occupational time where individuals were categorised as (1) *inactive*, (2) *moderately inactive*, (3) *moderately active* and (4) *active* according to Wareham *et al.*³³ with some modifications. In order to calculate physical activity volume, we assigned a physical activity level (PAL) value from the combined leisure time and occupational time SGPALS, which we derived from a previous validation study that calculated PAL as energy expenditure obtained from doubly labelled water divided by the estimated basal metabolic rate.²⁵ The classifications and the assigned PAL value are presented in table 1.

The physical activity frequency, intensity and duration questionnaire

The PAFID questionnaire (table 2) includes three questions referring to frequency, intensity and duration of physical activity. We generated an index to reflect METs by multiplying intensity (METs) by duration (minutes) by frequency (times per week), and the outcome was expressed as MET-hours per week.^{34 35} We also grouped

Table 1 Physical activity classification by the combined leisure time and occupational time SGPALS (n=4040)

	Light LPA (n=532)	Moderate LPA (n=2429)	Hard LPA (n=969)	Very hard LPA (n=109)
Light OPA (n=2263)	Inactive (n=349, 8.6%) PAL: 1.4	Moderately inactive (n=1346, 33.3%) PAL: 1.5	Active (n=507, 12.6%) PAL: 1.7	Active (n=61, 1.5%) PAL: 1.9
Moderate OPA (n=1018)	Moderately inactive (n=105, 2.6%) PAL: 1.5	Moderately active (n=648, 16.0%) PAL: 1.6	Active (n=234, 5.8%) PAL: 1.8	Active (n=31, 0.8%) PAL: 2.0
Heavy OPA (n=651)	Moderately active (n=61, 1.5%) PAL: 1.6	Active (n=386, 9.6%) PAL: 1.7	Active (n=190, 4.7%) PAL: 1.9	Active (n=14, 0.3%) PAL: 2.2
Very Heavy OPA (n=108)	Active (n=17, 0.4%) PAL: 1.7	Active (n=50, 1.2%) PAL: 1.8	Active (n=38, 0.9%) PAL: 2.1	Active (n=3, 0.1%) PAL: 2.3

Data are shown as n and %. The number of participants and percentage distribution derives from our study sample. The assigned PAL value derives from Johansson and Westertep,²⁵ who divided energy expenditure obtained from doubly labelled water by the estimated basal metabolic rate of their participants. LPA, leisure time physical activity; OPA, occupational time physical activity; PAL, physical activity level; SGPALS, Saltin-Grimby Physical Activity Level Scale.

MET-hours per week in quartiles in order to assess the validity of ranking physical activity in this PAQ.

The International physical activity questionnaire, sitting question

In this study, the IPAQ short-form sitting question²¹ was employed, asking participants to estimate their average amount of sitting hours on a typical week and weekend day during the last week. In addition to the reported volume, we also grouped sitting hours in quartiles to assess the validity of ranking sitting hours.

Accelerometry data processing

Accelerometry measured physical activity was measured with the triaxial (three planes; axial, coronal and sagittal) ActiGraph wGT3X-BT accelerometer (ActiGraph, LLC, Pensacola, USA), firmware 1.2.0 to 1.8.0. Trained technicians attached the accelerometer to the participants' right hip and instructed them to wear the accelerometer for 24 hours a day on eight consecutive days (the rest of the day following the visit in the clinic and seven more days) and only to remove the accelerometer during water-based activities (eg, showering or swimming) and contact sports. The accelerometer was returned by mail in a prepaid envelope. The ActiLife software (ActiGraph, LLC, Pensacola, USA) was used for initialisation and downloading the data. The accelerometer was initialised for raw data mode with a sampling frequency of 100 Hertz and recordings started at 00:00 the day following the visit in the clinic.

The raw acceleration files were filtered to 10s epochs using the normal (default) proprietary filter in the ActiLife software. The acceleration units are expressed in triaxial vector magnitude (VM) (the square root of the sum of squared activity counts) counts per minute (CPM). We also extracted the number of steps in the accelerometer, which derives from the axial plane in a proprietary algorithm by the manufacturer. The .agd-files (epoch files) were further converted to .csv-files and further analysed in the Quality Control & Analysis Tool software (a custom-made software developed in Matlab: The MathWorks, Inc, Natick, Massachusetts, USA).

The 10s epochs were further aggregated to 60s and an epoch was classified as wear time if two of the following three criteria were fulfilled: (1) an epoch >5VM CPM, (2) if at least two epochs >5VM CPM in the preceding 20 min or (3) at least two epochs >5VM CPM in the following 20 min. Otherwise the acceleration was considered to be noise and classified as non-wear time.³⁶

The triaxial VM CPM cut-points for different intensities are <150 VM CPM for sedentary behaviour³⁷ and ≥2690 VM CPM for moderate and vigorous physical activity

Table 2 Physical activity frequency, intensity and duration (PAFID) questionnaire. Number, MET-values and minutes in parentheses in answering alternatives represents the values for the calculation of MET-hours per week

Frequency (days)	Intensity (METs)	Duration (minutes)
<i>How frequently do you exercise? With exercise, we mean walking, cross-country skiing, swimming or other exercise/sports.</i>	<i>On average, how hard is the exercise?</i>	<i>On average, how long do you exercise?</i>
Never (0)	I take it easy without breaking into a sweat or losing my breath (3 METs)	<15 min (10 min)
Less than once a week (0.5)	I push myself so hard that I break into a sweat and lose my breath (6 METs)	15–29 min (22.5 min)
Once a week (1)	I push myself to near-exhaustion (9 METs)	30–60 min (45 min)
Two to three times per week (2.5)	N/A	>60 min (60 min)
Almost every day (5)	N/A	N/A

METs, metabolic equivalents of tasks.

(MVPA),³⁸ where light physical activity is between 150 to 2689 VM CPM.

Extracted accelerometry measures were volume measures (steps per day and mean VM CPM per day) in addition to intensity measures (minutes per day in sedentary behaviour, light physical activity, MVPA and ≥ 10 min bouts MVPA).

Statistical analyses

We calculated Pearson correlation coefficients to assess the correlation between the PAQs volume outcomes (SGPALS: PAL score, PAFID: MET-hours-week⁻¹, IPAQ sitting: hours spent sitting) and accelerometry outcomes (VM CPM, steps per day, minutes in sedentary behaviour, light physical activity, non-bouted and bouted MVPA) where a coefficient of 0.00 to 0.10, 0.10 to 0.39, 0.40 to 0.69 and ≥ 0.70 was considered a negligible, weak, moderate and strong correlation, respectively.³⁹ Univariate analyses of variance (ANOVA) were performed to assess associations of accelerometry measures (VM CPM, steps, minutes in sedentary behaviour, light physical activity, non-bouted and bouted MVPA) with the SGPALS physical activity ranking, quartiles of MET-hours per week from the PAFID questionnaire and quartiles of reported sitting from the IPAQ. For the IPAQ sitting question, a Bland-Altman plot was created (online supplementary figure 1). The Alpha level was set to 0.05 and data are presented as mean \pm SEM unless otherwise is stated. All data were confirmed to follow normal distribution by visual inspection of residuals when performing the above-mentioned analyses. The analyses were performed overall and in strata of sex, age (10 year groups), BMI (<25, 25 to 29, ≥ 30 kg·m⁻²) and education (primary, high school, <4 years university, ≥ 4 years university). The Statistical Package for Social Sciences (V.25, International Business Machines Corporation, Armonk, New York, USA) was used to perform all statistical analyses.

Patient and public involvement

Patients and/or the public were involved in the design, or conduct, or reporting or dissemination plans of this research. Refer to the Methods section for further details.

RESULTS

The descriptive characteristics of the participants wearing the accelerometers and completing the PAQs are presented in table 3.

PAL scores calculated from the SGPALS correlated weakly with VM CPM ($r=0.32$), steps per day ($r=0.27$), sedentary behaviour ($r=-0.20$), light physical activity ($r=0.22$), non-bouted MVPA ($r=0.25$) and bouted MVPA ($r=0.16$) (all $p<0.05$), which was consistent across sex, age, BMI and educational level (all $p<0.05$) (online supplementary table 2). All accelerometry measures increased by increasing rank of self-reported physical activity ($P_{\text{trend}} < 0.001$) (table 4).

Calculated MET-hours per week from the PAFID questionnaire showed negligible correlation with

Table 3 Participant characteristics

SGPALS	Women (n=1983)	Men (n=2057)	Total (n=4040)
Age (yrs)	58.9 \pm 9.5	61.0 \pm 9.9	60.0 \pm 9.7
Height (cm)	164.5 \pm 6.3	177.4 \pm 6.7	171.1 \pm 9.2
Weight (kg)	71.9 \pm 12.8	87.8 \pm 13.8	80.0 \pm 15.5
BMI (kg/m ²)	26.6 \pm 4.7	27.9 \pm 4.0	27.2 \pm 4.4
PAFID	Women (n=3174)	Men (n=2728)	Total (n=5902)
Age (yrs)	63.3 \pm 10.3	63.7 \pm 10.2	63.5 \pm 10.2
Height (cm)	163.6 \pm 6.3	176.9 \pm 6.7	169.8 \pm 9.3
Weight (kg)	71.7 \pm 12.8	87.0 \pm 13.8	78.8 \pm 15.3
BMI (kg/m ²)	26.8 \pm 4.7	27.8 \pm 3.9	27.3 \pm 4.4
IPAQ combined	Women (n=2495)	Men (n=2401)	Total (n=4896)
Age (yrs)	61.4 \pm 10.1	62.6 \pm 10.0	62.0 \pm 10.1
Height (cm)	164.2 \pm 6.2	177.2 \pm 6.6	170.6 \pm 9.2
Weight (kg)	71.5 \pm 12.8	87.1 \pm 13.7	79.1 \pm 15.4
BMI (kg/m ²)	26.5 \pm 4.7	27.7 \pm 3.9	27.1 \pm 4.3

Data are shown as mean \pm SD.

BMI, body mass index; IPAQ combined, International Physical Activity Questionnaire combined: mean of week and weekend; PAFID, Physical Activity Frequency, Intensity and Duration; SGPALS, Saltin-Grimby Physical Activity Level Scale.

accelerometry measured light physical activity ($r=0.06$), weak correlation with VM CPM ($r=0.34$), moderate correlation with steps per day ($r=0.43$) and weak and moderate correlation with non-bouted MVPA ($r=0.39$) and bouted MVPA ($r=0.44$), respectively ($p<0.001$). This was consistent across sex, age, BMI and educational level ($p<0.05$) except for light physical activity, which did not correlate with MET-hours per week in some age groups (40 to 49 years; $p=0.19$, 50 to 59 years; $p=0.13$, 60 to 69 years; $p=0.79$), BMI classifications (<25 kg/m²; $p=0.54$ and 25 to 29 kg/m²; $p=0.31$) and educational levels (high school; $p=0.07$ and university ≥ 4 years; $p=0.051$) (online supplementary table 3).

Quartiles of MET-hours per week from the PAFID questionnaire showed positive association with all accelerometry measures ($P_{\text{trend}} < 0.001$) (table 5).

Accelerometry measured sedentary hours per day correlated weakly with reported sitting hours from the IPAQ sitting question (week day; $r=0.22$, weekend day; $r=0.15$), combined (mean of week and weekend; $r=0.22$, all $p<0.01$), which was consistent across sex, age, BMI and educational level ($p<0.01$) (online supplementary table 4). There was a positive association between quartiles of reported sitting in the IPAQ and accelerometry measured sedentary time ($P_{\text{trend}} < 0.001$) (table 6).

DISCUSSION

We assessed the criterion validity of two PAQs inheriting different physical activity measurement properties (physical activity ranking, volume calculation) and one sedentary

Table 4 The combined leisure time and occupational time SGPALS, and the associations with the accelerometry estimates

n=4040	Inactive (n=349)	Moderately inactive (n=1451)	Moderately active (n=709)	Active (n=1531)
VM CPM*†	410.2±7.8	527.9±4.1	571.3±6.2	618.4±4.6
Steps per day*†	4900.5±107.8	7177.0±71.1	7487.2±103.7	8291.9±73.6
Light physical activity (min·day ⁻¹)*†	360.9±4.8	391.6±2.2	432.0±3.4	425.9±2.2
MVPA (min·day ⁻¹)*†	23.8±1.1	42.3±0.7	43.0±1.1	53.8±0.8
Bouted MVPA (min·day ⁻¹)*†	4.3±0.4	14.1±0.4	12.5±0.6	17.6±0.5

Data are shown as mean±SEM.

*Significant difference between ranks: $p<0.001$.

†Significant linear trend by increasing rank: $p<0.001$.

MVPA, moderate and vigorous physical activity; SGPALS, Saltin-Grimby Physical Activity Level Scale; VM CPM, vector magnitude counts per minute.

time questionnaire, processed as both ranking and volume calculations, against accelerometry as our criterion measure. We found positive associations between ranking of physical activity in both the SGPALS and the PAFID questionnaire, and accelerometry measured physical activity. When processed as calculated volume, we found at best moderate correlations between self-reported and accelerometry measured physical activity. The IPAQ sitting question showed weak correlations and a narrow range in mean accelerometry measured sedentary time between quartile 1 and 4 in the IPAQ (within 1 hour per day).

The validity of the questionnaires

We found positive associations between accelerometry measured physical activity and ranking in the SGPALS. For example, those who categorised themselves in the lowest rank in the combined SGPALS accumulated on average ~4900 steps and 23 min of MVPA per day, respectively, which is about half of the accumulated steps and MVPA per day in the highest rank (~8290 steps and 53 min MVPA). This illustrates the ability of the SGPALS to rank physical activity levels in a large cohort of adults and elderly. The findings of positive associations between SGPALS rankings and accelerometry measured physical activity are consistent with previous validation studies of the SGPALS.^{23 26}

In contrast, when estimating PAL volume scores from the SGPALS, the correlations between PAL scores and accelerometry measured physical activity were weak, which accentuates the biases associated with self-reported physical activity.^{2-4 6} These findings may suggest that the biases associated with self-reported physical activity are more pronounced when physical activity is processed as total volume (eg, PAL, MET-hours per week) compared with ranking individuals according to their self-reported physical activity.

We found positive associations between quartiles of MET-hours per week from the PAFID questionnaire and accelerometry estimates. However, correlations between MET-hours per week from the PAFID questionnaire and accelerometry estimates were weak and only moderate for bouted MVPA. Such correlations are consistent with a previous validation study of the PAFID questionnaire.¹⁸ As with the SGPALS, ranking by quartiles may be the preferred way of expressing self-reported physical activity.

Although we found a positive association between quartiles of reported sitting hours from the IPAQ and accelerometry measured sedentary time, the narrow 1 hour range between quartile 1 and 4 in the IPAQ suggests small differences in real sedentary time between quartiles in the IPAQ.

Table 5 Quartiles of MET-hours per week from the PAFID (n=5902)

Quartiles	1 (n=1355)	2 (n=1498)	3 (n=1473)	4 (n=1576)
Range MET-hours·week ⁻¹	0.00–2.50	2.81–9.00	11.25–11.25	15.00–45.00
MET-hours·week ⁻¹	1.03±0.02	5.13±0.03	11.25±0.00	21.44±0.16
VM CPM*†	448.3±4.4	508.9.5±4.3	557.4±4.3	610.5±4.6
Steps per day*†	5207.8±62.1	6342.9±63.4	7441.3±69.9	8559.4±78.2
Light physical activity (min·day ⁻¹)*†	386.4±2.6	406.2±2.3	407.9±2.3	404.9±2.0
MVPA (min·day ⁻¹)*†	25.9±0.7	35.2±0.7	44.6±0.7	55.8±0.8
Bouted MVPA (min·day ⁻¹)*†	3.9±0.2	9.4±0.3	15.2±0.4	23.7±0.5

Data are shown as mean±SEM.

*Significant difference between quartiles: $p<0.001$.

†Significant trend by increasing quartile: $p<0.001$.

Bouted MVPA, moderate and vigorous physical activity in ≥10 min bouts; MET, metabolic equivalent of tasks; MVPA, moderate and vigorous physical activity; PAFID, Physical Activity Frequency, Intensity and Duration; VM CPM, vector magnitude counts per minute.

**Table 6** Quartiles of reported hours sitting from the IPAQ sitting question, for a typical week and weekend day combined, and the association with accelerometry measured sedentary time

Quartiles	1 (n=783)	2 (n=1432)	3 (n=1277)	4 (n=1359)
Range IPAQ (hours·day ⁻¹)	0.0–4.0	4.0–5.0	6.0–7.0	8.0–24.0
IPAQ (hours·day ⁻¹)	2.8±0.03	4.7±0.03	6.6±0.5	9.7±1.9
Accelerometry sedentary time (hours·day ⁻¹)*†	9.3±0.06	9.6±0.04	9.9±0.04	10.3±0.04

Data are shown mean±SEM.

*Significant difference between quartiles: $p < 0.001$.

†Significant trend by increasing quartile: $p < 0.001$.

IPAQ, International Physical Activity Questionnaire.

Strengths

This study included one of the largest sample sizes in validation studies of PAQs, allowing us to assess the validity in a large heterogeneous sample with high participation rate, which may represent the heterogeneous population to a larger extent than smaller sample sizes. Consequently, the generalisability of the findings from this study is likely high, at least for adults >40 years in western high-income countries.

Limitations

Validation of PAQs is challenging. First of all, in contrast to doubly labelled water, which is the gold standard for measuring free-living energy expenditure,^{40–41} there is no gold standard to measure all aspects (domain, context, intensity, duration, frequency and volume) of physical activity accurately.^{16 42 43}

Second, we used specific cut-points to split intensity in the accelerometry data, which may not reflect the intended intensity by the participants when answering the PAQs. However, in general, accelerometry measured physical activity shows greater validity than self-reported methods when compared with energy expenditure estimated from doubly labelled water,^{44–46} thus, a criterion validation from accelerometry can be considered applicable.

Third, the time periods for self-reported physical activity and sedentary time were not aligned with the accelerometry assessment. However, most physical activity instruments are intended to assess habitual physical activity.⁴⁷ Moreover, as all included questionnaires (SGPALS: Kappa: 0.69,¹⁶ PAFID: Spearman's rho (ρ): 0.76 to 87),¹⁸ IPAQ: ρ : 0.50 to 0.94²¹) and a 7 day accelerometry recording with four valid days (intraclass correlation: 0.8)⁴⁷ are found to provide acceptable reliability, we believe that the included instruments provide reasonable estimates of habitual physical activity and our comparison is justified.

Finally, the waist placement of accelerometers in our study does not assess sitting per se. Other placements, such as thigh-worn accelerometers, may be more suitable for validating self-reported sitting. Nevertheless, our results are consistent with a previous study that employed thigh-worn accelerometers,⁴⁸ suggesting that hip-worn accelerometers are able to measure sedentary time more accurately than self-reported methods.

CONCLUSION

Ranking of physical activity seems to be the preferred method to process PAQs, exhibiting higher validity against accelerometry measures than volume calculations of self-reported physical activity. Self-reported sedentary time poorly reflects accelerometry measured sedentary time. The two PAQs can be used for ranking individuals into different physical activity categories supporting previous studies using these instruments when assessing associations with health outcomes.

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Data availability statement Data may be obtained from a third party and are not publicly available. The data that support the findings of this study are available from the Tromsø Study but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. The data can be made available from the Tromsø Study upon application to the Data and Publication Committee for the Tromsø Study.

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Paper III

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Original research

Do declines in occupational physical activity contribute to population gains in body mass index? Tromsø Study 1974–2016

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ABSTRACT

Objective To examine whether occupational physical activity changes predict future body mass index (BMI) changes.

Methods This longitudinal cohort study included adult participants attending ≥ 3 consecutive Tromsø Study surveys (examinations 1, 2 and 3) from 1974 to 2016 (N=11 308). If a participant attended >3 surveys, the three most recent surveys were included. Occupational physical activity change (assessed by the Saltin-Grimby Physical Activity Level Scale) was computed from the first to the second examination, categorised into persistently inactive (n=3692), persistently active (n=5560), active to inactive (n=741) and inactive to active (n=1315). BMI change was calculated from the second to the third examination (height being fixed at the second examination) and regressed on preceding occupational physical activity changes using analysis of covariance adjusted for sex, birth year, smoking, education and BMI at examination 2.

Results Overall, BMI increased by 0.84 kg/m^2 (95% CI 0.82 to 0.89). Following adjustments as described previously, we observed no differences in BMI increase between the occupational physical activity change groups (Persistently Inactive: 0.81 kg/m^2 , 95% CI 0.75 to 0.87; Persistently Active: 0.87 kg/m^2 , 95% CI 0.82 to 0.92; Active to Inactive: 0.81 kg/m^2 , 95% CI 0.67 to 0.94; Inactive to Active: 0.91 kg/m^2 , 95% CI 0.81 to 1.01; $p=0.25$).

Conclusion We observed no prospective association between occupational physical activity changes and subsequent BMI changes. Our findings do not support the hypothesis that occupational physical activity declines contributed to population BMI gains over the past decades. Public health initiatives aimed at weight gain prevention may have greater success if focusing on other aspects than occupational physical activity.

INTRODUCTION

Excessive adiposity and weight gain arise from an imbalance between energy intake and expenditure.¹ Increased energy intake is likely the main driver for population weight gains,² but declines in physical activity levels may also contribute.^{1 3} At the population level, it may be easier to prevent weight gain by increasing physical activity levels than changing food habits.¹ Although the evidence

Key messages

What is already known about this subject?

► The inconclusive results from observational studies on occupational physical activity change and body mass index (BMI) gain may be due to methodological issues.

What are the new findings?

► Occupational physical activity declines were not prospectively associated with BMI gains in this large population-based sample.

How might this impact on policy or clinical practice in the foreseeable future?

► Public health initiatives aimed at weight gain prevention may have greater success if focusing on other aspects than occupational physical activity.

for a prospective association between physical activity and weight gain is limited by methodological challenges,⁴ higher levels of physical activity are reported to prevent weight gain at the population level.⁵

Energy expenditure contribution from occupational physical activity is considered higher than that from leisure-time physical activity.^{3 6} Since leisure-time physical activity appears stable over the past decades and occupational physical activity has declined in western countries,^{3 7–10} lower levels of occupational physical activity, rather than leisure-time physical activity, may contribute to population gains in weight.^{3 11 12}

Studies assessing the association between occupational physical activity and body mass index (BMI) or weight show conflicting results.^{11–16} Some studies reported no association between baseline occupational physical activity and future BMI change^{11 13–16}; however, baseline physical activity does not take the reciprocal relationship of changing weight and physical activity into account (ie, physical activity level at baseline may change over time to follow-up, which may be related or unrelated to weight change).⁴ Other studies computed change scores for both occupational physical activity and BMI and reported conflicting results^{12 17}; however, without adjusting for previous physical activity or



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BMI/weight at baseline, this represents a cross-sectional analysis of change scores (ie, it is as likely that physical activity change leads to weight change as vice versa), and thus, the direction of the association is unexamined.⁴

To overcome these methodological challenges, the aim of this study was to assess whether changes in occupational physical activity predicted future changes in BMI over a 40-year period in a large cohort of Norwegian adults examined at three time points with ~6 years of follow-up between each time point.

METHODS

Design

The Tromsø Study is an ongoing population-based cohort study in the municipality of Tromsø, Norway, which includes seven repeated surveys with high attendance (%): 1974 (Tromsø 1) (83%), 1979–1980 (Tromsø 2) (85%), 1986–1987 (Tromsø 3) (81%), 1994–1995 (Tromsø 4) (77%), 2001 (Tromsø 5) (79%), 2007–2008 (Tromsø 6) (66%) and 2015–2016 (Tromsø 7) (65%). The cohort includes invited participants from total birth cohorts and random samples of inhabitants in the Tromsø municipality.^{10 18} Tromsø 1 included only men, while Tromsø 2–7 included both sexes (details described elsewhere (Tromsø 1–6¹⁸ and Tromsø 7¹⁰)). In this study, we included participants attending at least three consecutive surveys (hereafter examinations 1–3). We computed change in physical activity from examination 1 to 2 followed by change in BMI and weight from examination 2 to 3. Consequently, the follow-up period for physical activity change from examination 1 to 2 and BMI change from examination 2 to 3 were 6–7 years (mean: 6.5 years) for all included participants. Inclusion criteria were information on (1) physical activity at examination 1 and 2, and height and weight at examination 2 and 3; (2) educational level and smoking habits at examination 2; and (3) not pregnant at examination 2 and/or 3. If participants attended more than three consecutive surveys, data from the three most recent surveys were included in the main analyses (overall cohort), while one participant could be included in multiple period-specific samples (Tromsø 1–3: 1974–1987, Tromsø 2–4: 1979–1995, Tromsø 3–5: 1986–2001, Tromsø 4–6: 1994–2008 and Tromsø 5–7: 2001–2016). The layout for the analyses is illustrated in figure 1.

Participants

A flowchart illustrates the selection of participants for our samples (online supplemental figure 1). In short, the overall cohort comprised 11 308 participants with their three most recent attendances. The period-specific sample sizes were as follows: Tromsø 1–3 (1974–1987): n=3570, Tromsø 2–4 (1979–1995): n=9679, Tromsø 3–5 (1986–2001): n=3827, Tromsø

4–6 (1994–2008): n=2212 and Tromsø 5–7 (2001–2016): n=1146). Each individual was eligible for inclusion in multiple period-specific samples. Some participants were excluded due to missing confounders: Tromsø 1–3 (1974–1987): n=512, Tromsø 2–4 (1979–1995): n=595, Tromsø 3–5 (1986–2001): n=15, Tromsø 4–6 (1994–2008): n=39 and Tromsø 5–7 (2001–2016): n=20 (online supplemental figure 1).

The descriptive characteristics at examination 2 for the overall cohort and period-specific samples are presented in table 1. Tromsø 1 (1974) included only men; thus, the Tromsø 1–3 (1974–1987) sample included only men. All other cohorts are well balanced on sex distribution. Across period-specific samples, age distribution increases, current smokers decrease and educational-level increase (table 1).

Patient and public involvement

There was no public involvement in the design or implementation of this study. The Tromsø 7 advisory board included patient (University Hospital of North Norway) and public (Norwegian Health Association, Tromsø municipality) representatives, and some participants were invited as ambassadors during data collection where they actively contributed to participant recruitment.

Physical activity

Physical activity was measured using the Saltin-Grimby Physical Activity Level Scale (SGPALS) questionnaire^{19 20} for occupational and leisure-time physical activity (leisure time during the last 12 months) (four hierarchical levels), slightly modified compared with the original SGPALS from 1968¹⁹ (differences described in online supplemental file 1; the SGPALS layout is presented in online supplemental table 1). For the occupational SGPALS, those reporting rank 1, *predominantly sedentary work*, were considered inactive; those reporting rank 2, *sitting or standing work with some walking*; rank 3, *walking and some handling of material*; or rank 4, *heavy manual work*, were considered active (online supplemental table 1). Similar inactive/active categorisation was used for the leisure time SGPALS (online supplemental table 1). The occupational SGPALS has shown acceptable reliability²¹ and an ability to rank participants compared with accelerometry.²²

Change in occupational and leisure time SGPALS was computed as (1) *persistently inactive* (reporting rank 1 at examinations 1 and 2), (2) *persistently active* (rank ≥2 at examinations 1 and 2), (3) *active to inactive* (rank ≥2 at examination 1 and rank 1 at examination 2) and (4) *inactive to active* (rank 1 at examination 1 and rank ≥2 at examination 2).

The occupational time SGPALS was used in all surveys of the Tromsø Study, while the leisure time SGPALS was used in all except Tromsø 4 (1994–1995). In Tromsø 5 (2001), the leisure time SGPALS was answered by those under 70 years.

BMI and weight

Weight and height were measured in light clothing and expressed as kilogram (kg) and metre (m). BMI at examination 2 was calculated as weight divided by the square height (kg/m²). To eliminate the effect of possible height loss between examination 2 and 3, change in BMI at examination 3 was calculated as weight at examination 3 divided by the square height at examination 2. BMI change is our primary outcome, while weight change results are secondary outcomes (online supplemental tables 2 and 3 and 5–9).

Confounders and effect modifiers

Our selected confounders were sex, birth year, smoking, education and baseline BMI/weight (at examination 2). Effect

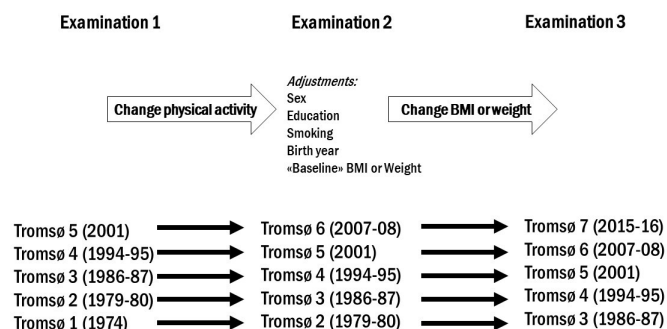


Figure 1 Layout for the analyses assessing the association between physical activity changes and future BMI change. BMI, body mass index.

Table 1 Descriptive characteristics of the overall cohort and period-specific samples. The Tromsø Study 1974-2016

Cohort	Overall cohort	Period-specific samples*				
	Tromsø 1-7 (1974-2016)	Tromsø 1-3 (1974-1986)	Tromsø 2-4 (1979-1995)	Tromsø 3-5 (1985-2001)	Tromsø 4-6 (1994-2008)	Tromsø 5-7 (2001-2016)
Baseline	Examination 2	Tromsø 2 (1979-1980)	Tromsø 3 (1986-1987)	Tromsø 4 (1994-1995)	Tromsø 5 (2001)	Tromsø 6 (2007-2008)
Total N (%)	11 308 (100)	3570 (100)	9679 (100)	3827 (100)	2212 (100)	1146 (100)
Sex, n (%)						
Female	5482 (48.8)	N/A	4820 (49.8)	2023 (52.8)	1183 (53.5)	611 (53.3)
Male	5826 (51.2)	3570 (100%)	4859 (50.2)	1806 (47.2)	1029 (46.5)	535 (46.6)
Age (years), n (%)						
≤39	4072 (36.0)	1819 (51)	3831 (39.6)	673 (17.6)	102 (4.6)	32 (2.8)
40-49	2461 (21.8)	1186 (33.2)	3509 (36.3)	342 (8.9)	341 (15.4)	251 (21.9)
50-59	2561 (22.6)	565 (15.8)	2107 (21.8)	1977 (51.7)	689 (31.1)	291 (25.4)
60-69	1981 (17.5)	N/A	232 (2.4)	831 (21.7)	944 (42.7)	465 (40.6)
≥70	233 (2.0)	N/A	N/A	4 (0.1)	136 (6.1)	107 (9.3)
Smoking, n (%)						
Current smoker	4480 (39.6)	1705 (47.8)	4221 (43.6)	1263 (33.0)	579 (26.2)	196 (17.1)
Previous smoker	1790 (15.8)	503 (14.1)	754 (7.8)	390 (10.2)	843 (38.1)	517 (45.1)
Never smoker	5038 (44.6)	1362 (38.2)	4704 (48.6)	2174 (56.8)	790 (35.7)	433 (37.8)
Education, n (%)						
Primary school	4698 (41.5)	1842 (51.6)	4324 (44.7)	1456 (38.0)	782 (35.3)	299 (26.1)
High school	3610 (31.9)	1002 (28.1)	2936 (30.3)	1408 (36.8)	665 (30.0)	419 (36.6)
University<4 years	1641 (14.5)	423 (11.8)	1380 (14.3)	551 (14.4)	364 (16.5)	209 (18.2)
University≥4 years	1359 (12.0)	303 (8.5)	1039 (10.7)	412 (10.8)	401 (18.1)	219 (19.1)

*Period-specific samples include all participants meeting our inclusion criteria for that period (ie, these samples do not add up to the overall cohort (Tromsø 1-7), which includes participants with their three most recent attendances).

modifiers included the abovementioned confounders, in addition to leisure-time physical activity change. Smoking (from questionnaire) was categorised into (1) current smoker, (2) previous smoker and (3) never smoker. Years of education (from questionnaire) were reported in Tromsø 2 (1979-1980), Tromsø 3 (1986-1987) and Tromsø 5 (2001), which we categorised into (1) primary school (<10 years), (2) high school (10-12 years), (3) university<4 years (13-15 years) and (4) university≥4 years (≥16 years). A five-group alternative for education was reported in Tromsø 4 (1994-1995) and Tromsø 6 (2007-2008), including the four aforementioned groups and a fifth named 'technical school 2 years senior high' (eg, craftsman, plumber, electrician and carpenter), which we categorised as high school. All confounders included in the models were retrieved from examination 2.

Statistical analyses

We used paired t-tests to assess whether participants changed BMI and weight from examination 2 to 3. We used analysis of covariance to assess whether physical activity changes from examination 1 to 2 predicted BMI or weight changes from examination 2 to 3 as overall and in strata of sex, birth year, smoking, education and leisure-time physical activity change, with adjustment for sex, birth year, smoking, education and BMI or weight at examination 2. Q-Q plots confirmed change in BMI and weight from examination 2 to 3 to not deviate from normal distribution. The Levene test of equality variance confirmed homogeneity of variance across occupational physical activity change groups (all $p>0.07$). We assessed interaction effects between occupational physical activity change and potential effect modifiers (sex, birth year, smoking, education and leisure-time physical activity change from examination 1 to 2) in the overall cohort. For sensitivity analyses, we computed occupational physical

activity change into six groups: (1) *Persistently Inactive*, (2) *Persistently Active*, (3) *active but decreasing* (rank 4 or 3→3 or 2), (4) *active and increasing* (rank 2 or 3→3 or 4), (5) *Active to Inactive* and (6) *Inactive to Active*. Data are shown as mean and 95% CIs unless otherwise stated. We used the Statistical Package for Social Sciences V.26 for all statistical analyses.

RESULTS

The participants in the overall cohort and period-specific samples increased their BMI from examination 2 to 3 (all $p<0.01$) (table 2). Weight change results are shown in online supplemental table 2).

Change in BMI by change in occupational physical activity

Changes in BMI by occupational physical activity change, overall and by strata of sex, birth year, smoking, education and leisure-time physical activity changes are presented in table 3. We observed no differences in BMI change from examination 2 to 3 by occupational physical activity changes from examination 1 to 2 (Persistently Inactive: 0.81 kg/m², 95% CI 0.75 to 0.87; Persistently Active: 0.87 kg/m², 95% CI 0.82 to 0.92; Active to Inactive: 0.81 kg/m², 95% CI 0.67 to 0.94; Inactive to Active: 0.91 kg/m², 95% CI 0.81 to 1.01; $p=0.25$), which was consistent in stratified analyses (all $p\geq 0.054$) (table 3).

We found no interaction effects of potential effect modifiers for the association between occupational physical activity changes and BMI changes (sex: $p=0.87$, smoking status: $p=0.64$, education: $p=0.25$ and leisure-time physical activity changes: $p=0.24$), except by birth year ($p=0.01$).

Overall and stratified weight change results for the overall cohort are found in online supplemental table 3; we found no differences in weight change from examination 2 to 3 by

Table 2 BMI at examinations 2 and 3 and BMI change in the overall cohort and period-specific samples. The Tromsø Study 1974–2016.

Overall cohort	N=11 308	Examination 2	Examination 3	Change
Examinations 2 and 3 BMI (kg/m ²)	Mean 95% CI	24.96 24.89 to 25.03	25.80 25.73 to 25.87	0.84 0.82 to 0.89
Period-specific samples*				
Tromsø 1–3 (1974–1987)†	N=3570			
Tromsø 2 and 3 (1979–1987) BMI (kg/m ²)	Mean 95% CI	24.65 24.56 to 24.74	25.14 25.04 to 25.24	0.49 0.44 to 0.54
Tromsø 2–4 (1979–1995)	N=9679			
Tromsø 3 and 4 (1986–1995) BMI (kg/m ²)	Mean 95% CI	24.25 24.18 to 24.32	25.38 25.31 to 25.45	1.13 1.09 to 1.17
Tromsø 3–5 (1986–2001)	N=3827			
Tromsø 4 and 5 (1994–2001) BMI (kg/m ²)	Mean 95% CI	25.53 25.42 to 25.64	26.49 26.36 to 26.62	0.95 0.90 to 1.01
Tromsø 4–6 (1994–2008)	N=2212			
Tromsø 5 and 6 (2001–2008) BMI (kg/m ²)	Mean 95% CI	26.66 26.50 to 26.82	26.78 26.61 to 26.95	0.12 0.04 to 0.20
Tromsø 5–7 (2001–2016)	n=1146			
Tromsø 6 and 7 (2007–2016) BMI (kg/m ²)	Mean 95% CI	27.01 26.76 to 27.26	27.22 26.96 to 27.48	0.21 0.09 to 0.33

Data are shown as unadjusted mean and 95% CI. Examination 2 refers to the second survey of the three attended surveys; examination 3 refers to the third survey of the three attended surveys.

*Period-specific samples include all participants meeting our inclusion criteria for that period (ie, these samples do not add up to the overall cohort (Tromsø 1–7), which includes participants with their three most recent attendances).

†Tromsø 1 included only men.

BMI, body mass index.

occupational physical activity change from examination 1 to 2 (all $p \geq 0.049$).

In the sensitivity analyses, where we computed occupational physical activity change into six groups (1) *Persistently Inactive*, (2) *Persistently Active*, (3) *Active but Decreasing* (rank 4 or 3 to 3 or 2), (4) *Active and Increasing* (rank 2 or 3 to 3 or 4), (5) *Active to Inactive* and (6) *Inactive to Active*, the results generally remained unchanged (overall analysis: $p=0.15$); however, some differences were observed in some strata analyses (birth year, born ≤ 1929 : $p=0.03$; education, high school: $p=0.04$, university ≥ 4 years: $p=0.049$; and leisure-time physical activity changes; PA: $p=0.003$) (online supplemental table 4). We found no interaction in the association between occupational physical activity change and BMI change (sex: $p=0.21$, smoking: $p=0.59$, education: $p=0.88$, leisure-time physical activity change: $p=0.12$, except by birth year: $p=0.04$).

We observed no differences in BMI change by occupational physical activity change in any period-specific sample (table 4): (1) there were no differences in BMI change from Tromsø 2 (1979–1980) to Tromsø 3 (1986–1987) between the physical activity change groups from Tromsø 1 (1974) to Tromsø 2 (1979–1980) ($p=0.68$), (2) BMI change from Tromsø 3 (1986–1987) to Tromsø 4 (1994–1995) between the physical activity change groups from Tromsø 2 (1979–1980) to Tromsø 3 (1986–1987) ($p=0.50$), (3) BMI change from Tromsø 4 (1994–1995) to Tromsø 5 (2001) between the physical activity change groups from Tromsø 3 (1986–1987) to Tromsø 4 (1994–1995) ($p=0.90$), (4) BMI change from Tromsø 5 (2001) to Tromsø 6 (2007–2008) between the physical activity change groups from Tromsø 4 (1994–1995) to Tromsø 5 (2001) ($p=0.98$), (5) BMI change from Tromsø 6 (2007–2008) to Tromsø 7 (2015–2016) between the physical activity change groups from Tromsø 5 (2001) to Tromsø 6 (2007–2008) ($p=0.20$). Stratified analyses for the period-specific samples are presented in online supplemental tables 5–9). We observed no differences in BMI or weight change by occupational physical activity change in any strata analysis

(all $p \geq 0.13$; except Tromsø 2–4 (1979–1995) sample, ≥ 4 years university education: $p \leq 0.04$; online supplemental table 8).

DISCUSSION

In this large Norwegian population-based prospective study over four decades, we found no association between occupational physical activity changes and future BMI and weight changes.

Most previous longitudinal studies examined the association between baseline occupational physical activity and future BMI change,^{13–16} which do not account for the reciprocal temporal changes in physical activity and BMI.⁴ Two studies assessed changes in both occupational physical activity and BMI where one found lower occupational physical activity to be associated with weight gain,¹² while one found no association.¹⁷ Without adjustment for previous physical activity levels, the direction of association and thus indication of causality, remains uncertain.⁴ Our study corroborates the findings of a recent study by Dobson *et al*,²³ which regressed trajectories of self-reported BMI (ie, weight and height) on physical work exertion trajectories over nine time points in Canadian adults and showed no association between physical work exertion change and BMI trajectories, except for higher odds of being in a very obese trajectory (from 36 to 40 kg/m² at follow-up) compared to a reference normal weight trajectory (22 to 24 kg/m²) with no higher odds of being in other BMI trajectories among those who decreased their physical work exertion compared with those who sustained low physical work exertion.²³ Our study expands the work by Dobson *et al*²³ by using measured weight and height on both examinations and non-dichotomized BMI change as the outcome. Consequently, with higher accuracy in the outcome,²⁴ the observed magnitudes in the association between occupational physical activity change and BMI change can be interpreted with higher confidence.⁴

As we did not adjust for energy intake due to unavailable data, our results may be influenced by residual confounding. Nevertheless, a previous study estimated that increasing physical activity

Table 3 BMI change by occupational physical activity change for the overall cohort and in strata of sex, birth year, smoking, education and leisure-time physical activity change. The Tromsø Study 1974-2016.

Tromsø 1-7 (1974-2016)	Change occupational physical activity examinations 1 and 2					P _{equality}
	Total	Persistently Inactive	Persistently Active	Active to Inactive	Inactive to Active	
BMI change examinations 2 and 3						
Total (N)	11 308	3692	5560	741	1315	
BMI (kg/m ²)	Mean	0.81	0.87	0.81	0.91	0.25
	95% CI	0.75 to 0.87	0.82 to 0.92	0.67 to 0.94	0.81 to 1.01	
Sex						
Women (n)	5482	1638	2925	319	600	
BMI (kg/m ²)	Mean	1.06	1.09	1.10	1.18	0.74
	95% CI	0.96 to 1.17	1.02 to 1.17	0.87 to 1.33	1.01 to 1.34	
Men (n)	5826	2054	2635	422	715	
BMI (kg/m ²)	Mean	0.56	0.67	0.55	0.66	0.11
	95% CI	0.49 to 0.63	0.61 to 0.74	0.39 to 0.71	0.54 to 0.78	
Birth year						
≤1929 (n)	748	239	350	60	99	
BMI (kg/m ²)	Mean	0.09	0.15	0.20	0.31	0.054
	95% CI	0.31 to 0.14	-0.03 to 0.33	-0.22 to 0.62	0.64 to 0.01	
1930-1939 (n)	2974	856	1580	189	349	
BMI (kg/m ²)	Mean	0.43	0.53	0.55	0.36	0.39
	95% CI	0.30 to 0.57	0.43 to 0.62	0.28 to 0.82	0.16 to 0.56	
1940-1949 (n)	4192	1483	2020	260	429	
BMI (kg/m ²)	Mean	0.85	0.92	0.73	1.06	0.10
	95% CI	0.75 to 0.95	0.84 to 1.00	0.50 to 0.96	0.88 to 1.24	
1950-1959 (n)	3947	932	1430	205	380	
BMI (kg/m ²)	Mean	1.34	1.28	1.28	1.52	0.12
	95% CI	1.22 to 1.45	1.19 to 1.37	1.04 to 1.52	1.34 to 1.70	
≥1960 (n)	447	182	180	27	58	
BMI (kg/m ²)	Mean	1.04	1.11	1.13	1.34	0.88
	95% CI	0.69 to 1.39	0.75 to 1.46	0.24 to 2.02	0.72 to 1.95	
Smoking						
Current smoker (n)	4480	1250	2343	306	581	
BMI (kg/m ²)	Mean	0.96	1.00	0.82	1.02	0.44
	95% CI	0.85 to 1.07	0.92 to 1.08	0.60 to 1.03	0.86 to 1.17	
Previous smoker (n)	1790	703	782	126	179	
BMI (kg/m ²)	Mean	0.34	0.42	0.52	0.43	0.71
	95% CI	0.19 to 0.48	0.28 to 0.55	0.19 to 0.85	0.16 to 0.71	
Never smoker (n)	5038	1739	2435	309	555	
BMI (kg/m ²)	Mean	0.87	0.91	0.91	0.95	0.79
	95% CI	0.78 to 0.95	0.83 to 0.98	0.71 to 1.10	0.81 to 1.10	
Education						
Primary school (n)	4698	878	3010	265	545	
BMI (kg/m ²)	Mean	0.75	0.83	0.68	0.79	0.52
	95% CI	0.62 to 0.88	0.76 to 0.90	0.45 to 0.92	0.63 to 0.95	
High school (n)	3610	1361	1566	271	412	
BMI (kg/m ²)	Mean	0.87	0.95	0.82	1.11	0.09
	95% CI	0.77 to 0.97	0.86 to 1.04	0.60 to 1.03	0.93 to 1.29	
University<4 years (n)	1641	787	539	117	198	
BMI (kg/m ²)	Mean	0.85	0.90	0.88	0.97	0.85
	95% CI	0.72 to 0.98	0.75 to 1.06	0.55 to 1.21	0.71 to 1.22	
University>4 years (n)	1359	666	445	88	160	
BMI (kg/m ²)	Mean	0.72	0.80	1.16	0.75	0.14
	95% CI	0.59 to 0.85	0.64 to 0.96	0.81 to 1.50	0.49 to 1.01	
Leisure time physical activity change examinations 1 and 2*						
Persistently Inactive (n)	813	332	317	63	101	
BMI (kg/m ²)	Mean	0.81	0.98	1.25	0.94	0.42
	95% CI	0.60 to 1.03	0.76 to 1.20	0.76 to 1.73	0.55 to 1.33	
Persistently Active (n)	5368	1599	2798	328	643	
BMI (kg/m ²)	Mean	1.00	1.02	0.82	1.13	0.08
	95% CI	0.91 to 1.08	0.95 to 1.08	0.63 to 1.02	1.00 to 1.27	

continued

Table 3 continued

Tromsø 1–7 (1974–2016)	Change occupational physical activity examinations 1 and 2					P _{equality}
	Total	Persistently Inactive	Persistently Active	Active to Inactive	Inactive to Active	
Active to Inactive (n)	974	291	469	71	143	
BMI (kg/m ²)	Mean	0.82	1.03	1.24	1.11	0.23
	95% CI	0.60 to 1.04	0.86 to 1.21	0.80 to 1.68	0.80 to 1.42	
Inactive to Active (n)	999	348	451	66	134	
BMI (kg/m ²)	Mean	0.90	1.09	0.89	0.77	0.31
	95% CI	0.69 to 1.11	0.91 to 1.28	0.42 to 1.37	0.43 to 1.10	

Data are adjusted for sex, birth year, smoking, education and BMI at examination 2, and are shown as adjusted mean and 95% CI. Examination 1 refers to the first survey of the three attended surveys; examination 2 refers to the second survey of the three attended surveys; examination 3 refers to the third survey of the three attended surveys. P_{equality} is the main difference between groups.

*The leisure-time Saltin-Grimby Physical Activity Scale was not included in Tromsø 4 (1994–1995).

BMI, body mass index.

energy expenditures of about 100 kcal/day would be sufficient for weight gain prevention at the population level,²⁵ indicating that equivalent decreases would result in weight gain. This is similar to the estimated lower energy expenditure deriving from declines in occupational physical activity.³ As leisure time physical activity influences energy expenditure, one could hypothesise that occupational physical activity decline is only hazardous for those being physically inactive in leisure time. However, we observed no effect modification by leisure time physical activity changes.

It has been suggested that achieving energy balance and weight stability is easier at higher energy turnover.¹ For example, energy intake increased by 500 kcal/day from the 1970s to 2000s in the USA, and 110–150 min of walking per day is needed to compensate for this increase.²⁶ Consequently, as 150 min of walking per day is up to seven times higher than the current minimum recommendations for physical activity (150 min/week),²⁷ and

considering that one out of three adults in Western high-income countries fail to meet the recommendations,²⁸ it is unlikely that the physical activity volume performed by the general population is sufficiently high to prevent weight gain.²⁹

As occupational physical activity energy expenditure is dependent on activity duration, the effect of occupational physical activity on weight gain prevention may be influenced by whether individuals work full or part time. Thus, as we did not adjust for full-time and part-time work due to unavailable data, this may also have introduced residual confounding. However, these energy expenditure differences may in reality be small. For example, heavy manual labour workers are estimated to work at ~30% to 35% of maximal oxygen uptake over an 8 hours work day,³⁰ which can be a sufficient volume to compensate the 500 kcal/day energy intake increase.²⁶ However, few individuals in the Tromsø Study report heavy manual labour (~8% in 1979–1980, ~2% in 2015–2016¹⁰). In contrast, most

Table 4 BMI changes by occupational physical activity change in period-specific samples. The Tromsø Study 1974–2016.

Period-specific samples*	Change occupational physical activity examinations 1 and 2					P _{equality}
	Total	Persistently inactive	Persistently active	Active to inactive	Inactive to active	
Tromsø 1–3 (1974–1987)#	n					
Tromsø 2–3 (1979–1987)	3570	1033	1805	366	366	
BMI (kg/m ²)	Mean	0.48	0.48	0.49	0.57	0.68
	95% CI	0.39 to 0.57	0.41 to 0.54	0.35 to 0.64	0.43 to 0.71	
Tromsø 2–4 (1979–1995)	n					
Tromsø 3 and 4 (1986–1995)	9679	2512	5179	665	1323	
BMI (kg/m ²)	Mean	1.12	1.15	1.12	1.07	0.50
	95% CI	1.05 to 1.19	1.10 to 1.20	0.99 to 1.26	0.98 to 1.17	
Tromsø 3–5 (1986–2002)	n					
Tromsø 4 and 5 (1994–2001)	3827	1315	1915	223	374	
BMI (kg/m ²)	Mean	0.96	0.96	1.02	0.91	0.90
	95% CI	0.86 to 1.05	0.87 to 1.04	0.79 to 1.25	0.73 to 1.09	
Tromsø 4–6 (1994–2008)	n					
Tromsø 5 and 6 (2001–2008)	2212	884	985	166	177	
BMI (kg/m ²)	Mean	0.12	0.12	0.15	0.07	0.98
	95% CI	–0.004 to 0.24	0.01 to 0.24	–0.13 to 0.43	–0.20 to 0.35	
Tromsø 5–7 (2001–2016)	n					
Tromsø 6 and 7 (2007–2016)	1146	481	501	60	104	
BMI (kg/m ²)	Mean	0.07	0.35	0.14	0.21	0.20
	95% CI	–0.11 to 0.25	0.17 to 0.53	–0.36 to 0.64	–0.17 to 0.60	

Data are adjusted for sex, birth year, smoking, education and BMI at examination 2, and are shown as adjusted mean and 95% CI. P_{equality} is the main difference between groups.

*Period-specific samples include all participants for that period (ie, these samples do not add up to the overall cohort (Tromsø 1–7), which includes participants with their three most recent attendances).

†Tromsø 1 included only men.

BMI, body mass index.

occupational physical activities in the Tromsø Study changed from standing and walking to sitting,¹⁰ which is consistent with some cohorts.^{3 11 12} The energy expenditure difference while sitting compared with standing is estimated to be 54 kcal over 6 hours (ie, 72 kcal over 8 hours),³¹ which is unlikely to have any apparent effect on weight gain.

Some study cohorts in Southern Europe include a substantially larger proportion of heavy manual labour workers (Portugal, 37%³²; Spain, Barcelona, 68%¹⁷); however, this is not consistent (Madrid, Spain: 2%,³³ Italy: 8%³⁴). Consequently, the generalisability of our findings may be limited to Northern/Central European^{8–10} and North American^{3 11} high-income countries. Studies examining weight gain prevention in heavy manual labour workers may be a future research target.

In our study, 741 (7%) participants are categorised as 'Active to Inactive', while 1315 (12%) participants were categorised as 'Inactive to Active' (table 3), indicating that more individuals increased their occupational physical activity level in our cohort. However, this is due to our crude categorisation of physical activity change; in our sensitivity analysis, 1315 (12%) are categorised as active but decreasing (rank 4 or 3→rank 3 or 2) (online supplemental table 4), where these are categorised as 'Persistently Active' in our main analysis (rank ≥ 2 →rank ≥ 2) (table 3). Thus, the consistent pattern of declining occupational physical activity levels as in previous studies^{3 7–10} is confirmed in our study.

Our results indicate that occupational physical activity declines play a minor, if any, role in the observed population gain in BMI and weight. Consequently, public health initiatives aimed at weight gain prevention may have greater success by focusing on other aspects than occupational physical activity, for example, intake of energy dense food.^{2 26}

The association between physical activity and BMI gain may also be reversed and/or bidirectional.⁴ High body weight appears causally associated with lower levels of physical activity when examining these associations using a Mendelian randomisation approach.³⁵ However, intuitively, leisure-time physical activity is self-regulated while occupational physical activity is less controllable by the individual. Whether individuals regulate their occupational physical activity level depending on their BMI gain is questionable.

Strengths

First, as population gains in BMI have gradually increased over decades,³⁶ the long follow-up time (~6 years) between each examination allowed us to examine whether occupational physical activity has contributed to BMI gain in this cohort.⁴ Second, by computing change in physical activity followed by change in BMI (accounting for previous physical activity level), we are able to interpret the direction of the association with more certainty.⁴ Third, by merging our period-specific samples to an overall cohort, we had higher power to examine multiple potential effect modifiers (table 3). For example, one warranted effect modification to be elucidated in associations between occupational physical activity and health outcomes is sex.³⁷ Although we found differences in BMI gain by sex, we observed no effect modification of the associations by sex. Fourth, we used measured weight and height to calculate BMI as our outcome, which are more valid than self-reported weight and height,²⁴ likely influenced by social desirability bias. Finally, the efforts to recruit representative samples and the high attendance in the Tromsø Study surveys indicate high representability of the population.¹⁸

Limitations

We categorised self-reported physical activity into crude groups, which have introduced misclassification, as described previously. Thus, we may have missed potential energy expenditure changes deriving from physical activity that could influence energy balance. However, crude groups of self-reported physical activity are valuable for categorisation of population levels of physical activity,³⁸ and the SGPALS categorisations have previously shown associations with multiple health outcomes, suggesting predictive validity of the instrument.²⁰ Moreover, our findings were unaltered when occupational physical activity change was categorised into six groups.

The recall and social desirability bias associated with self-reported physical activity likely results in over-reporting of physical activity levels,³⁹ which is also demonstrated in office workers.⁴⁰ Over-reporting of physical activity underestimates or overestimates the effect magnitude between physical activity and health outcomes.⁴ However, self-reported physical activity is currently the only instrument available in long-term ongoing cohort studies.⁴ Finally, as we did not adjust our models for energy intake and full-time/part-time work due to unavailable data, our results may be influenced by residual confounding.

CONCLUSION

We observed no association between changes in occupational physical activity and subsequent changes in BMI. Our findings do not support the hypothesis that occupational physical activity declines contributed to population gains in BMI over the past decades. Public health initiatives aimed at weight gain prevention may have greater success if focusing on other aspects than occupational physical activity.

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from the Tromsø Study, but restrictions apply to the availability of these data, which were used under licence for the current study, and so are not publicly available. The data can be made available from the Tromsø Study upon application to the Data and Publication Committee for the Tromsø Study (see www.tromsostudy.com).

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Paper IV

Sagelv EH, Ekelund U, Hopstock LA, Fimland MS, Løvsletten O, Wilsgaard T, Morseth B. The bidirectional associations between leisure time physical activity change and body mass index gain. The Tromsø Study 1974-2016. *Int J Obes (Lond)*. 2021;45(8):1830-43.



The bidirectional associations between leisure time physical activity change and body mass index gain. The Tromsø Study 1974–2016

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Abstract

Objectives To examine whether leisure time physical activity changes predict subsequent body mass index (BMI) changes, and conversely, whether BMI changes predict subsequent leisure time physical activity changes.

Methods This prospective cohort study included adults attending ≥ 3 consecutive Tromsø Study surveys (time: T1, T2, T3) during 1974–2016 ($n = 10779$). If participants attended >3 surveys, we used the three most recent surveys. We computed physical activity change (assessed by the Saltin-Grimby Physical Activity Level Scale) from T1 to T2, categorized as Persistently Inactive ($n = 992$), Persistently Active ($n = 7314$), Active to Inactive ($n = 1167$) and Inactive to Active ($n = 1306$). We computed BMI change from T2 to T3, which regressed on preceding physical activity changes using analyses of covariance. The reverse association (BMI change from T1 to T2 and physical activity change from T2 to T3; $n = 4385$) was assessed using multinomial regression.

Results Average BMI increase was 0.86 kg/m^2 (95% CI: 0.82–0.90) from T2 to T3. With adjustment for sex, birth year, education, smoking and BMI at T2, there was no association between physical activity change from T1 to T2 and BMI change from T2 to T3 (Persistently Inactive: 0.89 kg/m^2 (95% CI: 0.77–1.00), Persistently Active: 0.85 kg/m^2 (95% CI: 0.81–0.89), Active to Inactive: 0.90 kg/m^2 (95% CI: 0.79–1.00), Inactive to Active 0.85 kg/m^2 (95% CI: 0.75–0.95), $p = 0.84$). Conversely, increasing BMI was associated with Persistently Inactive (odds ratio (OR): 1.17, 95% CI: 1.08–1.27, $p < 0.001$) and changing from Active to Inactive (OR: 1.16, 95% CI: 1.07–1.25, $p < 0.001$) compared with being Persistently Active.

Conclusions We found no association between leisure time physical activity changes and subsequent BMI changes, whereas BMI change predicted subsequent physical activity change. These findings indicate that BMI change predicts subsequent physical activity change at population level and not vice versa.

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Introduction

The prevalence of overweight and obesity is continuously growing worldwide, and now over 50% of the population is classified as either overweight or obese in western high-income countries [1]. As overweight and obesity is associated with a substantial increased risk of non-communicable

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diseases and premature death [2], it is one of the greatest threats to public health in western high-income countries [1, 2].

Weight gain prevention at populational level is challenging. Obviously, excessive adiposity and weight gain are effects of an imbalanced energy intake and expenditure [3]. Thus, increasing physical activity levels could potentially serve as an effective public health strategy to prevent population weight gain [3, 4]. However, studies examining whether population levels of physical activity can prevent weight gain show conflicting results [4, 5], which may be attributed to methodological issues [5]. For example, although current weight is a strong predictor of future weight gain [5], some studies failed to adjust for baseline weight or body mass index (BMI) [6–14]. Moreover, most studies did not take the temporal reciprocal relationship between changing physical activity and weight into account [5], as they assessed the association between baseline physical activity level and future weight or BMI change [9, 10, 15–22]. Other studies examined the associations between change scores in both physical activity and weight or BMI [6, 8, 11–14, 23–37], which basically are cross-sectional analyses of change scores [5]. Finally, the association between physical activity and weight change may be reverse as weight change may lead to physical activity change [5, 6, 22, 25, 26, 35, 37–39], or this may be bidirectional [5].

Furthermore, the association between physical activity change and BMI change may be modified by other behavioural or societal factors, including sex [10], age [17, 18, 28–30], smoking [23, 29], education [24], physical activity domain (e.g., occupation or leisure time) [29], and baseline BMI [28, 29]. However, these observations are not

consistent [12, 15, 26, 33], which warrant further investigation.

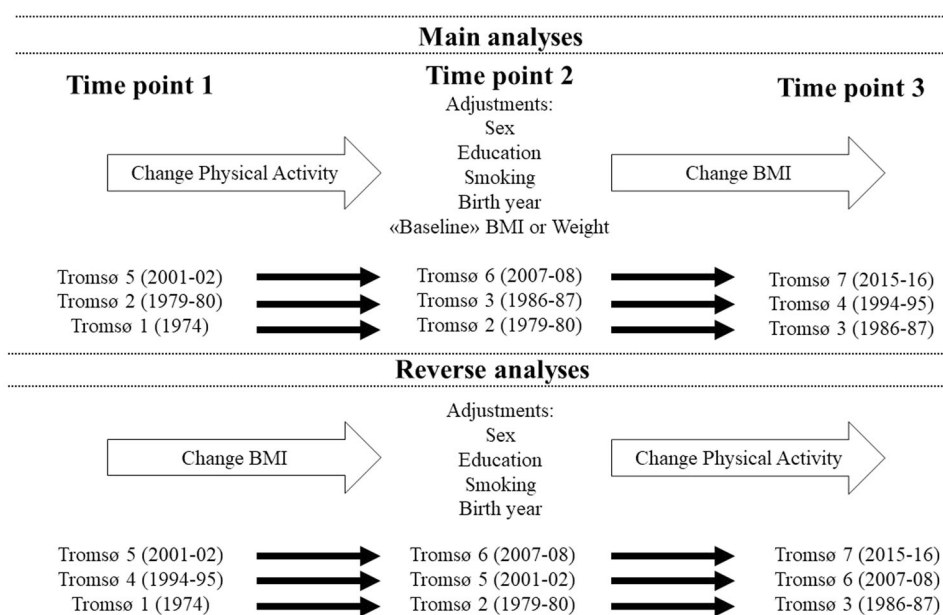
Declines in both leisure time and occupational physical activity may contribute to population BMI gains [4]. We have previously reported on the association between occupational physical activity and BMI change in a population-based cohort (The Tromsø Study) from Norway followed through repeated examinations every ~6 years. Our results suggested that occupational physical activity declines did not contribute to population BMI gains [40]. As large proportions of the population are inactive during work hours [41, 42], leisure time physical activity may have greater potential to prevent weight gain. Thus, the aims of this study were to assess: (1) Whether changes in leisure time physical activity from examination 1 (time (T) 1) to the next (T2) predicted subsequent changes in BMI from T2 to the next examination (T3), and (2) Whether BMI changes from T1 to T2 predicted subsequent leisure time physical activity changes from T2 to T3, with ~6 years follow up between each examination.

Materials and methods

Design

The study design is illustrated in Fig. 1. We studied participants from the Tromsø Study, a population-based cohort study in Tromsø Municipality, Norway. There are seven repeated Tromsø Study surveys (attendance of invited participants = %): 1974 (Tromsø 1; 83%), 1979–80 (Tromsø 2; 85%), 1986–87 (Tromsø 3; 81%), 1994–95 (Tromsø 4; 77%), 2001 (Tromsø 5; 79%), 2007–08 (Tromsø 6; 66%)

Fig. 1 The study design for assessing the association between physical activity changes and future BMI changes, and conversely for assessing BMI changes and physical activity changes. BMI body mass index.



and 2015–16 (Tromsø 7: 65%). Invited participants were selected from total birth cohorts and random samples of inhabitants in Tromsø municipality [41, 43]. Only men were invited to Tromsø 1 (1974), while in Tromsø 2–7 (1979–2016) both men and women were invited (details described elsewhere [41, 43]). In this study, we included participants attending at least three consecutive surveys (hereafter called T1, T2, T3). To assess the association between change in physical activity from T1 to T2 and change in BMI from T2 to T3, the inclusion criteria were information on: (1) physical activity at T1 and T2, and height and weight at T2 and T3; (2) information on educational level and smoking habits at T2; and (3) not pregnant at T2 and/or T3. We also reversed the analyses to assess whether BMI change from T1 to T2 predicted physical activity change from T2 to T3. Here, inclusion criteria were: (1) height and weight at T1 to T2, physical activity at T2 to T3; (2) educational level and smoking habits at T2; and (3) not pregnant at T1 and/or T2. If the participants attended more than three consecutive surveys, we used their data from the three most recent surveys in the analyses of the overall cohort, while their data could be included in multiple period-specific samples (Tromsø 1–3: 1974–1987, Tromsø 2–4: 1979–1995, Tromsø 5–7: 2001–2016).

Participants

Participant selection for our analyses is illustrated in Fig. 2. The overall cohort comprised 10779 participants, which

derive from the participants’ three most recent Tromsø Study attendances. We also created period-specific samples where each participant may be included in multiple period-specific samples: Tromsø 1–3 (1974–1987, $n = 3598$), Tromsø 2–4 (1979–1995, $n = 9691$) and Tromsø 5–7 (2001–2016, $n = 2206$). Therefore, the period-specific samples do not add up to the overall cohort, which only includes participants with their three most recent consecutive surveys (Fig. 2).

The reversed analyses (BMI change from T1 to T2 followed by physical activity change from T2 to T3) were assessed in an overall cohort comprising 4385 participants (Fig. 3). The leisure time physical activity questionnaire was not included in Tromsø 4 and only those <70 years answered the questionnaire in Tromsø 5; this explains the lower sample size in the reversed analyses compared with the main analyses.

All participants from Tromsø 4–7 provided written informed consent and the present study was approved by the Regional Ethics Committee for Medical Research (ref. 2016/758410).

Self-reported physical activity

Physical activity was measured with the Saltin-Grimby Physical Activity Level Scale (SGPALS) questionnaire [44, 45], which asks participants to rank their physical activity by four hierarchical levels for leisure- and occupational time physical activity, separately, during the last

Fig. 2 Flow chart of participant selection.

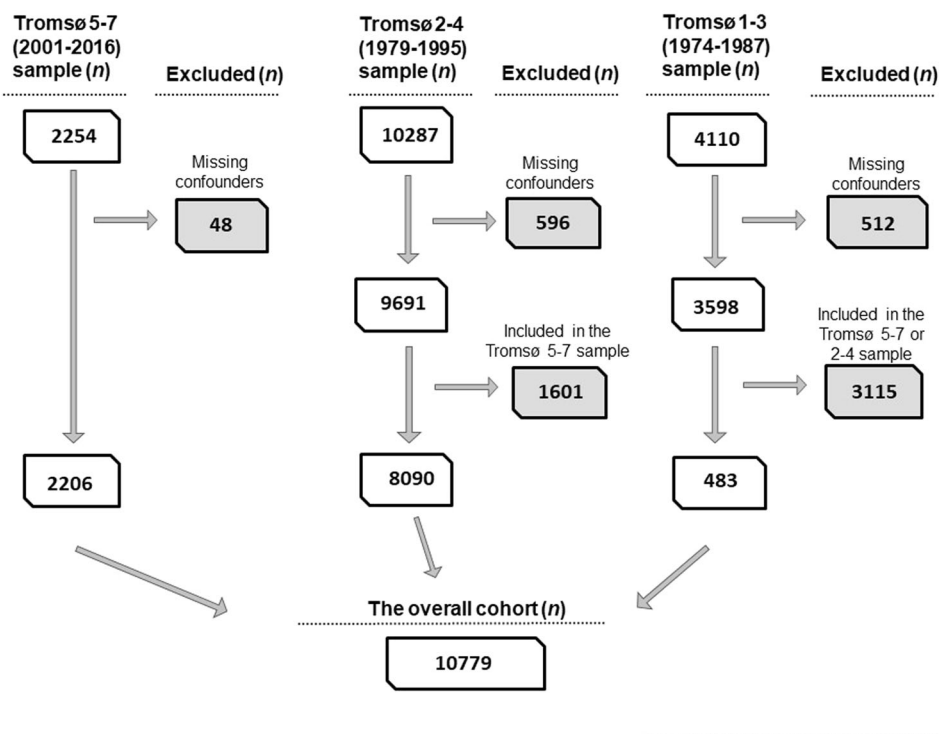
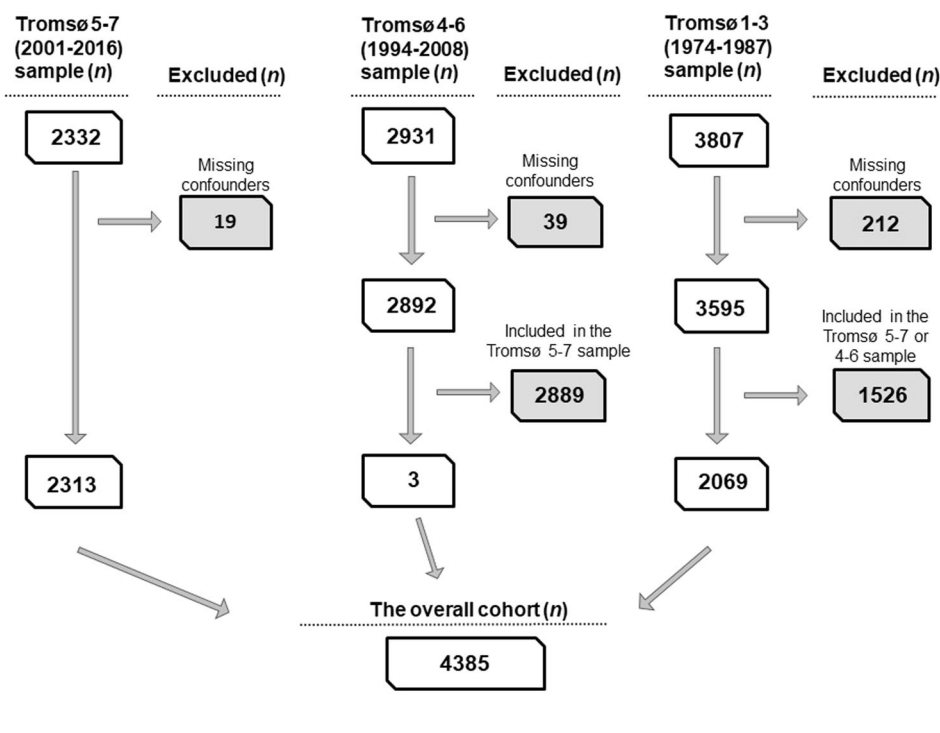


Fig. 3 Flow chart of participant selection for the reversed analyses.



12 months [44]. The SGPALS in the Tromsø Study is slightly modified compared to the original by Saltin and Grimby [44] (Supplementary Table 1). The SGPALS is found to provide acceptable reliability [45] and validation studies have demonstrated acceptable ability to rank physical activity level when evaluated against accelerometry and cardiorespiratory fitness as the criterions [45].

Physical activity change was computed as (1) *Persistently Inactive* (reporting rank 1 at T1 and T2; $n = 992$); (2) *Persistently Active* (rank ≥ 2 at T1 and T2; $n = 7314$); (3) *Active to Inactive* (rank ≥ 2 at T1 and rank 1 at T2; $n = 1167$); and (4) *Inactive to Active* (rank 1 at T1 and rank ≥ 2 at T2; $n = 1306$).

The leisure time SGPALS was used in all Tromsø Study surveys except Tromsø 4 (1994–95), and in Tromsø 5 (2001) not by those ≥ 70 years. The occupational time SGPALS was used in all surveys by participants of all ages.

Body mass index and weight

Weight and height were measured in light clothing and are expressed as kilograms (kg) and metres (m). BMI was calculated as kg/m^2 and categorized into normal weight ($<25 \text{ kg}/\text{m}^2$), overweight ($25\text{--}29 \text{ kg}/\text{m}^2$) and obese ($\geq 30 \text{ kg}/\text{m}^2$) for stratified analyses. Change in BMI from T2 to T3 was calculated with height being fixed at T2 and change in BMI from T1 to T2 fixed at T1, to avoid a possible effect of height loss between the measurements.

Confounders and effect modifiers

We included sex, birth year, smoking, education and BMI measured at T2 as confounders, and we also assessed potential effect modification of the confounders in addition to occupational physical activity change from T1 to T2. Data on smoking, education and occupational physical activity were retrieved from questionnaires. We categorized smoking into (1) Current smoker, (2) Previous smoker, and (3) Never smoker. The participants reported years of education in Tromsø 2 (1979–80), Tromsø 3 (1986–87) and Tromsø 5 (2001), which we categorized into (1) Primary school (<10 years), (2) High school (10–12 years), (3) University <4 years (13–15 years), and (4) University ≥ 4 years (≥ 16 years). In Tromsø 4 (1994–95) and Tromsø 6 (2007–08), the participants reported education with five response options, which included the four abovementioned groups and a fifth named “Technical school 2 years senior high” (vocational training), which we categorized as (2) High school.

Statistical analyses

Paired t tests were used to assess whether participants changed BMI from T2 to T3. Analyses of covariance (ANCOVA) were used to assess the association between physical activity change from T1 to T2 and BMI change from T2 to T3, adjusted for sex, birth year, smoking, education and BMI at T2. The ANCOVA was applied on the

overall cohort and the period-specific samples, in total and stratified by sex, birth year, smoking, education and occupational physical activity change from T1 to T2. We interpreted the Q-Q plots of BMI change from T2 to T3 to not deviate from normal distribution. Although the Levene's test of equality variance violated the assumption of homogeneity of variance across physical activity change groups ($p < 0.001$), we considered our large sample size in all physical activity change groups to make the ANCOVA robust for this heterogeneity. Interaction effects were tested between physical activity change and potential effect modifiers (sex, birth year, smoking, education and BMI at T2, and occupational time physical activity change from T1 to T2) in the overall cohort. We performed sensitivity analyses with leisure time physical activity change categorized into six groups; (1) *Persistently Inactive*, (2) *Persistently Active*, (3) *Active but decreasing* (rank 4 or 3 \rightarrow 3 or 2), (4) *Active and Increasing* (rank 2 or 3 \rightarrow 3 or 4), (5) *Active to Inactive* and (6) *Inactive to Active*. Alpha was set to 0.05 and data are shown as mean and 95% confidence intervals (CI) from t tests and ANCOVAs.

We performed multinomial logistic regressions to estimate odds ratios (OR) with 95% confidence intervals (CI) for changing leisure time physical activity from T2 to T3 per unit BMI change from T1 to T2, adjusted for sex, birth year, smoking and education at T2. The analyses were performed in the overall sample ($n = 4385$) and stratified by sex, birth year, smoking, education and occupational physical activity change (T1 to T2). We assessed interaction effects between BMI change and potential effect modifiers (sex, birth year, smoking, education and BMI at T2, and occupational physical activity change from T1 to T2). *Persistently Active* was set as reference category. We used the Statistical Package for Social Sciences (SPSS, Version 26, IBM, Armonk, NY, United States) for all statistical analyses.

Results

The descriptive characteristics at T2 for the overall cohort and period-specific samples (Tromsø 1–3, 1974–1987; Tromsø 2–4, 1979–1995; Tromsø 5–7, 2001–2016) are presented in Table 1. The participants increased their BMI from T2 to T3 (all $p < 0.001$), except for the Tromsø 5–7 sample ($p = 0.96$).

Change in BMI by preceding change in leisure time physical activity

Changes in BMI by preceding leisure time physical activity change are presented in Table 2, and BMI at T2 and T3 by leisure time physical activity change are presented in

Supplementary Table 2. In the overall cohort, we observed no differences in BMI change between categories of leisure time physical activity change ($p = 0.84$), and in general no associations in strata by sex, birth year, smoking, education and occupational physical activity change (Table 2).

In the period-specific sample Tromsø 5–7 (2001–2016), we observed differences in BMI change between the leisure time physical activity change groups, where those changing from Active to Inactive increased their BMI more than those changing from Inactive to Active ($p = 0.01$). In stratified analyses, higher BMI change was observed in those changing from Active to Inactive in men ($p = 0.02$) but not in women ($p = 0.22$), and among those born ≤ 1949 ($p = 0.05$). In those who never smoked, Persistently Inactive participants decreased their BMI more than those changing from Active to Inactive ($p = 0.03$). Finally, there were differences among the leisure time physical activity change groups among those having < 4 years university education; those changing from Active to Inactive increased their BMI more than all other leisure time physical activity change groups ($p = 0.003$) (Supplementary Table 3). There were no differences in BMI increase by leisure time physical activity change in the Tromsø 1–3 (1974–1987) and Tromsø 2–4 (1979–1995) samples (Supplementary Table 4–5).

In the overall cohort, we observed no interaction for the association between leisure time physical activity change and BMI change by sex ($p = 0.62$), birth year ($p = 0.23$), smoking ($p = 0.08$) or BMI ($p = 0.44$) at T2, or occupational physical activity change from T1 to T2 ($p = 0.10$). However, we observed that education modified the association between leisure time physical activity change and BMI change ($p = 0.002$).

In the sensitivity analyses (in the overall cohort), with six physical activity change groups, the results were similar (Supplementary Table 6).

Change in leisure time physical activity with preceding BMI change

Participants who increased their BMI from T1 to T2 were more likely to be Persistently Inactive (OR: 1.17, 95% CI: 1.08 to 1.27 per 1 unit increase in BMI (kg/m^2), $p < 0.001$) and to change from Active to Inactive (OR: 1.16, 95% CI: 1.07 to 1.25, $p < 0.001$) from T2 to T3 compared with those being Persistently Active at T2 and T3. Increasing BMI was not associated with changing from Inactive to Active (OR: 1.01, 95% CI: 0.94–1.08, $p = 0.97$) compared with those being Persistently Active at T2 and T3 (Table 3)

Sex, birth year, BMI, smoking and education at T2, and occupational physical activity change from T1 to T2, all modified the associations between BMI change and subsequent leisure time physical activity change (Table 3). Stratified analyses showed slight differences in ORs

Table 1 Descriptive characteristics of the overall cohort and period-specific samples.

Cohort		Overall cohort ^a		Period-specific samples ^b	
		Tromsø 1–7 (1974–2016)	Tromsø 1–3 (1974–1986)	Tromsø 2–4 (1979–1995)	Tromsø 5–7 (2001–2016)
Total <i>n</i> (%)		10779 (100%)	3598 (100%)	9691 (100%)	2206 (100%)
BMI (kg/m ²)					
Time point 2	Mean	24.81	24.65	24.25	26.93
	95% CI	24.74 to 24.88	24.56 to 24.74	24.18 to 24.32	26.75 to 27.11
Time point 3	Mean	25.67	25.15	25.38	26.93
	95% CI	25.60 to 25.74	25.05 to 25.25	25.31 to 25.45	26.75 to 27.11
Change time point 2–3	Mean	0.86	0.49	1.13	−0.002
	95% CI	0.82 to 0.90	0.44 to 0.53	1.10 to 1.17	−0.09 to 0.08
Baseline		Time point 2	Tromsø 2 (1979–80)	Tromsø 3 (1986–87)	Tromsø 6 (2007–08)
Sex					
Women	<i>n</i> (%)	5195 (48.2%)	N/A	4834 (49.9%)	1273 (57.7%)
Men	<i>n</i> (%)	5584 (51.8%)	3598 (100%)	4857 (50.1%)	933 (42.3%)
Age (yr)	Mean	46.19	39.78	42.59	62.04
	95% CI	45.96 to 46.42	39.51 to 40.05	42.42 to 42.76	61.65 to 62.43
10-year age groups					
≤39 years	<i>n</i> (%)	3837 (35.6%)	1824 (50.7%)	3836 (39.9%)	36 (1.6%)
40–49 years	<i>n</i> (%)	2917 (27.1%)	1199 (33.3%)	3512 (36.2%)	289 (13.1%)
50–59 years	<i>n</i> (%)	2238 (20.8%)	575 (16.0%)	2110 (21.8%)	327 (14.8%)
60–69 years	<i>n</i> (%)	1326 (12.3%)	N/A	233 (2.4%)	1093 (49.5%)
≥70 years	<i>n</i> (%)	461 (4.3%)	N/A	N/A	461 (20.9%)
BMI groups					
Normal weight	<i>n</i> (%)	6276 (58.2%)	2138 (59.4%)	6255 (64.5%)	759 (34.4%)
Overweight	<i>n</i> (%)	3594 (33.3%)	1313 (36.5%)	2920 (30.1%)	1011 (45.8%)
Obese	<i>n</i> (%)	909 (8.4%)	147 (4.1%)	516 (5.3%)	436 (19.8%)
Smoking					
Current smoker	<i>n</i> (%)	4316 (40.0%)	1720 (47.8%)	4226 (43.6%)	360 (16.3%)
Previous smoker	<i>n</i> (%)	1715 (15.9%)	505 (14.0%)	754 (7.8%)	1019 (46.2%)
Never smoker	<i>n</i> (%)	4748 (44.1%)	1373 (38.2%)	4711 (48.6%)	828 (37.5%)
Education					
Primary school	<i>n</i> (%)	4555 (42.3%)	1860 (51.7%)	4331 (44.7%)	719 (32.6%)
High school	<i>n</i> (%)	3368 (31.2%)	1009 (28.0%)	2938 (30.3%)	772 (35.0%)
University <4 years	<i>n</i> (%)	1576 (14.6%)	426 (11.8%)	1381 (14.3%)	364 (16.5%)
University ≥4 years	<i>n</i> (%)	1280 (11.9%)	303 (8.4%)	1041 (10.7%)	351 (15.9%)
Reverse analyses					
Total	<i>n</i> (%)	4385 (100%)	N/A	N/A	N/A
BMI (kg/m ²)	Mean	25.64	N/A	N/A	N/A
	95% CI	25.53 to 25.75			
Sex					
Women	<i>n</i> (%)	1307 (29.8%)	N/A	N/A	N/A
Men	<i>n</i> (%)	3078 (70.2%)	N/A	N/A	N/A
Age (yr)	Mean	50.63	N/A	N/A	N/A
	95% CI	50.16 to 51.10			
10-year age groups					
≤39 years	<i>n</i> (%)	1489 (34%)	N/A	N/A	N/A
40–49 years	<i>n</i> (%)	647 (14.8%)	N/A	N/A	N/A
50–59 years	<i>n</i> (%)	601 (13.7%)	N/A	N/A	N/A

Table 1 (continued)

Cohort		Overall cohort ^a Tromsø 1–7 (1974–2016)	Period-specific samples ^b		
			Tromsø 1–3 (1974–1986)	Tromsø 2–4 (1979–1995)	Tromsø 5–7 (2001–2016)
60–69 years	<i>n</i> (%)	1063 (24.2%)	N/A	N/A	N/A
≥70 years	<i>n</i> (%)	585 (13.3%)	N/A	N/A	N/A
BMI groups					
Normal weight	<i>n</i> (%)	2131 (48.6%)	N/A	N/A	N/A
Overweight	<i>n</i> (%)	1746 (39.8%)	N/A	N/A	N/A
Obese	<i>n</i> (%)	508 (11.6%)	N/A	N/A	N/A
Smoking					
Current smoker	<i>n</i> (%)	1396 (31.8%)	N/A	N/A	N/A
Previous smoker	<i>n</i> (%)	1372 (31.3%)	N/A	N/A	N/A
Never smoker	<i>n</i> (%)	1617 (36.9%)	N/A	N/A	N/A
Education					
Primary school	<i>n</i> (%)	1731 (39.5%)	N/A	N/A	N/A
High school	<i>n</i> (%)	1432 (32.7%)	N/A	N/A	N/A
University <4 years	<i>n</i> (%)	672 (15.3%)	N/A	N/A	N/A
University ≥4 years	<i>n</i> (%)	550 (12.5%)	N/A	N/A	N/A

The Tromsø Study 1974–2016.

Data are shown as unadjusted mean and 95% CI or as frequency and percentage.

CI confidence interval.

^aThe overall cohort includes participants attending ≥3 surveys and the analyses are based on their three most recent surveys.

^bPeriod specific samples include all participants meeting our inclusion criteria for that period, and each participant may contribute in more than one period; therefore, these samples do not add up to the overall cohort (Tromsø 1–7).

We only assessed the reverse association in an overall cohort, which explains the N/As in the period-specific samples for the reverse association.

between strata. For example, men were more likely to be Persistently Inactive than Persistently Active per BMI-unit increase, while this was not observed in women. Those in higher birth year strata (1940–49, ≥1950) were more likely to be Persistently Inactive or changing from Active to Inactive with increasing BMI, which was not observed in those born ≤1939 (Table 3).

Discussion

In this prospective cohort study, we found no association between leisure time physical activity changes and subsequent BMI changes, whereas BMI increases predicted subsequent low and decreasing physical activity levels.

Most previous studies assessing the prospective association between leisure time physical activity and BMI either used baseline physical activity as the predictor [9, 10, 15–23, 30], which do not take temporal changes between physical activity and BMI into account [5], or assessed associations between change scores for both physical activity and BMI [6, 8, 11–14, 23–37], which basically are cross-sectional analyses that cannot provide an

indication of the direction of the association [5]. One study examined the association between physical activity changes from a 1st to a 2nd examination and BMI changes from the 1st to a 3rd examination and found an association between physical activity decline and BMI gain [46]. Although assessing associations over three examinations are likely less influenced by confounding compared with two examinations, computing both exposure and outcome change from baseline still opens for reverse causation (i.e., weight gain potentially preceding physical activity decline). In the present study, we examined physical activity change from a 1st to a 2nd examination, followed by BMI change from the 2nd to a 3rd examination, which may be more suitable to assess the direction of the association, which provides an indication of causality [5].

Compared with the number of studies that examined whether physical activity is associated with BMI gain, fewer studies assessed a potential reverse association (i.e., BMI change predict physical activity change) [5]. In those that did, high baseline BMI [6, 37] and BMI gain [22, 25, 35, 37, 39] were associated with physical activity declines. In one study, baseline BMI, but not BMI changes, was associated with physical activity declines [26]. In a

Table 2 Change in BMI from T2 to T3 by leisure physical activity change from T1 to T2. The Tromsø Study 1974–2016.

Tromsø 1–7 (1974–2016)	Change leisure physical activity T1 to T2					P _{equality}
	Total	Persistently Inactive	Persistently Active	Active to Inactive	Inactive to Active	
<i>Total (n)</i>	10779	992	7314	1167	1306	
BMI T2 (kg/m ²) ^a	Mean	25.25	24.73	24.64	25.05	
	95% CI	24.99 to 25.51	24.65 to 24.81	24.43 to 24.85	24.83 to 25.27	
BMI change T2 to T3						
BMI change (kg/m ²)	Mean	0.89	0.85	0.90	0.85	0.84
	95% CI	0.77 to 1.00	0.81 to 0.89	0.79 to 1.00	0.75 to 0.95	
Sex						
<i>Women (n)</i>	5195	490	3481	594	630	
BMI change (kg/m ²)	Mean	1.23	1.08	1.13	1.08	0.48
	95% CI	1.05 to 1.41	1.01 to 1.15	0.96 to 1.29	0.92 to 1.24	
<i>Men (n)</i>	5584	502	3833	573	676	
BMI change (kg/m ²)	Mean	0.56	0.64	0.68	0.64	0.67
	95% CI	0.42 to 0.70	0.59 to 0.69	0.55 to 0.82	0.51 to 0.76	
Birth year						
<i>≤1929 (n)</i>	687	56	456	84	91	
BMI change (kg/m ²)	Mean	0.01	0.17	0.05	0.07	0.82
	95% CI	−0.42 to 0.43	0.02 to 0.32	−0.30 to 0.40	−0.26 to 0.41	
<i>1930–1939 (n)</i>	2868	234	2017	274	343	
BMI change (kg/m ²)	Mean	0.42	0.47	0.45	0.53	0.92
	95% CI	0.18 to 0.66	0.39 to 0.55	0.22 to 0.67	0.33 to 0.73	
<i>1940–1949 (n)</i>	4115	409	2804	412	490	
BMI change (kg/m ²)	Mean	1.01	0.93	0.95	0.94	0.89
	95% CI	0.82 to 1.19	0.86 to 1.00	0.77 to 1.14	0.77 to 1.10	
<i>1950–1959 (n)</i>	2821	269	1825	364	363	
BMI change (kg/m ²)	Mean	1.29	1.33	1.40	1.25	0.72
	95% CI	1.08 to 1.50	1.25 to 1.41	1.22 to 1.58	1.07 to 1.43	
<i>≥1960 (n)</i>	288	24	212	33	19	
BMI change (kg/m ²)	Mean	1.47	0.60	1.44	0.06	0.09
	95% CI	0.47 to 2.47	0.27 to 0.94	0.59 to 2.30	−1.07 to 1.19	
BMI groups						
<i>Normal weight (n)</i>	6276	524	4311	704	737	
BMI change (kg/m ²)	Mean	1.04	1.01	1.02	1.04	0.96
	95% CI	0.90 to 1.18	0.96 to 1.06	0.90 to 1.14	0.93 to 1.16	
<i>Overweight (n)</i>	3594	352	2440	376	426	
BMI change (kg/m ²)	Mean	0.86	0.81	0.92	0.83	0.77
	95% CI	0.66 to 1.07	0.73 to 0.89	0.72 to 1.16	0.65 to 1.02	
<i>Obese (n)</i>	909	116	563	87	143	
BMI change (kg/m ²)	Mean	0.06	0.05	0.06	−0.15	0.89
	95% CI	−0.45 to 0.56	−0.19 to 0.28	−0.53 to 0.65	−0.61 to 0.32	
Smoking						
<i>Current smoker (n)</i>	4316	521	2570	541	684	
BMI change (kg/m ²)	Mean	0.92	1.07	0.99	0.93	0.16
	95% CI	0.75 to 1.08	1.00 to 1.15	0.83 to 1.15	0.79 to 1.07	
<i>Previous smoker (n)</i>	1715	135	1224	190	166	
BMI change (kg/m ²)	Mean	0.34	0.29	0.46	0.30	0.71
	95% CI	0.02 to 0.66	0.19 to 0.40	0.19 to 0.73	0.01 to 0.59	
<i>Never smoker (n)</i>	4748	336	3520	436	356	
BMI change (kg/m ²)	Mean	1.07	0.88	0.98	0.96	0.15
	95% CI	0.89 to 1.26	0.82 to 0.93	0.81 to 1.15	0.80 to 1.13	
Education						
<i>Primary school (n)</i>	4555	465	2921	534	635	
BMI change (kg/m ²)	Mean	0.82	0.83	0.73	0.69	0.32
	95% CI	0.65 to 1.00	0.76 to 0.90	0.56 to 0.89	0.54 to 0.84	
<i>High school (n)</i>	3368	317	2300	368	383	
BMI change (kg/m ²)	Mean	0.93	0.91	0.87	0.96	0.92
	95% CI	0.72 to 1.13	0.83 to 0.98	0.68 to 1.06	0.78 to 1.15	

Table 2 (continued)

Tromsø 1–7 (1974–2016)	Change leisure physical activity T1 to T2					P _{equality}
	Total	Persistently Inactive	Persistently Active	Active to Inactive	Inactive to Active	
University < 4 years (<i>n</i>)	1576	106	1173	135	162	
BMI change (kg/m ²)	Mean	0.90	0.87	1.53	0.95	0.001
	95% CI	0.55 to 1.25	0.76 to 0.97	1.22 to 1.84	0.66 to 1.23	
University > 4 years (<i>n</i>)	1280	104	920	130	126	
BMI change (kg/m ²)	Mean	0.99	0.80	0.95	1.16	0.08
	95% CI	0.69 to 1.30	0.69 to 0.90	0.67 to 1.22	0.88 to 1.43	
Occupational Physical Activity Change T1 to T2						
Persistently Inactive	2637	340	1650	303	344	
BMI change (kg/m ²)	Mean	0.81	0.85	0.93	0.92	0.79
	95% CI	0.61 to 1.00	0.76 to 0.94	0.72 to 1.14	0.72 to 1.11	
Persistently Active	5014	372	3514	539	589	
BMI change (kg/m ²)	Mean	1.04	1.07	1.05	1.01	0.92
	95% CI	0.86 to 1.23	1.01 to 1.13	0.89 to 1.20	0.86 to 1.16	
Active to Inactive	673	62	439	96	76	
BMI change (kg/m ²)	Mean	1.43	0.89	0.88	0.95	0.13
	95% CI	1.01 to 1.86	0.73 to 1.04	0.54 to 1.22	0.57 to 1.33	
Inactive to Active	1277	1144	799	129	205	
BMI change (kg/m ²)	Mean	1.03	0.99	0.96	0.90	0.91
	95% CI	0.73 to 1.33	0.86 to 1.11	0.64 to 1.28	0.65 to 1.15	

Data are adjusted for sex, birth year, smoking, education and BMI at T2, and shown as adjusted mean BMI change with 95% CI.

CI confidence interval, BMI body mass index, *Pequality* main difference between groups, T1 time point 1, T2 time point 2, T3 time point 3.

^aData are shown as unadjusted mean BMI at T2 with 95% CI.

Mendelian randomization study, high body weight appeared causally associated with lower physical activity levels [38]. Thus, except for one previous study [26], our study corroborates previous studies, suggesting that BMI gain leads to lower physical activity level.

Lower physical activity levels following weight gain are likely due to movement limitations. In a case-control study of normal weight and obese adolescents, physical activity measured by accelerometry was substantially lower in obese individuals compared with their normal weight peers despite similar physical activity energy expenditures [47]. Similarly, this was also demonstrated in an experimental study of overfeeding with 4 MJ (1000 kilocalories (kcal)) per day over eight weeks, where free-living walking distances decreased due to lower walking velocity (i.e., movement limitation) in both normal weight and obese individuals following overfeeding, likely due to the increased weight [48].

Furthermore, our study contradicts a previous study, which reported that female but not male university alumni with high baseline BMI decreased their physical activity level over time [6], while we observed that both women and men were likely to decrease their physical activity with increasing BMI. This may be explained by demography (e.g., socioeconomic status, age) or by differences in analytical approach. In addition, we observed that sex, birth year, baseline (T2) BMI, smoking, education and occupational physical activity change all modified the association

between BMI change and subsequent physical activity change. This indicates that the effect of BMI change on physical activity change is dependent on multiple behavioural and societal factors, which warrants additional research.

A pertinent question may be whether population levels of physical activity are sufficiently high to prevent weight gain. One previous study estimated that a physical activity energy expenditure increase of ~0.4 megajoule (MJ) (i.e., 100 kcal) per day would be sufficient to prevent weight gain at population level [49], which could be feasible for the general population. However, highly active women who performed 60 minutes per day of moderate intensity activity (considerably higher physical activity energy expenditure than 0.4 MJ per day) seemed to still gain weight, but at a lower rate than their less active peers, indicating that such physical activity levels at best mitigates weight gain [28]. Moreover, in another study, women and men being physically active at baseline had a lower baseline weight, but similar weight gain rate as those being inactive [26]. Energy intake has increased with ~2 MJ (i.e., 500 kcal) per day from the 1970 to 2000s in the United States, [50], which is similar to Western European countries from the 1960s to 2011 in a recent global study [51]. About 110–150 min of walking per day is needed to compensate for the increased energy intake of 2 MJ [50]. This is seven times more than the current minimal recommendations for physical activity of 150 minutes per week [52]. In Western high-income

Table 3 Odds ratio of leisure time physical activity change with body mass index change (per kg/m² increase).

Tromsø 1–7 (1974–2016)		Persistently inactive	Active to inactive	Inactive to active	Persistently active
Total (<i>n</i>)	4385	378	397	512	3098
	OR	1.14	1.16	1.02	Ref.
	95% CI	1.07 to 1.22	1.09 to 1.24	0.96 to 1.09	
Sex					
	<i>P</i> _{interaction}	<0.001	0.003	0.59	
Women (<i>n</i>)	1307	107	102	118	980
	OR	1.09	1.21	1.05	Ref.
	95% CI	0.98 to 1.22	1.09 to 1.34	0.95 to 1.16	
Men (<i>n</i>)	3078	271	295	394	2118
	OR	1.19	1.14	1.02	Ref.
	95% CI	1.09 to 1.30	1.04 to 1.23	0.95 to 1.10	
Birth year					
	<i>P</i> _{interaction}	<0.001	<0.001	0.17	
≤1939 (<i>n</i>)	1473	135	132	203	1003
	OR	1.11	1.01	0.94	Ref.
	95% CI	0.99 to 1.24	0.90 to 1.14	0.85 to 1.04	
1940–49 (<i>n</i>)	1906	162	171	205	1368
	OR	1.13	1.21	1.06	Ref.
	95% CI	1.02 to 1.25	1.10 to 1.34	0.96 to 1.16	
≥1950 (<i>n</i>)	1006	81	94	104	727
	OR	1.23	1.28	1.10	Ref.
	95% CI	1.06 to 1.43	1.12 to 1.45	0.96 to 1.26	
BMI groups					
	<i>P</i> _{interaction}	<0.001	<0.001	0.29	
Normal weight (<i>n</i>)	2131	153	176	227	1575
	OR	0.94	1.07	0.96	Ref.
	95% CI	0.83 to 1.06	0.95 to 1.20	0.86 to 1.07	
Overweight (<i>n</i>)	1746	149	163	208	1226
	OR	1.15	1.12	1.01	Ref.
	95% CI	1.04 to 1.28	1.01 to 1.24	0.92 to 1.11	
Obese (<i>n</i>)	508	76	58	77	297
	OR	1.17	1.21	1.00	Ref.
	95% CI	1.03 to 1.31	1.07 to 1.38	0.88 to 1.13	
Smoking					
	<i>P</i> _{interaction}	<0.001	<0.001	0.61	
Current smoker (<i>n</i>)	1396	180	168	218	830
	OR	1.14	1.14	1.00	Ref.
	95% CI	1.02 to 1.28	1.02 to 1.28	0.90 to 1.11	
Previous smoker (<i>n</i>)	1372	93	102	152	1025
	OR	1.18	1.23	1.0	Ref.
	95% CI	1.06 to 1.32	1.11 to 1.37	0.95 to 1.15	
Never smoker (<i>n</i>)	1617	105	127	142	1243
	OR	1.13	1.14	1.02	Ref.
	95% CI	0.99 to 1.30	1.00 to 1.29	0.90 to 1.15	
Education					
	<i>P</i> _{interaction}	0.008	<0.001	0.47	
Primary school (<i>n</i>)	1731	188	171	124	1129
	OR	1.17	1.11	1.04	Ref.
	95% CI	1.07 to 1.28	1.00 to 1.22	0.95 to 1.13	

Table 3 (continued)

Tromsø 1–7 (1974–2016)		Persistently inactive	Active to inactive	Inactive to active	Persistently active
High school (<i>n</i>)	1432	113	117	164	1038
	OR	1.15	1.12	0.96	Ref.
	95% CI	1.01 to 1.30	0.99 to 1.26	0.86 to 1.06	
University <4 years (<i>n</i>)	672	44	60	65	503
	OR	1.13	1.20	1.17	Ref.
	95% CI	0.89 to 1.43	0.98 to 1.46	0.96 to 1.42	
University ≥4 years (<i>n</i>)	550	33	49	40	428
	OR	0.95	1.38	1.04	Ref.
	95% CI	0.76 to 1.18	1.17 to 1.64	0.85 to 1.28	
Occupational Physical Activity Change from T1 to T2					
<i>P</i> _{interaction}		0.01	<0.001	0.81	
Persistently Inactive (<i>n</i>)	1125	129	119	124	753
	OR	1.24	1.12	0.96	Ref.
	95% CI	1.09 to 1.42	0.98 to 1.28	0.85 to 1.08	
Persistently Active (<i>n</i>)	1536	106	142	178	1110
	OR	1.17	1.17	1.06	Ref.
	95% CI	1.04 to 1.32	1.05 to 1.30	0.96 to 1.18	
Active to Inactive (<i>n</i>)	248	19	37	36	156
	OR	0.96	1.23	0.88	Ref.
	95% CI	0.66 to 1.41	0.93 to 1.63	0.66 to 1.16	
Inactive to Active (<i>n</i>)	341	33	25	53	230
	OR	1.07	1.33	0.94	Ref.
	95% CI	0.83 to 1.38	1.01 to 1.75	0.76 to 1.16	

The Tromsø Study 1974–2016.

Data are adjusted for sex, birth year, smoking and education at T2, and shown as adjusted ORs with 95% CI. $P_{\text{interaction}}$ = interaction effect for the stratified variable and BMI change on physical activity change.

BMI body mass index, CI confidence interval, OR odds ratio, T2 time point 2.

countries, one out of three fail to meet these recommendations [53]. Consequently, the current physical activity levels in the general population is unlikely preventing population weight gain [5].

Our study with a comprehensive analytical approach showed no association between leisure time physical activity change and subsequent BMI change. However, we observed that BMI gains were associated with subsequent lower leisure time physical activity, which is consistent with previous studies [6, 22, 25, 26, 35, 37, 38]. These observations are important, as public health initiatives aimed at weight gain prevention must acknowledge the major societal drivers for obesity in order to be successful [54, 55]. As physical activity has numerous health effects independent of weight change [56], it should not be neglected, but simply acknowledged in its limited potential for weight gain prevention [5]. Although still ineffective [57], well-designed whole system approaches targeting multiple factors associated with population weight gain may be needed to shift the current curve of the obesity epidemic [55, 57, 58].

Strengths and limitations

As BMI has gradually increased over decades [1], the long observation period in this study (~6 years between each examination) allowed us to examine whether physical activity change have affected the gradual long-term BMI gain [5]. Further, our analytical approach allowed us to interpret the direction of the association with more certainty [5]. Furthermore, the merged overall cohort increased our sample size, which allowed us to assess effect modification in the association between physical activity and BMI. Finally, the Tromsø Study cohorts have high attendance of invited participants, which indicate high generalizability to high-income countries' populations [43].

There are also limitations that should be addressed. Self-reported physical activity change was categorized into crude groups; this may have introduced misclassification. Consequently, potential physical activity energy expenditure changes that could influence our results may have been missed. However, self-reported physical activity categorized into crude groups appears appropriate at population

levels [59] and moreover, the SGPALS indicate predictive validity by being associated with multiple health outcomes [45]. Moreover, our sensitivity analysis of six groups physical activity change showed similar results as our main analyses. Further, self-reported physical activity is likely influenced by recall and social desirability bias, which indicate that over-reporting of physical activity levels is inevitable [59]. This is illustrated in our study by low variability in leisure time physical activity change, with most of the included participants (68%) being classified as Persistently Active. These biases are likely to under- or overestimate the effect magnitude between physical activity and health outcomes [5] and might have influenced our results. Future long-term studies using physical activity instruments with higher accuracy (e.g., device measured physical activity) are warranted to further examine whether population levels of physical activity influence weight change. Furthermore, disease onset may drive physical activity and weight change, which thus could be included as a potential confounder in our models. However, it is more likely that disease onset is a *mediator* (i.e. physical activity decline leads to disease, which leads to BMI change) or *ancestor* (i.e., disease onset leads to physical activity decline, which leads to BMI change) in the association between physical activity and BMI. Consequently, as our study's aims were to assess the total effect of physical activity change on BMI change and vice versa, adjusting for disease would not assess the total effect [60]. Finally, our results may be influenced by residual confounding due to unavailable energy intake data.

Conclusion

In this prospective cohort study, there was no association between leisure time physical activity changes and subsequent BMI changes, whereas BMI increase was associated with subsequent consistently low and decreasing physical activity levels. These findings indicate that weight gain may lead to lower leisure time physical activity, while population levels of leisure time physical activity appears insufficient to prevent overweight and obesity.

Data availability

The data that support the findings of this study are available from the Tromsø Study but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. The data are however available from the Tromsø Study upon application to the Data and Publication Committee for the Tromsø Study: troomsous@uit.no.

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Author contributions EHS, BM, UE, LAH designed the study, EHS carried out data analysis, OL and TW provided statistical expertise, all authors interpreted the study results, EHS drafted the manuscript, and all authors contributed with manuscript revisions and approved the final version of the manuscript.

Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

Ethics approval and consent to participate All participants from Tromsø 4–7 provided written informed consent and the present study was approved by the Regional Ethics Committee for Medical Research (ref. 2016/758410).

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Paper V

Sagelv EH, Hopstock LA, Morseth B, Hansen BH, Steene-Johannessen J, Johansson J, Nordström A, Saint-Maurice PF, Løvsletten O, Wilsgaard T, Ekelund U, Tarp J. Device-measured physical activity, sedentary time, and risk of mortality. (*In review*).

1 **Title: Device-measured physical activity, sedentary time, and risk of all-cause mortality**

2 ***Subtitle: A one-step individual participant data meta-analysis of four prospective cohort***

3 ***studies***

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29

30 **ABSTRACT**

31 **Background:** Moderate-and-vigorous physical activity (MVPA) and sedentary time can be
32 combined differently to lower mortality risks, but the exact amounts are unclear. We aimed to
33 examine 1) effect modification of physical activity in the association between sedentary time
34 and mortality and *vice versa*, 2) joint associations of MVPA and sedentary time on mortality
35 risk.

36 **Methods:** One-step individual participant data meta-analysis of four prospective cohort
37 studies (Norway, Sweden, United States, baseline data: 2003-2016, 11 989 participants ≥ 50
38 years, 50.5% women) with accelerometry-measured physical activity and sedentary time.
39 Associations were examined using restricted cubic splines and fractional polynomials in Cox
40 regressions adjusted for sex, education, body mass index, smoking, alcohol, study cohort,
41 cardiovascular disease, cancer, and/or diabetes, accelerometry wear time, and age.

42 **Results:** 6.7% (n=805) died during follow-up (median: 5.2 years, interquartile range: 4.2
43 years). More than 12 daily sedentary hours (reference: 8 hours) were associated with higher
44 mortality risk only among those not meeting the MVPA guideline of 150 minutes per week
45 (HR:1.38,95%CI:1.10-1.74). Higher MVPA levels were associated with lower mortality risk
46 irrespective of sedentary time, *e.g.*, 10 daily minutes of MVPA (reference: 0 minutes) in those
47 accumulating <10.5 (HR:0.85,95%CI:0.74-0.96) and ≥ 10.5 daily sedentary hours
48 (HR:0.65,95%CI:0.53-0.79). Joint associations confirmed that higher MVPA was superior to
49 lower sedentary time in lowering mortality risk, *e.g.*, 10 daily minutes of MVPA were
50 associated with 28-55% lower mortality risk across the sedentary time spectrum (lowest
51 mortality risk, 10 daily sedentary hours: HR:0.45,95%CI:0.31-0.65).

52 **Conclusions:** Sedentary time associates with higher mortality risk only in individuals not
53 meeting the MVPA guideline. Higher MVPA levels associates with lower mortality risk
54 irrespective of sedentary time.

55 **Keywords:** Epidemiology, Public health, individual participant data, device-measured
56 physical activity, accelerometry-measured physical activity, device-measured sedentary time,
57 accelerometry-measured sedentary time, mortality

58

59 **Key messages**

- 60 - The World Health Organization suggest adults with high levels of sedentary time
61 should aim for the upper-limit of the moderate-and-vigorous physical activity
62 (MVPA) guideline of 150-300 minutes per week to reduce the detrimental effects of
63 high levels of sedentary time on health.
- 64 - In this one-step individual participant data meta-analysis of four prospective cohort
65 studies of adults aged 50 years and older, being sedentary for more than 12 hours per
66 day was associated with 38% higher mortality risk but only in individuals not meeting
67 the current lower-limit moderate-and-vigorous physical activity (MVPA) guideline of
68 150 minutes per week.
- 69 - Higher levels of MVPA were associated with lower mortality risk irrespective of
70 sedentary time; *e.g.*, 10 minutes higher MVPA per day was associated with 15% and
71 35% lower mortality risk in those being less and highly sedentary, respectively.
- 72 - Small amounts of MVPA may be an effective strategy to ameliorate mortality risks
73 from high sedentary time.

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79

80 **INTRODUCTION**

81 In western countries, adults spend an average of ~9 to 10 hours per day being sedentary (1-3),
82 mostly during working hours (4-7). As higher sedentary time is associated with higher risk of
83 non-communicable diseases and mortality (8-11), in-depth knowledge of preventive measures
84 is important.

85

86 Previous meta-analyses have shown that moderate-and-vigorous physical activity (MVPA)
87 and sedentary time can be combined differently to lower mortality risks (12-16).

88 Accumulating small amounts of MVPA may attenuate risks associated with high sedentary
89 time, while higher amounts of MVPA (40-60 minutes per day) appear to eliminate risks from
90 sedentary time (12-16). Consequently, the recent updated World Health Organization (WHO)
91 physical activity guidelines recommends individuals who are highly sedentary to engage in
92 300 minutes of more of MVPA (17). Moreover, light physical activity and total volume of
93 physical activity are also associated with lower mortality risk (11, 18). However, it is unclear
94 whether sedentary time modifies the associations between physical activity and mortality.

95

96 One-step individual participant data analyses allow for more standardized and advanced
97 analyses compared with meta-analyses using study-level data(19, 20). This may overcome
98 limitations of arbitrary categorisations from aggregated summary data to assess effect
99 modifications and joint associations between physical activity and sedentary time with
100 mortality risk. For example, in a recent meta-analysis, median MVPA ranged from 23 to 63
101 minutes per day in the most active category of the included cohorts (11). Such large variations
102 between categories may lead to loss of information (21) and challenge translation to absolute
103 physical activity targets for public health and clinical decision-making.

104

105 We pooled individual participant data from four prospective cohorts with device-measured
106 physical activity in a one-step meta-analysis and aimed to examine 1) whether the association
107 between sedentary time and mortality is modified by physical activity and *vice versa* (whether
108 the association between physical activity and mortality is modified by sedentary time), and 2)
109 joint associations of MVPA and sedentary time on mortality risk.

110

111 **METHODS**

112 Four prospective cohorts from Norway, Sweden, and the United States were pooled. Baseline
113 data were collected between 2003 and 2019: Tromsø Study 2015-2016 (22, 23); Healthy
114 Ageing Initiative (HAI) 2012-2019 (24); Norwegian National Physical Activity Survey
115 (NNPAS) 2008-2009 (25); and National Health and Nutrition Examination Survey
116 (NHANES) 2003-2006 (26, 27). Cohort descriptions are summarised in Supplementary File
117 S1. We included individuals aged ≥ 50 years, with ≥ 4 days of 10 hours with valid
118 accelerometry data (28), ≥ 2 years follow-up time, and information on sex, educational level,
119 weight, height, smoking, alcohol intake, and prevalent and/or previous cardiovascular disease
120 (CVD), cancer and/or diabetes. The Meta-analyses of Observational Studies in Epidemiology
121 (29) and individual participant data analysis-checklist (19) are found in Supplementary Tables
122 S1-S2.

123

124 **Patient and public involvement**

125 The Tromsø Study advisory board includes patient and public representatives. Some
126 participants acted as ambassadors in The Tromsø Study and HAI Study when data collection
127 was ongoing and actively contributed to recruitment of participants. There was no public
128 involvement when designing and conducting this study. There were no patient or public
129 involvement in the NNPAS or NHANES.

130

131 **Mortality**

132 Data on mortality was linked with the Norwegian and Swedish cause of death registries, and
133 the United States National Death Index, through 31 December 2020 (Tromsø Study), 31
134 December 2017 (NNPAS), 31 December 2019 (HAI) and 31 December 2015 (NHANES),
135 respectively.

136

137 **Accelerometry-measured physical activity**

138 All cohorts used a version of ActiGraph accelerometers (ActiGraph, Pensacola, Florida,
139 United States) placed at the hip (NHANES: AM-7164; NNPAS: GT1M; HAI: GT3X+;
140 Tromsø Study: wGT3X-BT) (Supplementary File S2). We analyzed accelerometry data using
141 KineSoft version 3.3.80 (Kinesoft, Loughborough, United Kingdom). We removed data
142 between 00:00-06:00 am and, for harmonization purposes, only considered data from the
143 vertical axis. Non-wear time was defined as 60 consecutive minutes of zero counts with
144 allowance for up to 2 minutes of non-zero counts over 100 counts per minute(30).

145

146 Total physical activity was defined as counts per minute divided by wear time(31), and
147 volume of intensity-specific physical activity as follows: Sedentary: <100 counts per minute
148 (32, 33), light physical activity: 100-2019 counts per minute(25), and MVPA: ≥ 2020 counts
149 per minute (30). As wear time differed across cohorts, we standardized all exposure variables
150 to 16 hours wear time per day: *e.g.* (MVPA per day/wear time per day) x 16. We determined
151 adherence to the lower-limit WHO's physical activity guideline(17) as not meeting (inactive)
152 or meeting (active) the guideline (≥ 150 minutes MVPA per week, equivalent to ≥ 22 minutes
153 per day).

154

155 **Covariates**

156 Covariates (sex, age, education (primary, high school, lower university, higher university),
157 body mass index (BMI, <25, 25-29, ≥ 30 kg/m²), smoking (current, previous, never), alcohol
158 intake (units per week), history of CVD, cancer and diabetes) were chosen *a priori* according
159 to previous literature (11, 24, 26, 34-36). History of CVD, cancer and diabetes were self-
160 reported or obtained from registries. Measurements and harmonization of covariates are
161 described in Supplementary File S3-4, and Table S3.

162

163 **Statistical analyses**

164 First, we performed Cox regressions with physical activity and sedentary time modelled using
165 restricted cubic splines and adjustment for sex, education, BMI, smoking, alcohol intake,
166 study cohort, CVD/cancer/diabetes, age (in years) as timescale (37), and additional mutual
167 adjustment of physical activity and sedentary time (11). To avoid influence of extreme values,
168 data outside the 1st and 99th percentile of exposure distributions were replaced with their
169 respective 1st and 99th percentile values. NHANES does not provide information on
170 attendance or death date (only follow-up time to censoring, death or study end), therefore, we
171 set attendance date to 01.01.2004 (wave 2003-2004) and 01.01.2006 (wave 2005-2006), and
172 calculated death date, censoring (emigration) by addition of follow-up time. Participants´
173 study entry was set two years after attendance (left-truncation) and followed to death,
174 censoring (lost-to-follow-up) or study end.

175

176 We thereafter stratified analyses to examine dose-response associations between physical
177 activity and mortality within strata of sedentary time, based on restricted cubic splines, and
178 with sedentary time and mortality within strata of MVPA. As there are no quantitative
179 international guidelines on sedentary time (17), we split sedentary time by full-sample median

180 as “low” (<10.5 hours·day⁻¹) and “high” (≥ 10.5 hours·day⁻¹). Similarly, MVPA was split by
181 the lower-limit WHO-guideline (150 min MVPA·week⁻¹ equivalent to 22 MVPA min·day⁻¹).
182 Knots in cubic splines were placed at the 5th, 50th and 95th percentiles of the analysis-specific
183 distributions (*e.g.*, dose-response association for MVPA and knot placements estimated
184 separately within low and high sedentary time). Changing knot locations or increasing knot
185 numbers did not change the results.

186

187 To keep the continuous data form and to handle the non-linear associations observed in spline
188 models in the joint analyses of MVPA and sedentary time with mortality, we used fractional
189 polynomials to identify the best fit Cox regression model. As light physical activity and
190 sedentary time were highly correlated ($r=-0.96$) and total physical activity includes sedentary
191 time (<100 counts per minute), we did not assess the joint associations of light or total
192 physical activity with sedentary time.

193

194 We applied the following sensitivity analyses: 1) Excluding the first 5 years of follow-up after
195 study attendance to limit reverse causation bias; 2) Median split sedentary time separately by
196 the Norwegian and Swedish (Tromsø, HAI and NNPAS) and United States (NHANES)
197 cohorts to evaluate demographic region differences; 3) Accounting for non-identical output
198 between AM-7164 and GT3X accelerometers by calibrating individual-level summary data in
199 the NHANES (38) (as described in Supplementary Table S9).

200

201 Schoenfeld’s residuals tests confirmed no violated proportional hazards for all covariates (all
202 $p \geq 0.08$), except possibly education in low sedentary participants ($p=0.02$). However, log-log
203 survival plots of education displayed reasonable parallel lines indicating no violated

204 proportional hazards. Statistical analyses were performed using Stata version 17.0 (StataCorp
205 LLC, Texas, United States) with alpha set to 0.05.

206

207 **RESULTS**

208 In total, 805 (6.7%) of the 11 989 participants died during follow-up (median 5.2 years,
209 interquartile range 4.2 years) (Table 1). The NHANES cohort had longest follow-up time and
210 contributed with 65% of total deaths (Supplementary Table S4). The range of physical
211 activity and sedentary time were reasonably similar among cohorts (Supplementary Figure
212 S1-4). Forty-nine percent adhered to the MVPA guideline (Table 1). A flow chart of
213 participant inclusion is found in Supplementary Figure S5.

214

215 Wald tests confirmed departure from linearity in all models (all $p < 0.001$). We observed two-
216 way interactions between all physical activity estimates and sedentary time ($p < 0.001$) but no
217 interactions between physical activity or sedentary time and any covariates (all $p > 0.07$). In
218 analyses stratified by < 10.5 (low) and ≥ 10.5 (high) sedentary hours per day, MVPA was
219 curvilinearly associated with mortality risk with a steeper dose-response curve among
220 participants with high compared with low sedentary time (Figure 1A). For example, compared
221 with 0 minutes per day, 10 minutes of MVPA were associated with 15% (HR:0.85,
222 95%CI:0.74-0.96) and 35% (HR: 0.65, 95%CI:0.53-0.79) lower mortality among those with
223 < 10.5 and ≥ 10.5 sedentary hours per day, respectively.

224

225 Among participants meeting the MVPA guideline, sedentary time was not associated with
226 mortality (12 hours·day⁻¹: HR:1.08, 95%CI:0.66-1.77) compared with 8 hours per day
227 reference (Figure 1B). Among participants not meeting the MVPA guideline, sedentary time
228 was curvilinearly associated with mortality; those who were sedentary more than 12 hours per

229 day had higher mortality risk (12 hours·day⁻¹, HR:1.38, 95%CI:1.10-1.74; 13 hours·day⁻¹, HR:
230 1.98, 95%CI:1.53-2.57) compared with 8 hours per day reference (Figure 1B).

231

232 For joint associations combining MVPA and sedentary time, the best fit fractional polynomial
233 model included log(MVPA), sedentary time raised to power of 3 (sedentary time³),

234 “log(sedentary time)*sedentary time³”, and we included the main effect of these transformed

235 variables along with two way cross products of log(MVPA) with each transformed term of

236 sedentary time. This model was different from a model including linear continuous interaction

237 of “MVPA*sedentary time” with their main effects (likelihood ratio=p<0.001). Joint

238 associations confirmed results from stratified analyses. Higher MVPA was associated with

239 lower mortality risk irrespective of amounts of sedentary time whereas the association

240 between sedentary time and mortality was largely influenced by MVPA levels (Figure 2).

241 Compared with keeping MVPA constant at 0 minutes and 8 hours of daily sedentary time as

242 reference, being sedentary 6 hours per day was associated with 56% higher mortality risk

243 (HR:1.56, 95%CI:1.01-2.39), while more than 8 hours of sedentary time displayed

244 overlapping CIs, even at 13 hours per day (HR:1.35, 95%CI:0.81-2.24) (Figure 2). Ten

245 minutes of MVPA per day were associated with 32% (HR:0.68, 95%CI:0.49-0.95) lower

246 mortality risk at 6 hours, 55% (HR:0.45, 95%CI:0.31-0.65) lower risk at 10 hours, and 28%

247 (HR:0.72, 95%CI:0.65-0.81) lower risk at 13 hours per day of sedentary time (Figure 2).

248

249 Light physical activity was curvilinearly associated with lower mortality risk but only in

250 highly sedentary participants (Figure 3A). Compared with 183 minutes per day as reference,

251 15 more minutes of light physical activity were associated with 11% (HR:0.89, 95%CI:0.85-

252 0.95) lower mortality risk, and maximal risk reduction was observed at 330 minutes per day

253 (HR:0.61, 95%CI:0.43-0.86).

254
255 Finally, total physical activity was inversely and curvilinearly associated with mortality risk in
256 both low and high sedentary participants (Figure 3B). The lowest mortality risk (HR:0.17,
257 95%CI:0.08-32) in those with low sedentary time was observed at 690 counts per minute, and
258 in those with high sedentary time at 450 counts per minute (HR:0.33, 95%CI:0.20-54).

259
260 In analyses with mutual adjustment of physical activity and sedentary time, higher physical
261 activity of all intensities was associated with lower mortality risk (Supplementary Table S5).
262 Higher MVPA was curvilinearly associated with lower mortality risk; for example, mortality
263 risk was 27% lower (HR:0.73, 95%CI:0.65-0.82) at 10 minutes of MVPA per day and 61%
264 lower (HR:0.39, 95%CI:0.30-0.51) at 50 minutes MVPA per day, compared to reference 0
265 minutes per day. There was no association between sedentary time and mortality below 11
266 hours per day. However, we observed a higher risk above >12 sedentary hours per day (12
267 hours·day⁻¹: HR:1.53, 95%CI:1.27-1.84; 13 hours·day⁻¹: HR:2.08, 95%CI:1.65-2.62)
268 (Supplementary Table S5).

269

270 **Sensitivity analyses**

271 When excluding the first five years of follow-up (n=7266, deaths=463), associations between
272 physical activity and mortality were generally attenuated although in the expected direction
273 (Supplementary Table S6). In contrast, the association between sedentary time and mortality
274 was unchanged (Supplementary Figure S6). In analyses split by Norwegian and Swedish
275 (Tromsø, HAI and NNPAS) and United States (NHANES) cohorts, results remained
276 unchanged (Supplementary Table 7-8), except among inactive participants in the Norwegian
277 and Swedish cohorts, where 9-11 hours per day of sedentary time was associated with lower
278 mortality risk but associated with higher risk at 12-13 hours per day (Supplementary Table

279 S7). When calibrating NHANES estimates to newer ActiGraph accelerometers, results were
280 unchanged compared with the main analyses (Supplementary Table S9).

281

282 **DISCUSSION**

283 In this individual-participant data analysis of 11,989 participants from four prospective cohort
284 studies, higher levels of MVPA were associated with lower mortality risk irrespective of
285 amounts of sedentary time. In contrast, higher sedentary time was only associated with
286 mortality risk in participants with low levels of MVPA. MVPA equivalent to the WHO
287 physical activity guideline (17) eliminated the association between sedentary time and
288 mortality. Total physical activity was associated with lower mortality risk both in individuals
289 below and above median sedentary time while light intensity physical activity was only
290 associated with mortality risk in highly sedentary individuals.

291

292 These results suggest that although many adults spend most of the day being sedentary (1-3),
293 performing low amounts of MVPA and even light physical activity may lower their risk of
294 mortality. The recent updated WHO guidelines suggest aiming for the upper-limit of 300
295 minutes per week of MVPA for those who are highly sedentary(17), while this study suggest
296 adhering to the lower limit (>150 min per week) is sufficient to eliminate mortality risks
297 associated with high sedentary time.

298

299 In non-stratified analyses, higher physical activity was associated with lower mortality risk,
300 and higher sedentary time associated with higher mortality risk. This is consistent with
301 previous studies examining associations between device-measured physical activity (11, 24,
302 26, 34-36) and sedentary time (11, 24, 26, 34, 39) with mortality. However, we observed
303 effect modifications by sedentary time, which have been indicated by previous meta-analyses

304 examining joint associations of physical activity and sedentary time with mortality(12-16, 40)
305 but not explicitly tested. Although those with higher sedentary time yielded larger benefits
306 from an equivalent amount of MVPA compared with less sedentary participants in our study,
307 small amounts of MVPA were also associated with lower mortality risk among those with low
308 sedentary time.

309

310 Total physical activity, including both light intensity physical activity and MVPA, was
311 associated with lower mortality risks. The lowest mortality risk appeared to be among those
312 accumulating low sedentary time, however, accumulating large volumes of total physical
313 activity and thus maximise risk reduction is only achievable in combination with low
314 sedentary time. Moreover, we observed no excess risk at higher ends of total physical activity,
315 which is consistent with previous studies using both self-reported(41) and device-
316 measured(11, 36) physical activity.

317

318 In joint analyses of MVPA and sedentary time, higher MVPA was associated with lower
319 mortality risk at any given amount of sedentary time. Interestingly, this association was U-
320 shaped with the lowest mortality risk observed at 10 hours of sedentary time. This is partly
321 inconsistent with our analyses stratified by sedentary time (Figure 1A), suggesting a J-shaped
322 pattern. We speculate this may be explained by a cohort effect, as a U-shaped pattern of lower
323 mortality risk with higher sedentary time was also observed in the analysis restricted to the
324 Norwegian and Swedish cohorts. Both wear time and sedentary time were higher in these
325 cohorts compared with the NHANES. While we excluded all data between 00:00 and 06:00
326 for harmonisation purposes, it is plausible that some sleep may have been misclassified as
327 sedentary time.

328

329 Previous individual participant analyses examining joint associations with device-measured
330 physical activity and sedentary time have reported higher mortality risks with ~10-14 hours of
331 sedentary time per day in combination with low MVPA (~2min) (15, 16). We observed no
332 higher mortality risk with higher sedentary time compared with reference 8 hours among
333 those accumulating low MVPA in our joint analysis. This may be attributed to our one-step
334 individual participant data analysis, which overcome limitations of aggregated study-level
335 data (19, 20) used by others (15, 16). Additionally, this may also be attributed to our
336 participants being mostly older adults and our use of continuous data, the latter which
337 preserves data information and statistical power (21).

338

339 **Limitations**

340 We lacked repeated measures of exposures and covariates during follow-up, which makes our
341 analyses susceptible to changes in physical activity and confounders. A recent study reported
342 lower mortality risk of long-term exposure of physical activity compared with a single
343 baseline measure (42). However, other studies have reported that high baseline physical
344 activity yield similar lower mortality risk as increasing physical activity from low to high
345 levels (43-45). Moreover, a seven-day accelerometry recording appears reasonably stable over
346 time (46, 47).

347

348 Statistical adjustments were limited to covariates that could be harmonized, leaving potential
349 residual confounding from variables such as mobility limitations, diet, and general health
350 status. Putative sources like education, smoking and disease, which are associated with diet
351 quality (48), may to some degree act as proxies for non-included confounding sources.
352 Although our sensitivity analyses excluding the first five years of follow-up suggest robust
353 results, follow-up time was short in some cohorts. This may influence our results as excluding

354 follow-up years is likely insufficient to minimize influence of reverse causation bias,
355 particularly for sedentary time (49). Larger studies of device-measured physical activity with
356 longer follow-up are warranted to validate our findings.

357

358 Further, misclassification of sedentary time with non-wear time and/or light physical activity
359 may have influenced our results, as mentioned above. Furthermore, this study includes mostly
360 older adults, and whether the observed dose-response associations are generalizable to
361 younger adults is unknown. Finally, due to the one-step approach, we were unable to use the
362 sample-weights provided by the NHANES to yield nationally representative estimates (50).
363 However, sample-weighted NHANES analyses were used in sensitivity analysis by the
364 NHANES cohort, and were consistent with our main analyses.

365

366 **CONCLUSION**

367 Higher amounts of physical activity, at any intensity, were associated with lower mortality
368 risk even among those being highly sedentary. Sedentary time was associated with higher
369 mortality risk only in individuals not meeting the MVPA guideline. Efforts to promote
370 physical activity may have substantial health benefits for individuals, and small amounts of
371 MVPA may be an effective strategy to ameliorate mortality risk associated with high
372 sedentary time.

373

374 **Figure legends**

375 **Figure 1.** Cubic spline regressions of hazard ratio (solid line) and 95% confidence intervals
376 (transparent area) with higher (A) MVPA stratified by <10.5 (blue) and ≥ 10.5 (red) hours per
377 day of sedentary time, and (B) sedentary time stratified by meeting (blue) and not meeting
378 (red) the MVPA guideline (<150 min \cdot week $^{-1}$ of MVPA). Knots are placed at the 5th, 50th and

379 95th percentile of the distributions, separately (A) at <10.5 and ≥ 10.5 hours·day⁻¹ of sedentary
380 time and (B) at meeting and not meeting the MVPA guideline. Reference of both strata are set
381 to (A) 0 minutes per day and (B) 8 hours per day. Data are adjusted for sex, education, BMI,
382 smoking, alcohol intake, study cohort, history of CVD, cancer and/or diabetes, age (in years)
383 as timescale, and accelerometry wear time.

384

385 **Figure 2.** Combined associations modelled as fractional polynomials of sedentary time and
386 MVPA on risk of mortality. Hazard ratios are based on a reference of 8 hours per day of
387 sedentary time and 0 minutes per day of MVPA. A) Arbitrary shown hazard ratios (solid line)
388 and 95% confidence intervals (transparent area), red line=6 hours of sedentary time, black
389 line=8 hours of sedentary time, green line=10 hours of sedentary time, yellow line=12 hours
390 of sedentary time. B) Arbitrary shown hazard ratios (point estimate) with 95% confidence
391 intervals (parentheses), bold numbers indicate significant association, $p < 0.05$. Data are
392 adjusted for sex, education, BMI, smoking, alcohol intake, study cohort, history of CVD,
393 cancer and/or diabetes, age (in years) as timescale, and accelerometry wear time.
394 MVPA=moderate-and-vigorous physical activity. HR=hazard ratio, CI=95% confidence
395 interval. N/A=not applicable due to unobserved data.

396

397 **Figure 3.** Cubic spline regressions of hazard ratio (solid line) and 95% confidence intervals
398 (transparent area) with higher (A) light physical activity and (B) total physical activity,
399 stratified by sedentary time (<10.5 hours·day⁻¹ (blue) and ≥ 10.5 hours·day⁻¹ (red)). Knots are
400 placed at the 5th, 50th and 95th percentile of the distributions. References are strata-specific
401 10th percentile: (A) low sedentary: 300 minutes per day, high sedentary: 183 minutes per day;
402 (B) low sedentary: 231 counts per minute per day, high sedentary: 115 counts per minute per

403 day. Data are adjusted for sex, education, BMI, smoking, alcohol intake, study cohort, history
404 of CVD, cancer and/or diabetes, age (in years) as timescale, and accelerometry wear time.

405

406 **DECLERATIONS**

407 **Disclaimer**

408 The National Center for Health Statistics was not involved in analyzing, interpreting, nor
409 necessarily endorses any of the conclusions of the present study. The content is solely the
410 responsibility of the authors.

411

412 **Ethics approval**

413 All cohort studies were conducted according to the Declaration of Helsinki for Medical
414 Research and all participants in all studies provided written informed consent. The Regional
415 Ethics Committee for Medical and Health Research (REK) North approved the present study
416 (reference 2016/1792), and the Tromsø Study (reference 2014/940). The Regional Ethical
417 Review Board in Umeå, Sweden, approved the HAI study (reference 07-031M). The REK
418 region South-East B approved the NNPAS study (reference S-08046b). The National Centre
419 for Health Statistics Research Ethics Review Board approved the NHANES by (available at:
420 <https://www.cdc.gov/nchs/nhanes/irba98.htm>).

421

422 **Author contributions**

423 EHS, BM, UE and LAH designed the study. LAH, BM, JJ, AN, JSJ, BHH, and SAA
424 contributed to acquisition and processing of raw data. EHS act as guarantor for the study.
425 EHS processed the Tromsø Study and HAI accelerometry data, BHH processed the NNPAS
426 accelerometry data, and JT processed the NHANES accelerometry data. EHS merged and
427 harmonized data. EHS and TW performed statistical analyses. TW, OL, and JT provided

428 statistical expertise. EHS wrote the initial draft of the manuscript. All authors critically
429 reviewed the study's results, contributed to revisions and approved the final version of the
430 manuscript.

431

432 **Data availability**

433 Tromsø Study, HAI and NNPAS: The data underlying this article were provided by third
434 parties (described below) under license. Data can be shared on request to the third parties.

435 NHANES data are available online at: <https://wwwn.cdc.gov/nchs/nhanes/>.

436 *Access to data:*

437 Tromsø Study upon application to the Data and Publication Committee for the Tromsø Study:

438 <https://uit.no/research/tromsostudy>.

439 HAI upon request to principal investigator Professor Anna Nordström, mail:

440 anna.h.nordstrom@umu.se.

441 NNPAS upon request to principal investigator Professor Sigmund Alfred Anderssen, mail:

442 sigmundaa@nih.no.

443

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456

457 **Supplementary data**

458 Supplementary data are available at IJE online.

459

460 **Conflict of interest**

461 None declared.

462

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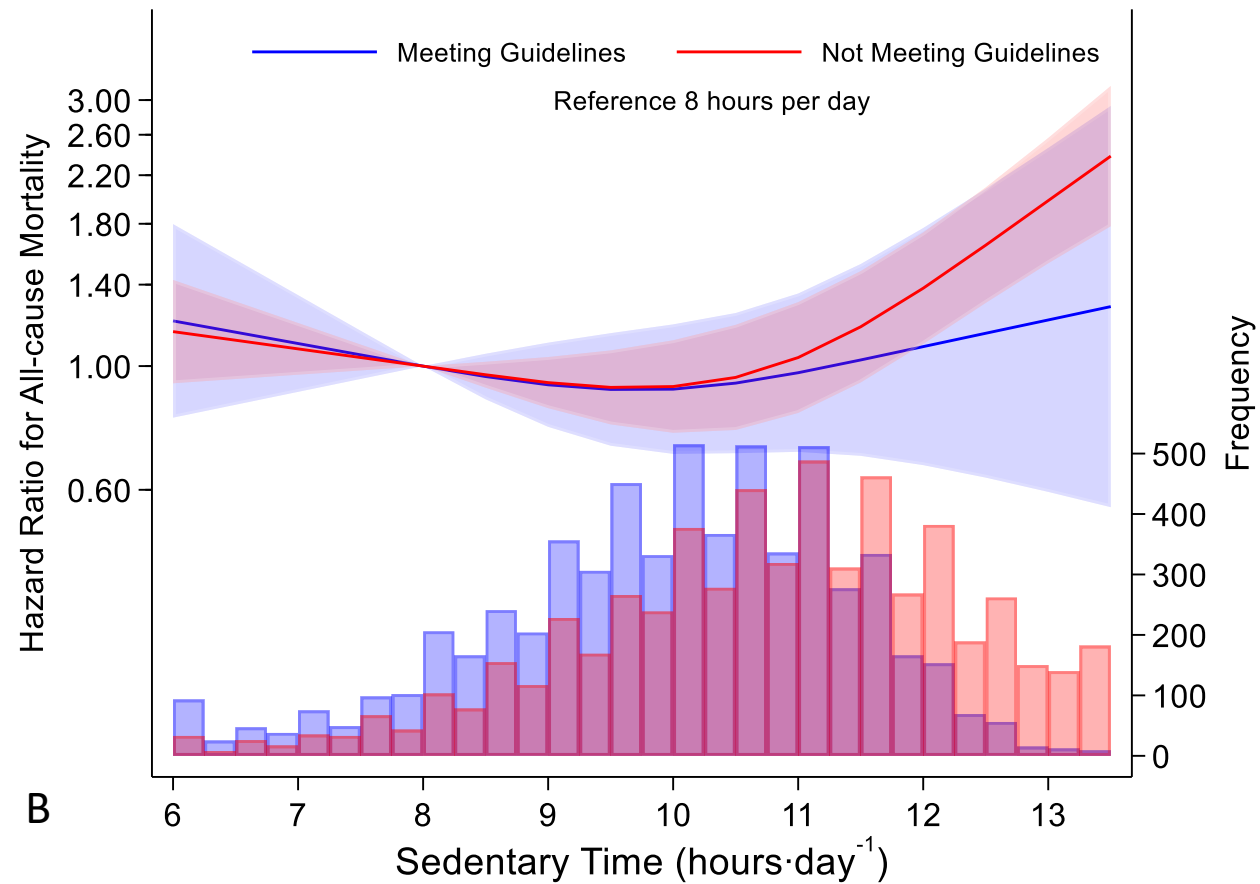
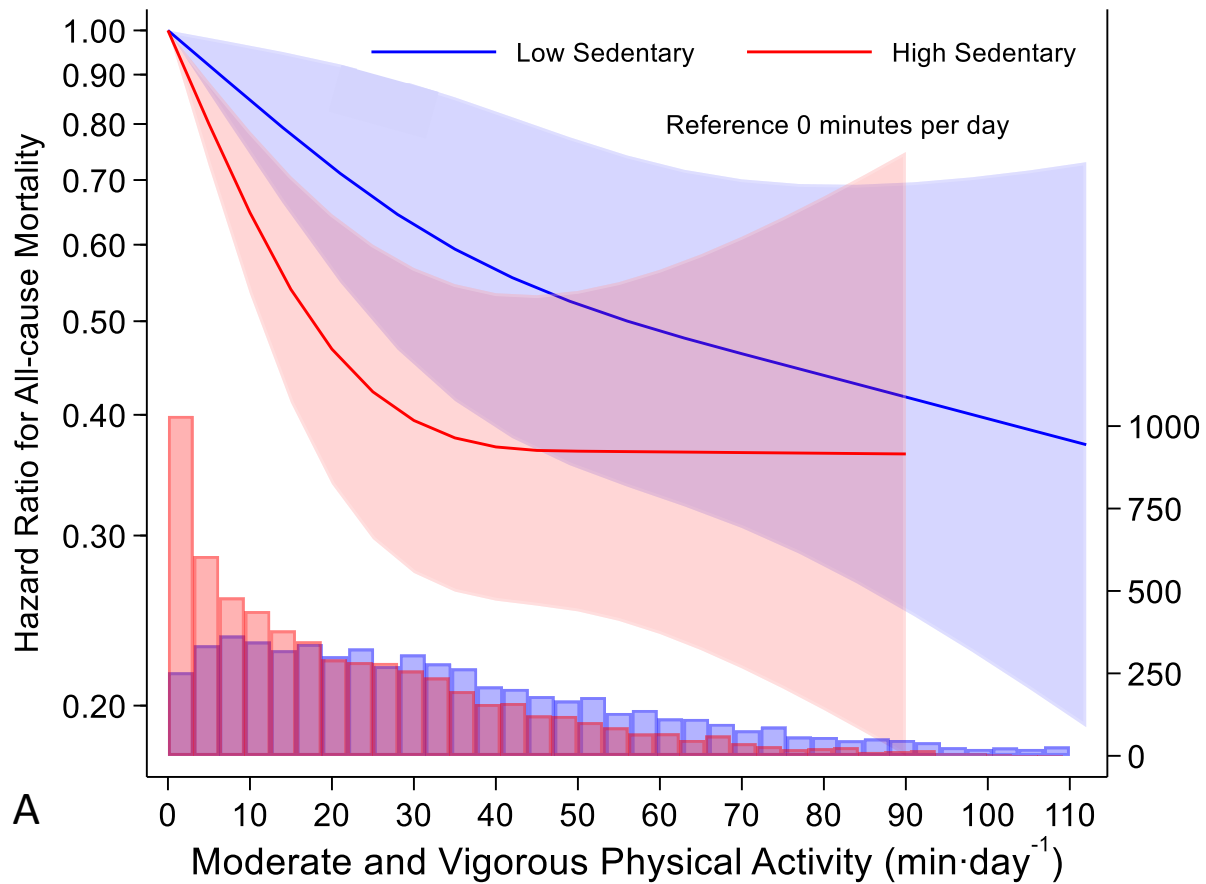
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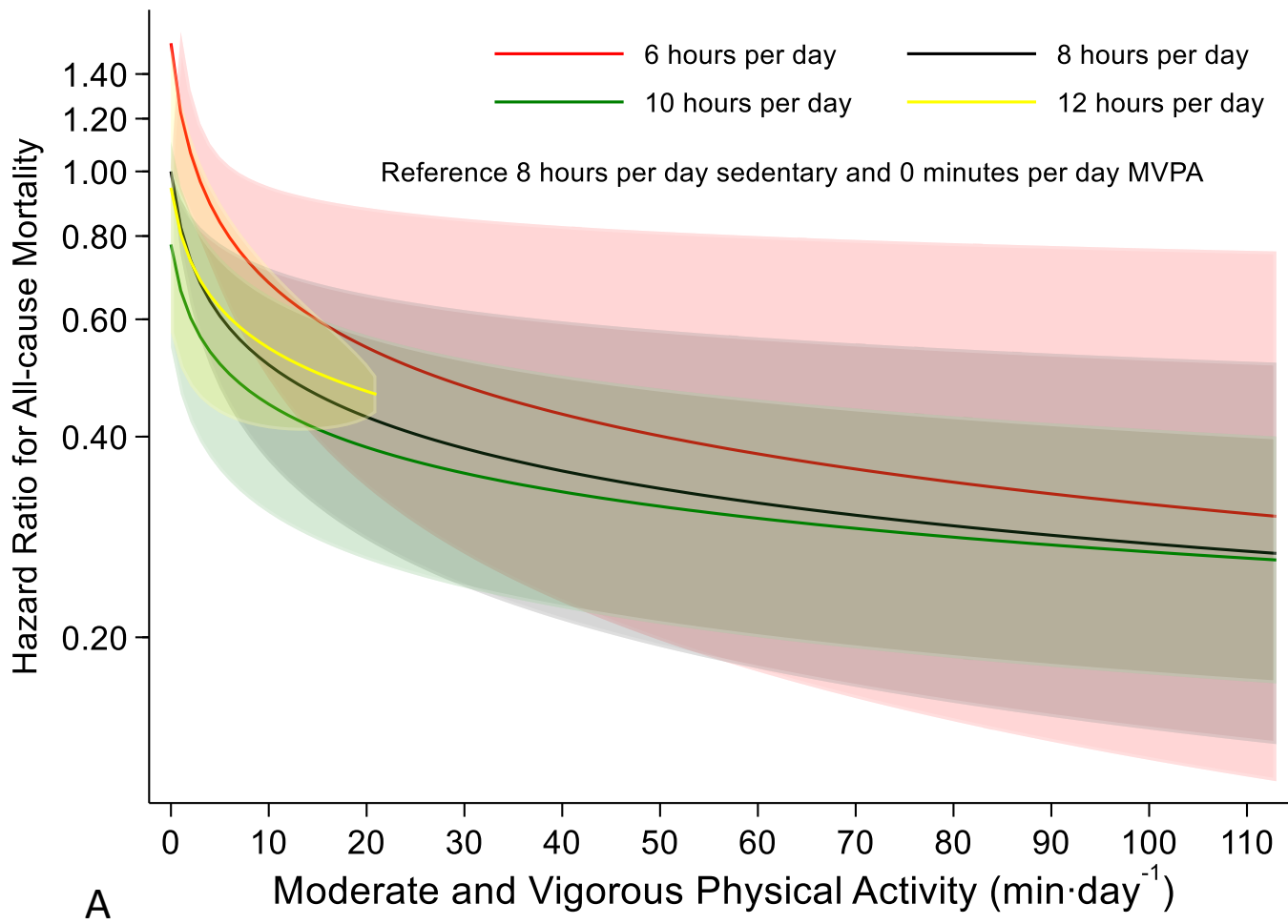
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- 612

Table 1. Descriptive characteristics of the participants.

	All	Sedentary Time	
		<10.5 hours·day ⁻¹	≥10.5 hours·day ⁻¹
Total (N)	11 989	5943	6042
Dead, n (%)	805 (6.7)	357 (6.0)	448 (7.4)
Follow-up time (years)			
Median (25-75th percentile)	5.24 (4.66-8.85)	5.53 (4.70-9.25)	5.10 (4.64-5.94)
Min-max	2.02-13.08	2.02-13.08	2.03-13.08
Sex			
Women, n (%)	6057 (50.5)	3187 (53.6)	2870 (47.5)
Men, n (%)	5932 (49.5)	2756 (46.4)	3176 (52.5)
Age (mean ± SD)	66.7 ± 7.6	65.5 ± 7.6	67.9 ± 7.4
50-59 years, n (%)	2595 (21.6)	1571 (26.4)	1024 (16.9)
60-69 years, n (%)	3363 (28.1)	1691 (28.5)	1672 (27.7)
70-79 years, n (%)	5607 (46.8)	2551 (42.9)	3056 (50.6)
≥80 years, n (%)	424 (3.5)	130 (2.2)	294 (4.9)
Birth year			
<1940, n (%)	1925 (16.1)	881 (14.8)	1044 (17.3)
1940-49, n (%)	6591 (55.0)	3232 (54.4)	3359 (55.6)
≥1950, n (%)	3473 (28.9)	1830 (30.8)	1643 (27.2)
BMI (mean ± SD)	27.0 ± 4.5	26.6 ± 4.4	27.4 ± 4.7
<25 kg/m ² , n (%)	4203 (35.1)	2254 (37.9)	1949 (32.2)
25-29 kg/m ² , n (%)	5218 (43.5)	2600 (43.8)	2618 (43.3)
≥30 kg/m ² , n (%)	2568 (21.4)	1089 (18.3)	1479 (24.5)
Smoking			
Current smoker, n (%)	1434 (11.9)	696 (11.7)	738 (12.2)
Previous smoker, n (%)	5584 (46.6)	2646 (44.5)	2938 (48.6)
Never smoker, n (%)	4971 (41.5)	2601 (43.8)	2370 (39.2)
Education			
Primary school, n (%)	3035 (25.3)	1506 (25.3)	1529 (25.3)
High School, n (%)	3883 (32.4)	1941 (32.7)	1942 (32.1)
University some, n (%)	2722 (22.7)	1443 (24.3)	1279 (21.2)
University long, n (%)	2349 (19.6)	1053 (17.7)	1296 (21.4)
Alcohol intake (mean ± SD)	2.3 ± 3.2	2.1 ± 3.0	2.6 ± 3.4
Never, n (%)	1720 (14.3)	913 (15.4)	807 (13.4)
<1.99 units·week ⁻¹ , n (%)	5921 (49.4)	3044 (51.2)	2877 (47.6)
≥2 units·week ⁻¹ , n (%)	4348 (36.3)	1986 (33.4)	2362 (39.0)
Disease, n (%)	6179 (51.5)	2757 (46.7)	3442 (57.1)
CVD, n (%)	1858 (15.5)	710 (12.0)	1148 (19.0)
Cancer, n (%)	1982 (16.5)	912 (15.4)	1070 (17.7)
Diabetes, n (%)	1032 (8.6)	417 (7.0)	615 (10.2)
Hypertension, n (%)	3722 (31.1)	1633 (27.7)	2089 (34.9)
Physical activity			
Meeting the MVPA guideline, n (%)			
<150 min·week ⁻¹	6162 (51.4)	2444 (41.1)	3718 (54.7)
≥150 min·week ⁻¹	5827 (48.6)	3499 (58.9)	2328 (38.5)
Wear time (hours·days ⁻¹) ^a			
Mean ± SD	14.90 ± 1.60	14.88 ± 1.58	14.92 ± 1.63
Total physical activity (counts·min ⁻¹)			
Mean ± SD	300.6 ± 140.4	377.5 ± 131.7	224.8 ± 102.4
Sedentary Time (hours·day ⁻¹)			
Mean ± SD	10.35 ± 1.50	9.15 ± 1.04	11.53 ± 0.76
Light Physical Activity (min·day ⁻¹)			
Mean ± SD	306.9 ± 84.4	371.1 ± 65.4	243.7 ± 43.5
MVPA (min·day ⁻¹)			
Mean ± SD	28.7 ± 24.7	35.2 ± 26.6	22.2 ± 20.8

Data are shown as mean ± SD, or as frequency (percentage). ^awear time is displayed prior to standardizing the physical activity and sedentary time estimates to 16 hours·day⁻¹. CVD=cardiovascular disease, MVPA=moderate and vigorous physical activity, BMI=body mass index, SD=standard deviation.





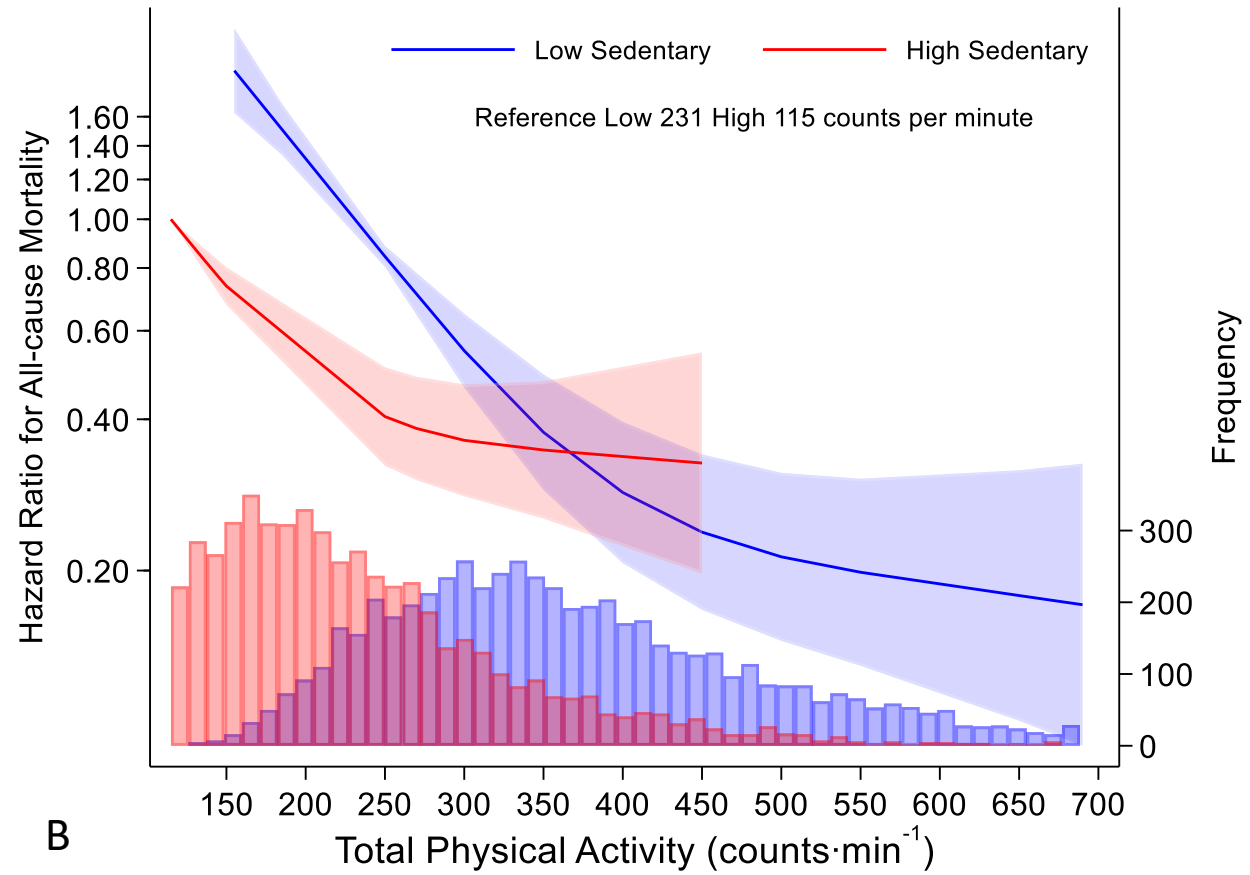
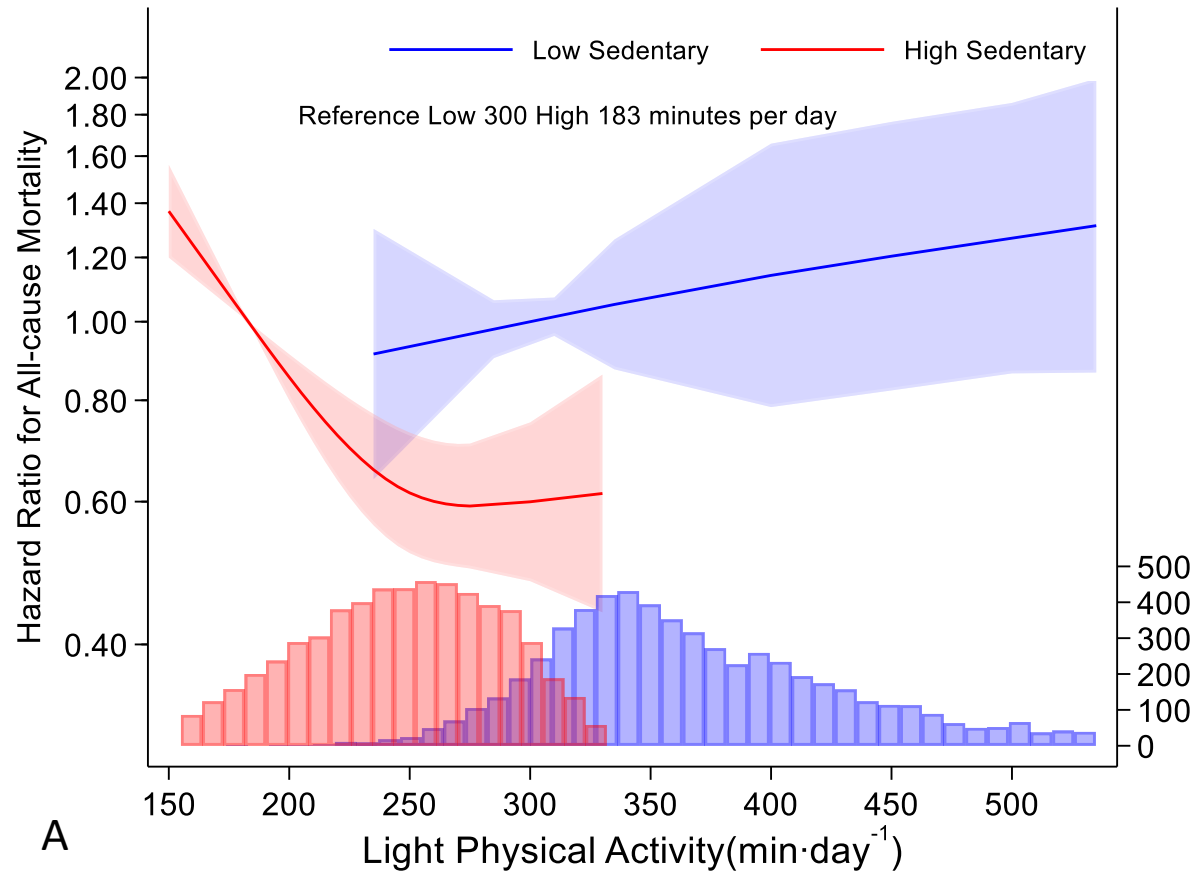
B

HR (95%CI)

Sedentary Time ($\text{hours}\cdot\text{day}^{-1}$)

	6	7	8	9	10	11	12	13
0	1.56	1.24		0.85	0.78	0.80	0.95	1.35
10	(1.01-2.39)	(1.00-1.53)	Ref.	(0.70-1.03)	(0.55-1.11)	(0.50-1.26)	(0.57-1.56)	(0.81-2.24)
20	0.68	0.59	0.51	0.47	0.45	0.47	0.54	0.72
30	(0.49-0.95)	(0.43-0.81)	(0.37-0.72)	(0.32-0.67)	(0.31-0.65)	(0.33-0.67)	(0.41-0.72)	(0.65-0.81)
40	0.55	0.48	0.43	0.40	0.39	0.40	0.47	
50	(0.34-0.88)	(0.31-0.75)	(0.28-0.65)	(0.26-0.60)	(0.26-0.57)	(0.30-0.55)	(0.43-0.52)	N/A
60	0.48	0.42	0.38	0.36	0.35	0.37		
70	(0.27-0.85)	(0.25-0.71)	(0.24-0.62)	(0.23-0.56)	(0.24-0.52)	(0.28-0.49)	N/A	N/A
80	0.43	0.39	0.36	0.34	0.33	0.35		
90	(0.23-0.83)	(0.22-0.69)	(0.21-0.60)	(0.21-0.54)	(0.22-0.49)	(0.27-0.45)	N/A	N/A
100	0.40	0.36	0.33	0.32	0.31	0.33		
110	(0.20-0.81)	(0.20-0.67)	(0.19-0.58)	(0.19-0.52)	(0.21-0.47)	(0.27-0.42)	N/A	N/A
120	0.38	0.34	0.32	0.30	0.30	0.32		
130	(0.18-0.80)	(0.18-0.65)	(0.18-0.56)	(0.18-0.50)	(0.20-0.46)	(0.26-0.39)	N/A	N/A
140	0.36	0.33	0.31	0.29	0.29	0.31		
150	(0.16-0.79)	(0.17-0.65)	(0.17-0.55)	(0.17-0.49)	(0.19-0.44)	(0.26-0.37)	N/A	N/A
160	0.34	0.31	0.29	0.28	0.28	0.30		
170	(0.15-0.78)	(0.16-0.64)	(0.16-0.54)	(0.17-0.48)	(0.19-0.43)	(0.26-0.35)	N/A	N/A
180	0.33	0.30	0.29	0.27	0.28	0.29		
190	(0.14-0.77)	(0.15-0.63)	(0.15-0.53)	(0.16-0.47)	(0.19-0.42)	(0.26-0.33)	N/A	N/A
200	0.32	0.29	0.28	0.27	0.27	0.29		
210	(0.13-0.77)	(0.14-0.62)	(0.15-0.53)	(0.15-0.46)	(0.18-0.41)	(0.26-0.32)	N/A	N/A
220	0.31	0.29	0.27	0.26	0.26	0.28		
230	(0.12-0.76)	(0.13-0.62)	(0.14-0.52)	(0.15-0.45)	(0.17-0.40)	(0.26-0.30)	N/A	N/A

Moderate and Vigorous Physical Activity ($\text{min}\cdot\text{day}^{-1}$)



Supplementary materials

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Supplementary Files

Supplementary File S1. Descriptions of the study cohorts

The Tromsø Study 2015-16

The Tromsø Study is an ongoing population-based cohort study in Tromsø Municipality in Northern Norway. It includes seven surveys (1974, 1979-80, 1986-87, 1994-95, 2001, 2007-08, 2015-16), of which the seventh survey in 2015-16 included accelerometry measurements of 6778 participants in a sub-sample of the 21083 (participation 65%) attending participants. The ActiGraph wGT3X-BT (ActiGraph, LLC, Pensacola, United States) accelerometer was handed out at attendance and used on the right hip for eight consecutive days and mailed back in a pre-paid envelope, and the age-span of participants was 40-84 years (2). The Tromsø Study was approved by the Regional Ethics Committee for Medical and Health Research (reference 2014/940). The Tromsø Study data was linked to the Norwegian Cause of Death Registry through 2020, which is consistently found to provide 100% completeness of registered deaths compared with global vital statistics (3-5). In total, 4836 participants had valid accelerometry data and information on all covariates (alcohol, body mass index, cohort, smoking, education, sex, prevalent cardiovascular disease (myocardial infarction, stroke, angina pectoris, atrial fibrillation), prevalent and previous cancer, prevalent and previous diabetes) in addition to ≥ 2 years follow-up time.

Healthy Ageing Initiative (HAI) 2012-2019

The HAI study is an ongoing population-based cohort study in Umeå, Sweden. It invites all adults aged >70 years every year from inception in 2012. The primary aim is to identify risk factors for cardiovascular disease, falls and fractures. Participation is 70%. The ActiGraph GT3X+ (ActiGraph, LLC, Pensacola, United States) accelerometer was handed out in the clinic and used on the right hip and worn for seven consecutive days (6, 7). The HAI study was approved by the Regional Ethical Review Board in Umeå, Sweden (reference number: 07-031M). We extracted data from inception in 2012 through 2019, which was linked to the Swedish Cause of Death Registry (8) through 2019, which is consistently proved to provide 100% completeness of registered deaths compared with global vital statistics (3-5). In total, 4312 participants had valid accelerometry data and information on all covariates (alcohol, body mass index, cohort, smoking, education, sex, prevalent cardiovascular disease (myocardial infarction, stroke), prevalent and previous cancer, prevalent and previous diabetes) in addition to ≥ 2 years follow-up time.

The Norwegian National Physical Activity Survey (NNPAS) 2008-09

The NNPAS is an ongoing national representative cohort study aimed at monitoring physical activity levels of Norwegians with 2 completed (2008-09 and 2014-15) and one ongoing data collection (2021-22). We extracted data from the first wave conducted in 2008-09 (9). Of the 11248 invited participants, 3485 (34%) accepted the invitation. The ActiGraph GT1M (ActiGraph, LLC, Pensacola, FL) accelerometer was used on the right hip, and were sent by mail to participants with order to wear it for worn for seven consecutive days. The age-span of the participants was 20-85 years (9). The REK region South-East B approved the study (Reference number: S-08046b). Data on mortality was linked with the Norwegian Cause of Death Registry through 2017. In total, 1465 participants had valid accelerometry data and information on all covariates (alcohol, body mass index, cohort,

smoking, education, sex, prevalent and previous cardiovascular disease (myocardial infarction, stroke, angina pectoris), prevalent and previous cancer, prevalent and previous diabetes) in addition to ≥ 2 years follow-up time.

The National Health and Nutrition Examination Survey (NHANES) 2003-06

The NHANES is an ongoing national representative survey in the United States with 19 complete surveys since inception in 1959-62. We downloaded data from the 2003-04 and 2005-06 survey (available at <https://wwwn.cdc.gov/nchs/nhanes/>), as they used the ActiGraph 7164 (ActiGraph, LLC, Pensacola, FL) accelerometer on the right hip and worn for seven consecutive days. The NHANES is approved by the National Centre for Health Statistics Research Ethics Review Board. Mortality was linked with the United States National Death Index through 2015 (10), which is previously found to provide 100% completeness of deaths compared with global vital statistics (3). Of the 5147 who wore an accelerometer, 2221 (43%) participants provided valid accelerometry data and information on all confounders (alcohol, body mass index, cohort, smoking, education, sex, prevalent cardiovascular disease (myocardial infarction, stroke, angina pectoris), prevalent and previous cancer, prevalent and previous diabetes) in addition to ≥ 2 years follow-up time.

Supplementary File S2. Harmonization of the exposure

Participants from all studies used ActiGraph accelerometers (ActiGraph, LLC, Pensacola, FL United States) on their hip, but used different generations of the device; AM-7164 (NHANES), GT1M (NNPAS), GT3X+ (HAI), wGT3X-BT (Tromsø Study). As the AM-7164 and GT1M records per 60-seconds epochs (acceleration counts, proprietary) from the vertical axis, we reduced raw vertical acceleration units (gravitational force) from the GT3X+ (HAI, sampled at 30 Hz) and wGT3X-BT (Tromsø Study, sampled at 100 Hz) to 60 second epochs using the ActiLife Software (ActiGraph, LLC, Pensacola, FL United States). The HAI, NNPAS and NHANES used a seven-day wear protocol and participants were instructed to wear the device while being awake and remove it for sleeping and water activities (6, 7, 9, 11-13), while the Tromsø Study used a 24-hour wear protocol (also while sleeping but not water activities) (2). Therefore, all accelerometer data between 0 and 6am from all study cohorts were removed from further analyses, as also previously applied in the NNPAS sample (9). The data were further analyzed using the KineSoft software (KineSoft version 3.3.80, Loughborough, United Kingdom). Non-wear time was defined as 60 consecutive minutes of zero acceleration with 2 min spike-allowance (14). Wear time was defined as 4 days of at least 10 hours (15).

Supplementary File S3. Harmonization of covariates

Body weight and height were measured in at study visit in the Tromsø Study, HAI and NHANES, while this was self-reported in the NNPAS. BMI was calculated as kg/m^2 and classified as normal weight ($< 25 \text{ kg/m}^2$), overweight ($25\text{-}29 \text{ kg/m}^2$) and obese ($\geq 30 \text{ kg/m}^2$). Smoking, alcohol, education, and disease were retrieved from questionnaires, except for education in the HAI study, which was retrieved from Statistics Sweden (6). Smoking was grouped as current, previous, and never smoker. Similar questions on alcohol intake were used in all cohorts but the Tromsø Study, HAI and NNPAS had similar categorical answer alternatives, while the NHANES reported their alcohol intake by number of days over a year. To harmonize alcohol intake, we calculated units of alcohol per week for all cohorts by multiplying frequency with usual number of drinks (Supplementary Table S3). Education in The Tromsø Study and NNPAS was grouped as primary school (≤ 10 years school), high

school (11-13 years school), university <4 years and university \geq 4 years, while education in the HAI was grouped as primary school, high school, and university <3 years and \geq 3 years, and NHANES data were grouped as primary school, high school, and university (any year). To harmonize education, we grouped education as primary school, high school, university short (Tromsø and NNPAS: <4 years, HAI: <3 years, NHANES: university any degree), and university long (Tromsø and NNPAS: \geq 4 years, HAI: \geq 3 year, NHANES: N/A).

Supplementary File S4. Disease information

Information on diseases were retrieved from questionnaires in the Tromsø Study, NNPAS and NHANES with participants answering the following question, “*Have your doctor ever told you had X (disease)*” (NNPAS, NHANES and HAI) and “*Do you have or have you had X (cancer, diabetes)*” and “*Have you had X (cardiovascular diseases)*” in The Tromsø Study, which was dichotomized as yes/no. In the HAI data, we combined Swedish national registry data of myocardial infarction, stroke and cancer with self-reported disease as self-reported disease appeared to be underreported. Diseases was dichotomized as yes (1) and no (0).

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Supplementary Tables

Supplementary Table S1. MOOSE Checklist for Meta-analyses of Observational Studies.*

Item No	Recommendation	Reported on Page No
Reporting of background should include		
1	Problem definition	5
2	Hypothesis statement	6
3	Description of study outcome(s)	6
4	Type of exposure or intervention used	7
5	Type of study designs used	6
6	Study population	6, 9-10, Table 1, Suppl Table S4
Reporting of search strategy should include		
7	Qualifications of searchers (eg, librarians and investigators)	N/A
8	Search strategy, including time period included in the synthesis and key words	N/A
9	Effort to include all available studies, including contact with authors	N/A
10	Databases and registries searched	N/A
11	Search software used, name and version, including special features used (eg, explosion)	N/A
12	Use of hand searching (eg, reference lists of obtained articles)	N/A
13	List of citations located and those excluded, including justification	N/A
14	Method of addressing articles published in languages other than English	N/A
15	Method of handling abstracts and unpublished studies	N/A
16	Description of any contact with authors	N/A
Reporting of methods should include		
17	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	9-10, Table 1, Suppl Table S4
18	Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	6-8
19	Documentation of how data were classified and coded (eg, multiple raters, blinding and interrater reliability)	6-9, Suppl table 3, Suppl file 3-4
20	Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	N/A
21	Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	N/A
22	Assessment of heterogeneity	Suppl Table S4, S6-9, Suppl Figure 1-4
23	Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	8-9
24	Provision of appropriate tables and graphics	Table 1, Figure 1-3
Reporting of results should include		
25	Graphic summarizing individual study estimates and overall estimate	Figure 1-3, Suppl table S6-9

26	Table giving descriptive information for each study included	Suppl table S4
27	Results of sensitivity testing (eg, subgroup analysis)	12, Suppl table S6-9,
28	Indication of statistical uncertainty of findings	95%CIs

Reporting of discussion should include		
29	Quantitative assessment of bias (eg, publication bias)	12, Suppl Table S6, S9
30	Justification for exclusion (eg, exclusion of non-English language citations)	8-9
31	Assessment of quality of included studies	N/A
Reporting of conclusions should include		
32	Consideration of alternative explanations for observed results	12-16
33	Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	12-16
34	Guidelines for future research	15-16
35	Disclosure of funding source	19

*From: Stroup DF, Berlin JA, Morton SC, et al, for the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) Group. Meta-analysis of Observational Studies in Epidemiology. A Proposal for Reporting. *JAMA*. 2000;283(15):2008-2012. doi: 10.1001/jama.283.15.2008. N/A=not applicable

Supplementary Table S2. Suggested information to report for individual participant data analysis.*

Supplement to MOOSE*	Page number or method
Whether there was a protocol for the individual participant data project, and where it can be found	The corresponding author's PhD proposal. Are made available upon reasonable request
Whether ethics approval was necessary and (if appropriate) granted	Yes. See "Ethics approval", page 18.
Why the individual participant data approach was initiated	Page 5.
The process used to identify relevant studies for the meta-analysis	Not applicable.
How authors of relevant studies were approached for individual participant data	Through mail and personal communication
How many authors (or collaborating groups) were approached for individual participant data, and the proportion that provided such data	3, 100%. Page 6.
The number of authors who did not provide individual participant data, the reasons why, and the number of patients (and events) in the respective study	Not applicable.
Whether those authors who provided individual participant data gave all their data or only a proportion; if the latter, then describe what information was omitted and why	All available data relevant as exposure, outcome and covariates were provided. Non-relevant data were excluded.
Whether there were any qualitative or quantitative differences between those studies providing individual participant data and those studies not providing individual participant data (if appropriate)	Not applicable.
The number of patients within each of the original studies and, if appropriate, the number of events	See Supplementary table S4.
Details of any missing individual level data within the available individual participant data for each study, and how this was handled within the meta-analyses performed	Supplementary figure S5 for flow-chart.
Details and reasons for including (or excluding) patients who were originally excluded (or included) by the source study investigators	Not applicable.
Whether a one step or a two step individual participant data meta-analysis was performed, and the statistical details thereof, including how clustering of patients within studies was accounted for	One-step approach, see page 5-6.
How many patients from each study were used in each meta-analysis performed	Supplementary figure S5.
Whether the assumptions of the statistical models were validated (for example, proportional hazards) within each study	See page 8-9.
Whether the individual participant data results for each study were comparable with the published results, and, if not, why not (for example, individual participant data contained updated or modified information)	See page 12, and Supplementary table S7-8.
How individual participant data and non-individual participant data studies were analysed together (if appropriate).	Page 7-9. Suppl file 2-3

The robustness of the meta-analysis results following the inclusion or exclusion of nonindividual participant data studies (if appropriate)	Not applicable.
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*Supplementary information as suggested by Riley RD, Lambert PC, Abo-Zaid G. Meta-analysis of individual participant data: rationale, conduct, and reporting. *BMJ*. 2010;340:c221.

Supplementary Table S3. Alcohol questionnaire in the cohorts and the processing of the data

<i>Answer alternatives</i>	Tromsø, HAI and NNPAS		NHANES	
	<i>Question</i>		<i>Question</i>	
	<i>How often do you usually drink alcohol? (times per week)</i>	<i>How many units of alcohol do you usually drink? (usual drinks per time)</i>	<i>In the past 12 months, how often did drink any type of alcoholic beverage? Reported in days 0-365 (times per week)</i>	<i>In the past 12 months, on those days that you drank alcoholic beverages, on the average, how many drinks did you have? Reported in units, 1-50 (usual drinks per time)</i>
1	Never (0)	1-2 (1.5)	0 =never (0)	1-2 (1.5)
2	Monthly or less frequently (0.25)	3-4 (3.5)	1-12 days =Monthly or less frequently (0.25)	3-4 (3.5)
3	2-4 times a month (0.75)	5-6 (5.5)	13-48 days =2-4 times a month (0.75)	5-6 (5.5)
4	2-3 times a week (2.5)	7-9 (8)	49-156=2-3 times a week (2.5)	7-9 (8)
5	4 or more times a week (4)	10 or more (10)	157 to highest=4 or more times a week (4)	>10 (10)
	Units per week =	Times per week x usual drinks per time	Times per week x usual drinks per time	

Tromsø=The Tromsø Study, HAI=Healthy Ageing Initiative, NNPAS=National Norwegian Physical Activity Survey, NHANES=National Health and Nutrition Examination Survey.

Supplementary Table S4. Descriptive characteristics by cohort

	Tromsø	HAI	NNPAS	NHANES
Total (N)	4836	3467	1465	2221
Dead (n (%))	94 (1.9)	91 (2.6)	100 (6.8)	520 (23.4)
Follow up time (years)				
Median (25-75th percentile)	5.03 (4.72-5.27)	4.40 (3.20-5.71)	9.05 (8.88-9.18)	10.58 (9.50-11.67)
Min-max	2.05-5.70	2.02-7.58	2.41-9.63	2.08-13.08
Sex (n (%))				
Women	2552 (52.8)	1748 (50.4)	738 (50.4)	1019 (45.9)
Men	2284 (47.2)	1719 (49.6)	727 (49.6)	1202 (54.1)
Age (mean ± SD)	65.9 ± 7.6	70.4 ± 0.2	61.9 ± 8.5	65.7 ± 9.7
50-59 years (n (%))	1185 (24.5)	N/A	715 (48.8)	695 (31.3)
60-69 years (n (%))	2130 (44.0)	N/A	470 (32.1)	763 (34.4)
70-79 years (n (%))	1370 (28.3)	3467 (100)	239 (16.3)	531 (23.9)
≥80 years (n (%))	151 (3.1)	N/A	41 (2.8)	232 (10.4)
Birth year (n (%))				
<1940	528 (10.9)	N/A	301 (20.5)	1096 (49.3)
1940-1949	1862 (38.5)	3467 (100)	543 (37.1)	719 (32.4)
≥1950	2446 (50.6)	N/A	621 (42.4)	406 (18.3)
BMI (mean ± SD)	27.2 ± 4.3	26.5 ± 4.2	25.6 ± 3.7	28.5 ± 5.6
<25 kg/m ² (n (%))	1529 (31.6)	1357 (39.1)	700 (47.8)	617 (27.8)
25-29 kg/m ² (n (%))	2234 (46.2)	1500 (43.3)	597 (40.7)	887 (39.9)
≥30 kg/m ² (n (%))	1073 (22.2)	610 (17.6)	168 (11.5)	717 (32.3)
Smoking (n (%))				
Current smoker	561 (11.6)	243 (7.0)	242 (16.5)	388 (17.5)
Previous smoker	2448 (50.6)	1589 (45.8)	593 (40.5)	954 (42.9)
Never smoker	1827 (37.8)	1635 (47.2)	630 (43.0)	879 (39.6)
Education (n (%))				
Primary school	1502 (31.1)	577 (16.6)	321 (21.9)	635 (28.6)
High school	1371 (28.3)	1406 (40.6)	542 (37.0)	564 (25.4)
University some	899 (18.6)	486 (14.0)	315 (21.5)	1022 (46.0)
University long	1064 (22.0)	998 (28.8)	287 (19.6)	N/A
Alcohol intake (mean ± SD)	2.8 ± 3.0	2.7 ± 3.4	2.9 ± 3.5	0.5 ± 1.4
Never (n (%))	422 (8.7)	410 (11.8)	149 (10.2)	739 (33.3)
<1.99 units·week ⁻¹ (n (%))	2265 (46.8)	1597 (46.1)	635 (43.3)	1424 (64.3)
≥2 units·week ⁻¹ (n (%))	2149 (44.5)	1460 (42.1)	681 (46.5)	58 (2.6)
Disease (n (%))	2212 (45.7)	2456 (71.5)	388 (26.5)	1123 (50.6)
CVD	867 (17.9)	380 (11.0)	188 (12.8)	423 (19.1)
Cancer	552 (11.4)	969 (28.0)	130 (8.9)	331 (14.9)
Diabetes	319 (6.6)	285 (8.2)	83 (5.7)	345 (15.5)
Hypertension	1272 (26.7)	1871 (54.5)	44 (3.0)	535 (24.1)
Physical activity				
<i>Meeting physical activity guidelines (n (%))</i>				
<150 min·week ⁻¹	2452 (50.7)	1425 (41.1)	561 (38.3)	1724 (77.6)
≥150 min·week ⁻¹	2384 (49.3)	2042 (58.9)	904 (61.7)	497 (22.4)
<i>Wear time (hours·days⁻¹)*</i>				
Mean ± SD	16.20 ± 1.15	14.00 ± 1.15	14.56 ± 1.09	13.68 ± 1.27
<i>Total physical activity (counts·min⁻¹)</i>				
Mean ± SD	253.2 ± 112.1	340.7 ± 146.7	354.0 ± 147.6	305.8 ± 147.6
<i>Sedentary time (hours·day⁻¹)</i>				
Mean ± SD	10.77 ± 1.30	10.38 ± 1.35	10.11 ± 1.45	9.53 ± 1.76
<i>Light physical activity (min·day⁻¹)</i>				
Mean ± SD	286.7 ± 71.3	289.8 ± 71.9	316.5 ± 81.0	371.0 ± 97.4
<i>MVPA (min·day⁻¹)</i>				
Mean ± SD	26.5 ± 22.0	36.2 ± 27.1	36.1 ± 26.2	16.7 ± 19.2

Data are shown as mean ± SD, or as frequency (percentage). *wear time is displayed prior to standardizing the physical activity and sedentary time estimates to 16 hours·day⁻¹ wear time. CVD=cardiovascular disease, MVPA=moderate and vigorous physical activity, SD=standard deviation,

Tromsø=The Tromsø Study 2015-16, HAI=Healthy Ageing Initiative, NNPAS=Norwegian National Physical Activity Survey, NHANES=National Health and Nutrition Examination Survey.

Supplementary Table S5. Hazard ratio of mortality by physical activity and sedentary time.

Total Physical Activity (counts·min⁻¹)*	
	<i>HR (95%CI)</i>
100 counts·min ⁻¹	1.20 (1.14-1.26)
150 counts·min ⁻¹	<i>Ref.</i>
200 counts·min ⁻¹	0.77 (0.71-0.82)
250 counts·min ⁻¹	0.63 (0.56-0.71)
300 counts·min ⁻¹	0.54 (0.46-0.63)
350 counts·min ⁻¹	0.49 (0.41-0.58)
400 counts·min ⁻¹	0.46 (0.39-0.55)
450 counts·min ⁻¹	0.45 (0.37-0.55)
500 counts·min ⁻¹	0.45 (0.36-0.56)
550 counts·min ⁻¹	0.45 (0.35-0.57)
600 counts·min ⁻¹	0.44 (0.34-0.59)
Light Physical Activity (min·day⁻¹)*	
150 min·day ⁻¹	1.30 (1.19-1.42)
180 min·day ⁻¹	1.11 (1.07-1.15)
200 min·day ⁻¹	<i>Ref.</i>
210 min·day ⁻¹	0.95 (0.93-0.97)
240 min·day ⁻¹	0.81 (0.76-0.87)
270 min·day ⁻¹	0.71 (0.63-0.80)
300 min·day ⁻¹	0.64 (0.55-0.74)
330 min·day ⁻¹	0.60 (0.51-0.71)
360 min·day ⁻¹	0.59 (0.50-0.70)
390 min·day ⁻¹	0.59 (0.50-0.70)
420 min·day ⁻¹	0.61 (0.51-0.73)
450 min·day ⁻¹	0.63 (0.52-0.77)
480 min·day ⁻¹	0.65 (0.52-0.82)
510 min·day ⁻¹	0.68 (0.52-0.88)
Moderate and Vigorous Physical Activity (min·day⁻¹)*	
0 min·day ⁻¹	<i>Ref.</i>
10 min·day ⁻¹	0.73 (0.65-0.82)
20 min·day ⁻¹	0.55 (0.45-0.68)
30 min·day ⁻¹	0.46 (0.36-0.59)
40 min·day ⁻¹	0.41 (0.32-0.53)
50 min·day ⁻¹	0.39 (0.30-0.51)
60 min·day ⁻¹	0.37 (0.28-0.50)
70 min·day ⁻¹	0.36 (0.26-0.51)
80 min·day ⁻¹	0.35 (0.23-0.52)
90 min·day ⁻¹	0.34 (0.21-0.55)
100 min·day ⁻¹	0.33 (0.19-0.57)
Sedentary Time (hours·day⁻¹)[‡]	
6 hours·day ⁻¹	1.14 (0.94-1.38)
7 hours·day ⁻¹	1.07 (0.97-1.18)
8 hours·day ⁻¹	<i>Ref.</i>
9 hours·day ⁻¹	0.95 (0.87-1.04)
10 hours·day ⁻¹	0.97 (0.83-1.13)
11 hours·day ⁻¹	1.15 (0.97-1.37)
12 hours·day ⁻¹	1.53 (1.27-1.84)
13 hours·day ⁻¹	2.08 (1.65-2.62)

Data are shown as HR with 95%CI, adjusted for age (in timescale), alcohol, BMI, smoking, education, sex, CVD, diabetes, cancer, and accelerometry wear time (data are standardized to 16 hours·day⁻¹ wear time), and additionally adjusted for: *sedentary time ‡moderate-and-vigorous physical activity. Hazard ratios are displayed at arbitrary values of the cubic spline cox regression, references are set to the 10th percentile of the distribution within strata for total- and light physical activity, and at 0 minutes MVPA and 8 hours sedentary time. Bold numbers indicate significant association, p<0.05. Ref.=reference, HR=hazard ratio, CI=confidence interval, N/A=not applicable due to unobserved data.

Supplementary Table S6. Hazard ratio of mortality with higher physical activity stratified by median sedentary time and excluding first 5 years follow-up time

	Sedentary Time	
	<10.5 hours·day ⁻¹	≥10.5 hours·day ⁻¹
<i>n</i> (dead)	3947(231)	3319(232)
Total Physical Activity (counts·min⁻¹)	HR (95%CI)	HR (95%CI)
120 counts·min ⁻¹	N/A	Ref.
150 counts·min ⁻¹	N/A	0.82 (0.73-0.91)
200 counts·min ⁻¹	1.11 (0.99-1.26)	0.61 (0.48-0.78)
250 counts·min ⁻¹	Ref.	0.51 (0.38-0.70)
300 counts·min ⁻¹	0.90 (0.80-1.00)	0.47 (0.35-0.62)
350 counts·min ⁻¹	0.83 (0.67-1.02)	0.46 (0.29-0.71)
400 counts·min ⁻¹	0.78 (0.60-1.01)	N/A
450 counts·min ⁻¹	0.76 (0.57-1.01)	N/A
Light Physical Activity (min·day⁻¹)		
150 min·day ⁻¹	N/A	0.99 (0.82-1.20)
180 min·day ⁻¹	N/A	Ref.
210 min·day ⁻¹	N/A	1.00 (0.83-1.19)
240 min·day ⁻¹	N/A	0.94 (0.70-1.25)
270 min·day ⁻¹	N/A	0.79 (0.58-1.06)
300 min·day ⁻¹	Ref.	0.61 (0.43-0.86)
330 min·day ⁻¹	0.96 (0.78-1.20)	0.47 (0.29-0.76)
360 min·day ⁻¹	0.94 (0.63-1.39)	N/A
390 min·day ⁻¹	0.93 (0.57-1.53)	N/A
420 min·day ⁻¹	0.95 (0.56-1.61)	N/A
450 min·day ⁻¹	0.98 (0.59-1.64)	N/A
480 min·day ⁻¹	1.02 (0.62-1.68)	N/A
510 min·day ⁻¹	1.06 (0.64-1.75)	N/A
Moderate and Vigorous Physical Activity (min·day⁻¹)		
0 min·day ⁻¹	Ref.	Ref.
10 min·day ⁻¹	0.94 (0.80-1.11)	0.70 (0.53-0.94)
20 min·day ⁻¹	0.89 (0.65-1.22)	0.54 (0.33-0.88)
30 min·day ⁻¹	0.84 (0.55-1.28)	0.48 (0.28-0.82)
40 min·day ⁻¹	0.79 (0.50-1.27)	0.46 (0.27-0.81)
50 min·day ⁻¹	0.75 (0.46-1.21)	0.47 (0.27-0.84)
60 min·day ⁻¹	0.70 (0.43-1.15)	0.48 (0.25-0.93)
70 min·day ⁻¹	0.66 (0.39-1.13)	0.50 (0.23-1.07)
80 min·day ⁻¹	0.62 (0.34-1.14)	0.51 (0.20-1.27)
90 min·day ⁻¹	0.59 (0.29-1.19)	0.52 (0.18-1.52)
100 min·day ⁻¹	0.55 (0.24-1.25)	N/A
110 min·day ⁻¹	0.52 (0.20-1.34)	N/A
	Moderate and Vigorous Physical Activity	
	<150 min·week ⁻¹	≥150 min·week ⁻¹
<i>n</i> (dead)	3674 (372)	3592 (91)
Sedentary Time		
6 hours·day ⁻¹	1.01 (0.77-1.33)	1.42 (0.87-2.32)
7 hours·day ⁻¹	1.01 (0.88-1.15)	1.19 (0.93-1.52)
8 hours·day ⁻¹	Ref.	Ref.
9 hours·day ⁻¹	1.00 (0.87-1.14)	0.86 (0.70-1.07)
10 hours·day ⁻¹	1.02 (0.80-1.30)	0.81 (0.58-1.13)
11 hours·day ⁻¹	1.14 (0.86-1.52)	0.87 (0.56-1.36)
12 hours·day ⁻¹	1.41 (1.05-1.89)	1.00 (0.49-2.04)
13 hours·day ⁻¹	1.83 (1.29-2.59)	1.15 (0.40-3.28)

Data are shown as HR with 95%CI, adjusted for age (in timescale), alcohol, BMI, smoking, education, sex, CVD, diabetes, cancer, and accelerometry wear time (data are standardized to 16 hours·day⁻¹ wear time). Hazard ratios are displayed at arbitrary values of the cubic spline cox regression, references are set to the 10th percentile of the distribution within strata for total- and light physical activity, and at 0 minutes MVPA and 8 hours sedentary time. Bold numbers indicate significant

association, $p < 0.05$. Ref.=reference, HR=hazard ratio, CI=confidence interval, N/A=not applicable due to unobserved data.

Supplementary Table S7. Hazard ratio of mortality with higher physical activity stratified by median < 10.9 and ≥ 10.9 hours per day of sedentary time in the Norwegian and Swedish cohorts (Tromsø Study, HAI, NNPAS).

	Sedentary Time	
	< 10.6 hours·day ⁻¹	≥ 10.6 hours·day ⁻¹
<i>n</i> (dead)	4814 (108)	4954 (177)
Total Physical Activity (counts·min⁻¹)	HR (95%CI)	HR (95%CI)
100 counts·min ⁻¹	N/A	Ref.
150 counts·min ⁻¹	N/A	0.60 (0.50-0.72)
200 counts·min ⁻¹	N/A	0.38 (0.27-0.53)
250 counts·min ⁻¹	ref	0.20 (0.10-0.49)
300 counts·min ⁻¹	0.84 (0.70-1.02)	0.24 (0.16-0.37)
350 counts·min ⁻¹	0.72 (0.52-1.00)	0.23 (0.14-0.36)
400 counts·min ⁻¹	0.63 (0.43-0.94)	0.21 (0.12-0.38)
450 counts·min ⁻¹	0.57 (0.37-0.87)	0.20 (0.11-0.39)
500 counts·min ⁻¹	0.49 (0.30-0.79)	N/A
550 counts·min ⁻¹	0.47 (0.28-0.79)	N/A
600 counts·min ⁻¹	0.45 (0.25-0.79)	N/A
650 counts·min ⁻¹	0.40 (0.19-0.82)	N/A
Light Physical Activity (min·day⁻¹)		
160 min·day ⁻¹	N/A	1.58 (1.31-1.92)
190 min·day ⁻¹	N/A	Ref.
220 min·day ⁻¹	N/A	0.68 (0.59-0.79)
250 min·day ⁻¹	N/A	0.60 (0.49-0.74)
280 min·day ⁻¹	Ref.	0.70 (0.51-0.95)
310 min·day ⁻¹	1.10 (0.84-1.44)	0.88 (0.51-1.51)
340 min·day ⁻¹	1.20 (0.75-1.92)	N/A
370 min·day ⁻¹	1.29 (0.74-2.38)	N/A
400 min·day ⁻¹	1.37 (0.79-2.38)	N/A
430 min·day ⁻¹	1.42 (0.82-2.47)	N/A
Moderate and Vigorous Physical Activity (min·day⁻¹)		
0 min·day ⁻¹	Ref.	Ref.
10 min·day ⁻¹	0.81 (0.66-1.00)	0.68 (0.53-0.87)
20 min·day ⁻¹	0.66 (0.44-0.99)	0.49 (0.32-0.75)
30 min·day ⁻¹	0.55 (0.31-0.96)	0.40 (0.24-0.65)
40 min·day ⁻¹	0.47 (0.24-0.90)	0.35 (0.22-0.57)
50 min·day ⁻¹	0.41 (0.21-0.81)	0.33 (0.20-0.54)
60 min·day ⁻¹	0.37 (0.19-0.72)	0.30 (0.17-0.53)
70 min·day ⁻¹	0.34 (0.17-0.65)	0.28 (0.15-0.55)
80 min·day ⁻¹	0.31 (0.16-0.62)	0.27 (0.12-0.59)
90 min·day ⁻¹	0.28 (0.13-0.60)	N/A
100 min·day ⁻¹	0.26 (0.11-0.61)	N/A
110 min·day ⁻¹	0.24 (0.09-0.63)	N/A
	Moderate and Vigorous Physical Activity	
Sedentary Time	< 150 min·week⁻¹	≥ 150 min·week⁻¹
<i>n</i> (dead)	4249 (180)	5519 (105)
6 hours·day ⁻¹	2.15 (1.38-3.35)	0.69 (0.35-1.37)
7 hours·day ⁻¹	1.47 (1.18-1.83)	0.83 (0.59-1.17)
8 hours·day ⁻¹	Ref.	Ref.
9 hours·day ⁻¹	0.68 (0.55-0.85)	1.20 (0.86-1.68)
10 hours·day ⁻¹	0.48 (0.31-0.74)	1.36 (0.78-2.36)
11 hours·day ⁻¹	0.43 (0.25-0.76)	1.37 (0.77-2.42)
12 hours·day ⁻¹	0.65 (0.37-1.15)	1.27 (0.67-2.43)
13 hours·day ⁻¹	1.29 (0.74-2.24)	1.18 (0.49-2.86)

Data are shown as HR with 95%CI, adjusted for age (in timescale), alcohol, BMI, smoking, education, sex, CVD, diabetes, cancer, and accelerometry wear time (data are standardized to 16 hours·day⁻¹ wear time). Hazard ratios are displayed at arbitrary values of the cubic spline cox regression, references are set to the 10th percentile of the distribution within strata for total- and light physical activity, and at 0 minutes MVPA and 8 hours sedentary time. Bold numbers indicate significant association, p<0.05. Ref.=reference, HR=hazard ratio, CI=confidence interval, N/A=not applicable due to unobserved data.

Supplementary Table S8. Hazard ratio of mortality with higher physical activity stratified by median <9.6 and ≥9.6 hours per day of sedentary time in the NHANES*.

	Sedentary Time	
	<9.6 hours·day ⁻¹	≥9.6 hours·day ⁻¹
<i>n (dead)</i>	1104 (165)	1117 (335)
Total Physical Activity (counts·min⁻¹)	HR (95%CI)	HR (95%CI)
160 counts·min ⁻¹	N/A	Ref.
280 counts·min ⁻¹	Ref.	N/A
305 counts·min ⁻¹	N/A	0.56 (0.42-0.75)
380 counts·min ⁻¹	0.94 (0.70-1.25)	N/A
480 counts·min ⁻¹	0.93 (0.63-1.37)	N/A
580 counts·min ⁻¹	0.96 (0.63-1.48)	N/A
Light Physical Activity (min·day⁻¹)		
230 min·day ⁻¹	N/A	Ref.
260 min·day ⁻¹	N/A	0.83 (0.73-0.96)
290 min·day ⁻¹	N/A	0.74 (0.59-0.93)
350 min·day ⁻¹	N/A	0.74 (0.53-1.05)
380 min·day ⁻¹	Ref.	N/A
410 min·day ⁻¹	1.23 (0.91-1.68)	N/A
440 min·day ⁻¹	1.45 (0.86-2.47)	N/A
470 min·day ⁻¹	1.56 (0.86-2.84)	N/A
500 min·day ⁻¹	1.54 (0.88-2.68)	N/A
Moderate and Vigorous Physical Activity (min·day⁻¹)		
0 min·day ⁻¹	Ref.	Ref.
10 min·day ⁻¹	1.03 (0.80-1.35)	0.45 (0.33-0.61)
20 min·day ⁻¹	1.05 (0.65-1.70)	0.35 (0.24-0.51)
30 min·day ⁻¹	1.04 (0.57-1.89)	0.36 (0.25-0.53)
	Moderate and Vigorous Physical Activity	
Sedentary Time	<150 min·week⁻¹	≥150 min·week⁻¹
<i>n (dead)</i>	1617 (455)	604 (65)
6 hours·day ⁻¹	0.99 (0.68-1.44)	1.54 (0.60-3.94)
7 hours·day ⁻¹	1.00 (0.83-1.20)	1.22 (0.82-1.81)
8 hours·day ⁻¹	Ref.	Ref.
9 hours·day ⁻¹	1.03 (0.88-1.21)	0.87 (0.71-1.07)
10 hours·day ⁻¹	1.13 (0.89-1.44)	0.79 (0.50-1.26)
11 hours·day ⁻¹	1.38 (1.08-1.76)	0.73 (0.33-1.64)
12 hours·day ⁻¹	1.80 (1.37-2.38)	N/A
13 hours·day ⁻¹	2.41 (1.61-3.61)	N/A

Data are shown as HR with 95%CI, adjusted for age (in timescale), alcohol, BMI, smoking, education, sex, CVD, diabetes, cancer, and accelerometry wear time (data are standardized to 16 hours·day⁻¹ wear time). Hazard ratios are displayed at arbitrary values of the cubic spline cox regression, references are set to the 10th percentile of the distribution within strata for total- and light physical activity, and at 0 minutes MVPA and 8 hours sedentary time. Bold numbers indicate significant association, p<0.05. Ref.=reference, HR=hazard ratio, CI=confidence interval, N/A=not applicable due to unobserved data, NHANES=National Health and Nutrition Examination Survey.*NHANES estimates are sample-weighted to provide nationally representative estimates.

Supplementary Table S9. Hazard ratio of mortality with higher physical activity stratified by median sedentary time and adjusted NHANES estimates of physical activity and sedentary time.

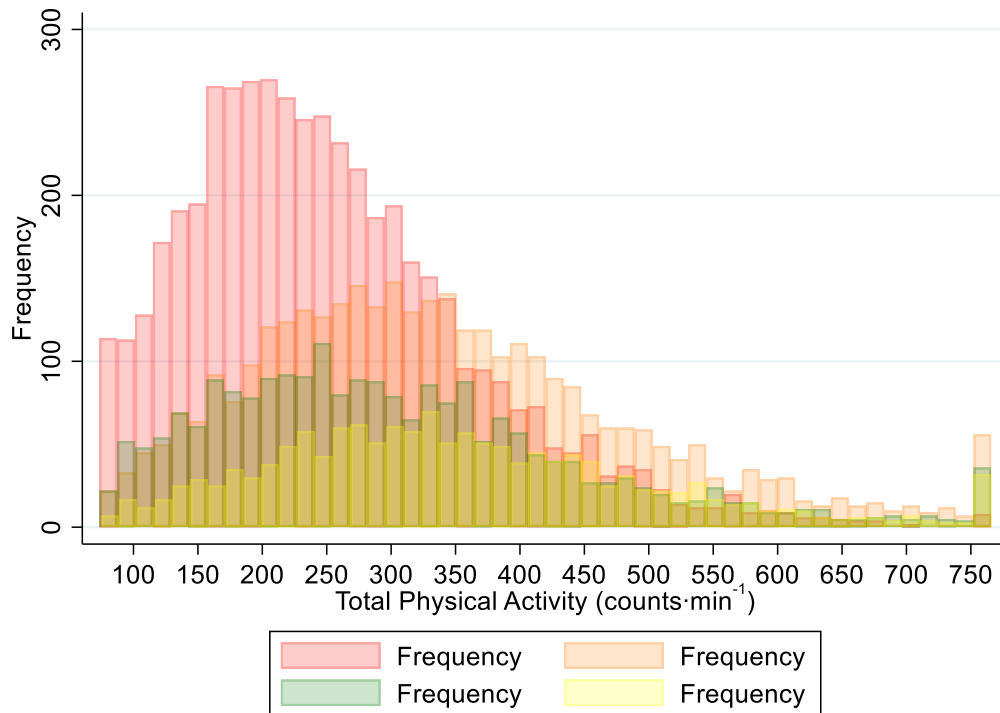
	Sedentary Time	
	<10.5 hours·day ⁻¹	≥10.5 hours·day ⁻¹
<i>n (dead)</i>	5848(331)	6141 (474)
Total Physical Activity (counts·min⁻¹)	HR (95%CI)	HR (95%CI)
100 counts·min ⁻¹	N/A	Ref.
150 counts·min ⁻¹	N/A	0.67 (0.59-0.75)
200 counts·min ⁻¹	N/A	0.47 (0.38-0.59)
250 counts·min ⁻¹	Ref.	0.38 (0.30-0.49)
300 counts·min ⁻¹	0.89 (0.81-0.99)	0.34 (0.26-0.45)
350 counts·min ⁻¹	0.81 (0.68-0.96)	0.32 (0.23-0.45)
400 counts·min ⁻¹	0.76 (0.61-0.94)	N/A
450 counts·min ⁻¹	0.72 (0.57-0.91)	0.30 (0.18-0.50)
Light Physical Activity (min·day⁻¹)		
150 min·day ⁻¹	N/A	1.35 (1.20-1.52)
180 min·day ⁻¹	N/A	Ref.
210 min·day ⁻¹	N/A	0.76 (0.68-0.84)
240 min·day ⁻¹	N/A	0.64 (0.55-0.75)
270 min·day ⁻¹	N/A	0.65 (0.55-0.77)
300 min·day ⁻¹	Ref.	0.73 (0.55-0.97)
330 min·day ⁻¹	1.11 (0.95-1.30)	N/A
360 min·day ⁻¹	1.22 (0.94-1.58)	N/A
390 min·day ⁻¹	1.29 (0.96-1.73)	N/A
420 min·day ⁻¹	1.33 (0.98-1.79)	N/A
450 min·day ⁻¹	1.36 (1.00-1.85)	N/A
Moderate and Vigorous Physical Activity (min·day⁻¹)		
0 min·day ⁻¹	Ref.	Ref.
10 min·day ⁻¹	0.84 (0.72-0.97)	0.65 (0.53-0.80)
20 min·day ⁻¹	0.71 (0.54-0.94)	0.47 (0.34-0.66)
30 min·day ⁻¹	0.62 (0.43-0.89)	0.40 (0.28-0.58)
40 min·day ⁻¹	0.55 (0.37-0.83)	0.37 (0.26-0.54)
50 min·day ⁻¹	0.51 (0.33-0.77)	0.36 (0.24-0.55)
60 min·day ⁻¹	0.47 (0.31-0.73)	0.35 (0.21-0.58)
70 min·day ⁻¹	0.44 (0.28-0.71)	0.34 (0.18-0.63)
80 min·day ⁻¹	0.42 (0.25-0.71)	N/A
90 min·day ⁻¹	0.39 (0.21-0.72)	N/A
100 min·day ⁻¹	0.37 (0.18-0.75)	N/A
	Moderate and Vigorous Physical Activity	
<i>n (dead)</i>	6162 (652)	5827(153)
Sedentary Time	<150 min·week⁻¹	≥150 min·week⁻¹
6 hours·day ⁻¹	1.17 (0.94-1.45)	1.23 (0.81-1.88)
7 hours·day ⁻¹	1.08 (0.97-1.20)	1.11 (0.90-1.37)
8 hours·day ⁻¹	Ref.	Ref.
9 hours·day ⁻¹	0.93 (0.83-1.03)	0.92 (0.76-1.10)
10 hours·day ⁻¹	0.91 (0.75-1.10)	0.90 (0.68-1.20)
11 hours·day ⁻¹	1.01 (0.80-1.27)	0.99 (0.70-1.38)
12 hours·day ⁻¹	1.32 (1.05-1.66)	1.13 (0.69-1.87)
13 hours·day ⁻¹	1.86 (1.44-2.39)	1.30 (0.63-2.70)

Data are shown as HR with 95%CI, adjusted for age (in timescale), alcohol, BMI, smoking, education, sex, CVD, diabetes, cancer, and accelerometry wear time (data are standardized to 16 hours·day⁻¹ wear time). Hazard ratios are displayed at arbitrary values of the cubic spline cox regression, references are set to the 10th percentile of the distribution within strata for total- and light physical activity, and at 0 minutes MVPA and 8 hours sedentary time. Bold numbers indicate significant association, p<0.05. Ref.=reference, HR=hazard ratio, CI=confidence interval, N/A=not applicable due to unobserved data. NHANES data are calibrated by individual-level summary data in the NHANES, accounting for non-identical output between AM-7164 and GT3X accelerometers (CPM x 0.92, light physical activity (min·day⁻¹) x 0.88, and sedentary time (hours·day⁻¹) x 1.02), while MVPA appears comparable between ActiGraph generations (Ried-Larsen M, Brønd JC, Brage S, Hansen BH,

Grydeland M, Andersen LB, et al. Mechanical and free living comparisons of four generations of the Actigraph activity monitor. *Int J Behav Nutr Phys Act.* 2012;9:113.)

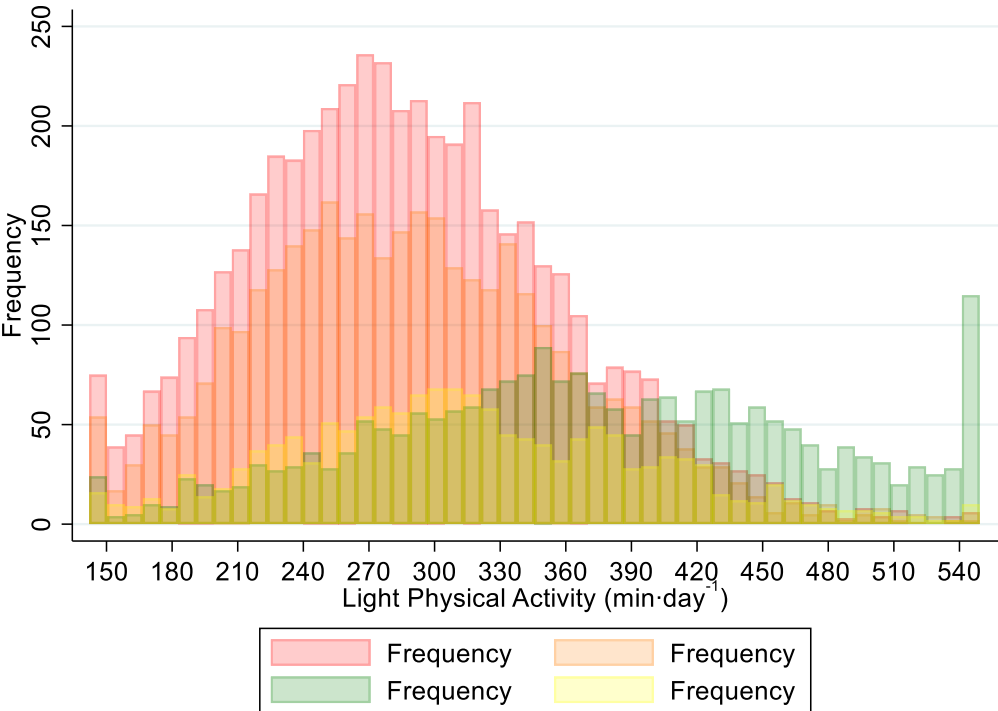
Supplementary Figures

Supplementary Figure S1. Histogram of total physical activity measured as counts per minute by cohort.



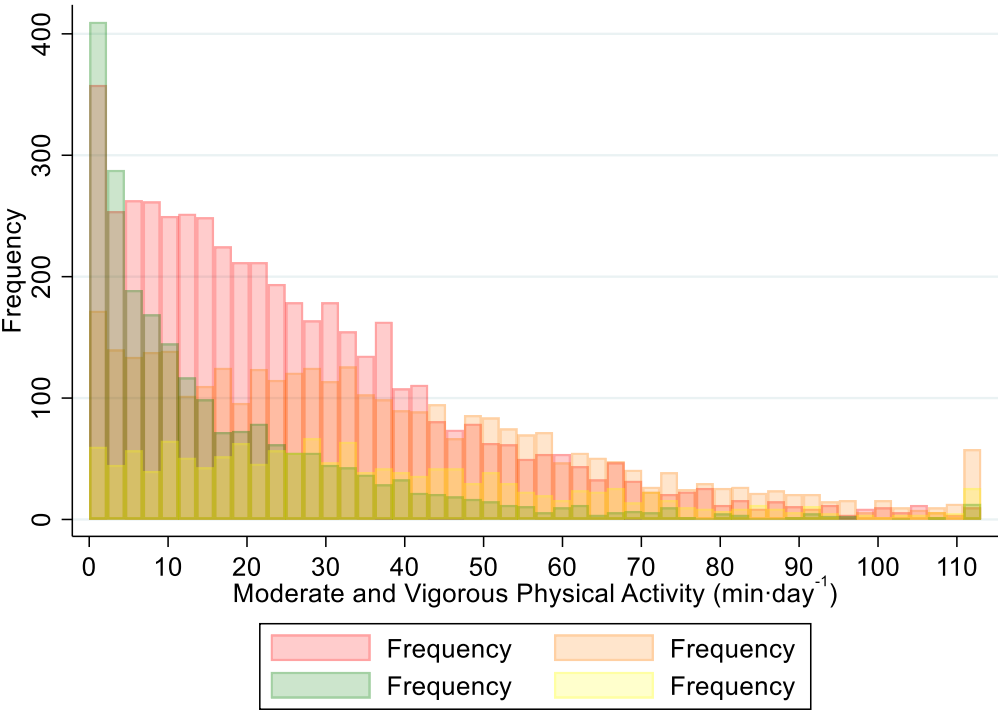
Tromsø=The Tromsø Study, HAI=Healthy Ageing Initiative, NNPAS=Norwegian National Physical Activity Survey, NHANES=National Health and Nutrition Examination Survey

Supplementary Figure S2. Histogram of minutes per day of light physical activity by cohort.



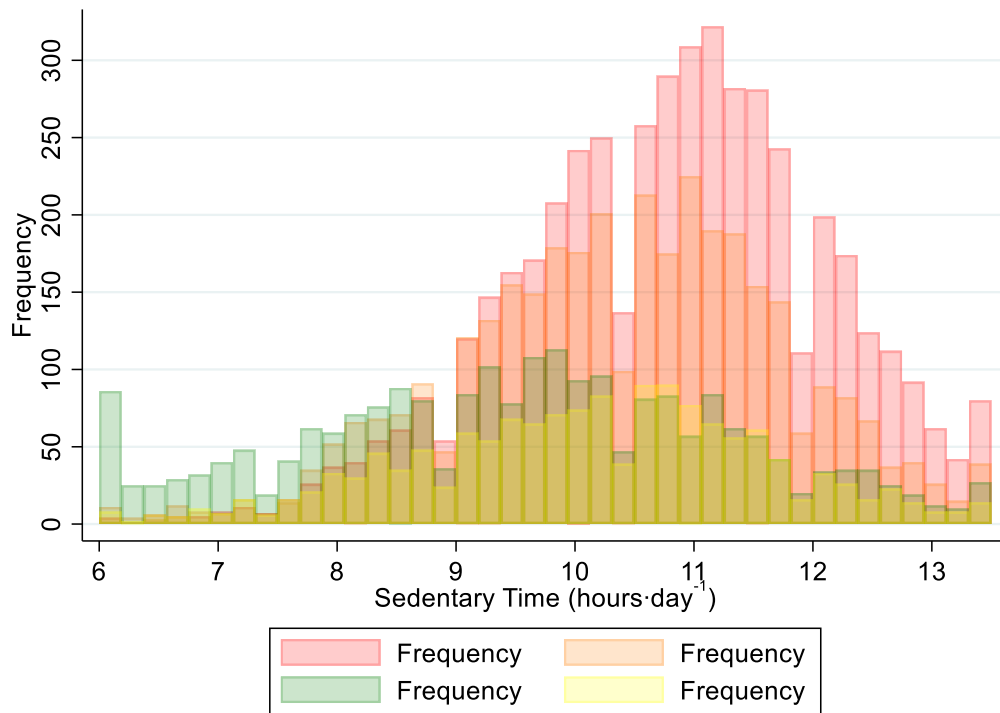
Tromsø=The Tromsø Study, HAI=Healthy Ageing Initiative, NNPAS=Norwegian National Physical Activity Survey, NHANES=National Health and Nutrition Examination Survey

Supplementary Figure S3. Histogram of minutes per day of moderate-vigorous physical activity by cohort.



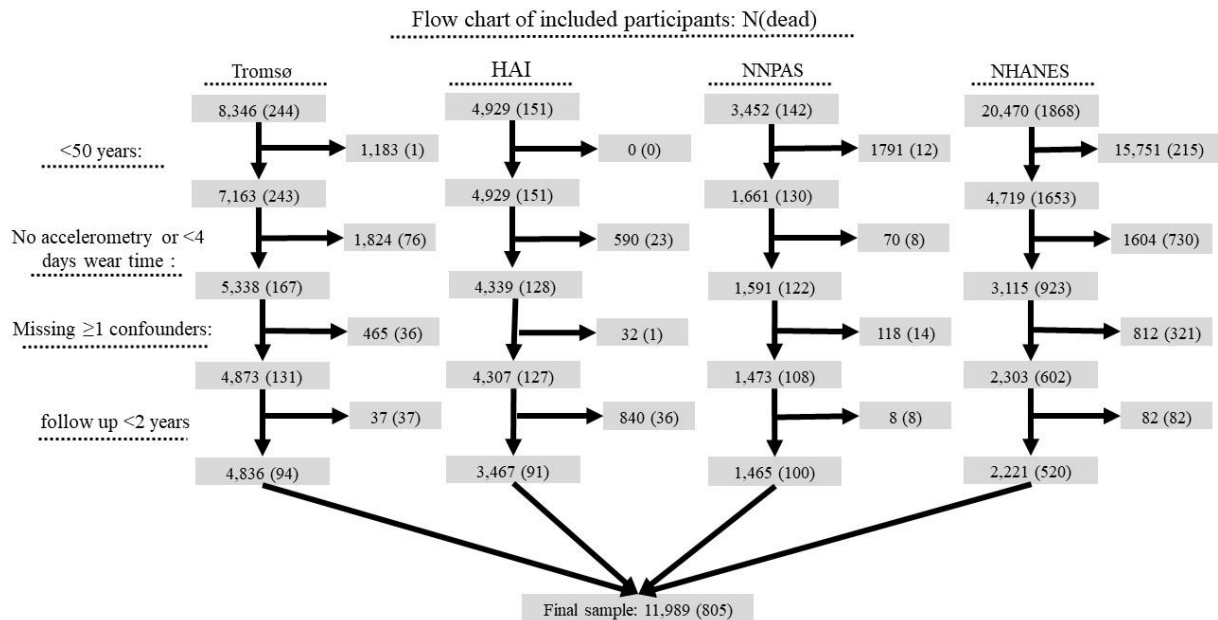
Tromsø=The Tromsø Study, HAI=Healthy Ageing Initiative, NNPAS=Norwegian National Physical Activity Survey, NHANES=National Health and Nutrition Examination Survey

Supplementary Figure S4. Histogram of hours per day of sedentary time by cohort.



Tromsø=The Tromsø Study, HAI=Healthy Ageing Initiative, NNPAS=Norwegian National Physical Activity Survey, NHANES=National Health and Nutrition Examination Survey

Supplementary Figure S5. Flow chart of included participants.



Tromsø= The Tromsø Study 2015-16, HAI=Healthy Ageing initiative, NNPAS=Norwegian National Physical Activity Survey 2008-09, NHANES=National Health and Nutrition Examination Survey 2003-06.

Appendix A

Ethical Approval, Regional Ethics Committee for Medical and Health Research, REC North;
Reference number 2016/1792/REK nord, date 01.11.2016.

Region:
REK nord

Saksbehandler:

Telefon:

Vår dato:
01.11.2016
Deres dato:
20.09.2016

Vår referanse:
2016/1792/REK nord
Deres referanse:

Vår referanse må oppgis ved alle henvendelser

Bente Morseth
Institutt for idrettsfag/Institutt for samfunnsmedisin

2016/1792 Stillesitting og kardiometabolsk helse

Forskningsansvarlig: UiT Norges arktiske universitet
Prosjektleder: Bente Morseth

Vi viser til søknad om forhåndsgodkjenning av ovennevnte forskningsprosjekt. Søknaden ble behandlet av Regional komité for medisinsk og helsefaglig forskningsetikk (REK nord) i møtet 20.10.2016. Vurderingen er gjort med hjemmel i helseforskningsloven (hfl.) § 10, jf. forskningsetikkloven § 4.

Prosjektleders prosjekttale

Prosjektet har som mål å gi ny kunnskap om aktivitetsnivået i Tromsø befolkning, og om stillesitting som risikofaktor for kardiometabolsk helse, uavhengig av fysisk aktivitetsnivå. Datamaterialet hentes fra Tromsøundersøkelsens 7. runde (Tromsø 7) som gjennomføres 2015-2016, hvor alle innbyggere i Tromsø fra 40 år inviteres. I Tromsø 7 måles fysisk aktivitet, stillesitting og søvn ved hjelp av objektive målemetoder (akselerometer, ActiGraph og Actiwave Cardio) på 8000 deltakere, og der samles inn en rekke data på helse og livsstil fra spørreskjema, kliniske undersøkelser og blodprøver. Mål på fysisk aktivitet og stillesitting hentes fra akselerometre og spørreskjema, og som markører på kardiometabolsk helse benyttes kroppsmasseindeks, kroppssammensetning, blodtrykk, hvilepuls, lipider, blodsukker og insulin.

Vurdering

Data

Datamaterialet hentes fra Tromsøundersøkelsens 7. runde (Tromsø 7) hvor alle innbyggere i Tromsø fra 40 år inviteres til deltakelse.

Data som samles inn gjelder fødselsår, demografiske data. Data på fysisk aktivitetsnivå (innhentet via spørreskjema og aktivitetsmåler). Antropometriske data: Høyde/vekt, BMI, midjemål, midje-hofte ratio, kroppssammensetning (DEXA-målinger).

Kliniske data: Blodtrykk, hvilepuls. Verdier fra blodprøveanalyser: Triglyceride, total kolesterol, high density lipoprotein kolesterol, HbA1c, insulin, glucose.

Data skal utleveres aidentifisert.

Forespørsel/informasjonskriv/samtykkeskriv - Tromsøundersøkelsene

Det vises til allerede innhentet samtykke i forbindelse med helseundersøkelsen Tromsø 7

Komiteen vurderer at samtykket er dekkende.

Vedtak

Med hjemmel i helseforskningsloven §§ 2 og 10 godkjennes prosjektet.

Sluttmelding og søknad om prosjektendring

Prosjektleder skal sende sluttmelding til REK nord på eget skjema senest 30.06.2021, jf. hfl. § 12. Prosjektleder skal sende søknad om prosjektendring til REK nord dersom det skal gjøres vesentlige endringer i forhold til de opplysninger som er gitt i søknaden, jf. hfl. § 11.

Klageadgang

Du kan klage på komiteens vedtak, jf. forvaltningsloven § 28 flg. Klagen sendes til REK nord. Klagefristen er tre uker fra du mottar dette brevet. Dersom vedtaket opprettholdes av REK nord, sendes klagen videre til Den nasjonale forskningsetiske komité for medisin og helsefag for endelig vurdering.

Med vennlig hilsen

May Britt Rossvoll
Sekretariatsleder

Kopi til: magritt.brustad@uit.no
postmottak@uit.no

Appendix B

Ethical Approval, Regional Ethics Committee for Medical and Health Research, REC North;
extension of the PhD project. Reference number 14289, date 26.11.2020.

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK nord	Monika Rydland	77620756	26.11.2020	14289

Deres referanse:

Bente Morseth

14289 Stillesitting og kardiometabolsk helse

Forskningsansvarlig: UiT Norges arktiske universitet

Søker: Bente Morseth

REKs vurdering

Vi viser til søknad om prosjektendring for ovennevnte forskningsprosjekt mottatt 21.11.2020. Søknaden er behandlet av sekretariatet i REK nord på delegert fullmakt fra komiteen, med hjemmel i forskningsetikkforskriften § 7, første ledd, tredje punktum. Søknaden er vurdert med hjemmel i helseforskningsloven § 11.

Av endringssøknaden fremgår det at prosjektperioden søkes forlenget til 31.12.2023 da PhD-kandidaten har en 4-årig PhD (01.02.2019-31.01.2023) og oppstart ble noe forskjøvet på grunn av finansiering og andre arbeidsoppgaver. Det søkes derfor om forlengelse av perioden i henhold til kandidatens PhD-periode.

REK har ingen innvendinger til omsøkte forlengelse av prosjektperiode.

Etter fullmakt er det fattet slikt

Vedtak

Godkjent

Med hjemmel i helseforskningsloven § 11 godkjennes prosjektendringen.

Prosjektet er godkjent frem til ny omsøkt sluttdato 31.12.2023.

Av dokumentasjonshensyn skal opplysningene oppbevares i fem år etter prosjektslutt. Enhver tilgang til prosjektdataene skal da være knyttet til behovet for etterkontroll. Prosjektdata vil således ikke være tilgjengelig for prosjektet. Prosjektleder og forskningsansvarlig institusjon er ansvarlige for at opplysningene oppbevares indirekte personidentifiserbart i denne perioden, dvs. atskilt i en nøkkel- og en datafil.

Etter denne femårsperioden skal opplysningene slettes eller anonymiseres. Komiteen gjør

oppmerksom på at anonymisering er mer omfattende enn å kun slette koblingsnøkkelen, jf. Datatilsynets veileder om anonymiseringsteknikker.

Vi gjør samtidig oppmerksom på at etter personopplysningsloven må det også foreligge et behandlingsgrunnlag etter personvernforordningen. Dette må forankres i egen institusjon.

Med vennlig hilsen

May Britt Rossvoll
sekretariatsleder

Monika Rydland
rådgiver

Søknad om å foreta vesentlige endringer

Dersom man ønsker å foreta vesentlige endringer i forhold til formål, metode, tidsløp eller organisering, skal søknad sendes til den regionale komiteen for medisinsk og helsefaglig forskningsetikk som har gitt forhåndsgodkjenning. Søknaden skal beskrive hvilke endringer som ønskes foretatt og begrunnelsen for disse, jf. hfl. § 11.

Sluttmelding

Søker skal sende sluttmelding til REK nord på eget skjema senest seks måneder etter godkjenningsperioden er utløpt, jf. hfl. § 12.

Klageadgang

Du kan klage på komiteens vedtak, jf. forvaltningsloven § 28 flg. Klagen sendes til REK nord. Klagefristen er tre uker fra du mottar dette brevet. Dersom vedtaket opprettholdes av REK nord, sendes klagen videre til Den nasjonale forskningsetiske komité for medisin og helsefag (NEM) for endelig vurdering.

Appendix C

Ethical approval, Regional Ethics Committee for Medical and Health Research, REC North; changes in outcome to mortality, and including The Healthy Ageing Initiative, The Norwegian National Physical Activity Survey and the National Health and Nutrition Examination Survey. Reference number 14289, date 26.11.2020.

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK nord	Monika Rydland	77620756	26.11.2020	14289

Deres referanse:

Bente Morseth

14289 Stillesitting og kardiometabolsk helse

Forskningsansvarlig: UiT Norges arktiske universitet

Søker: Bente Morseth

REKs vurdering

Vi viser til søknad om prosjektendring for ovennevnte forskningsprosjekt mottatt 21.11.2020. Søknaden er behandlet av sekretariatet i REK nord på delegert fullmakt fra komiteen, med hjemmel i forskningsetikkforskriften § 7, første ledd, tredje punktum. Søknaden er vurdert med hjemmel i helseforskningsloven § 11.

Av endringssøknaden fremgår det at artikkel 4 i PhD-prosjektet er endret til følgende problemstilling: "*Examine the joint and independent longitudinal association of objectively physical activity, sedentary time and adiposity (WC and BMI) on CVD and mortality*" og vil benytte data fra Tromsøundersøkelsen, NHANES, HAI-studien og KAN-studien, samt at en masterstudent inngår som ny medarbeider i prosjektet og at hans masteroppgave i medisin med problemstilling: "*Examine whether cardiorespiratory fitness mediate the association between physical activity and mortality*" vil benytte data fra prosjektet.

REK har ingen innvendinger til endret problemstilling til 4. artikkel med nevnte koblinger og masterstudentens bruk av prosjektets data. Vi gjør imidlertid oppmerksom på at det i informasjonsskrivet til KAN-studien er opplyst at: "*Alle innsamlede opplysninger anonymiseres senest innen 31.12.2020, med mindre vi innen da har kontaktet deg med forespørsel om noe annet.*» Deltakerne må derfor informeres om forlengelse av prosjektperioden/forlenget oppbevaring av data.

Etter fullmakt er det fattet slikt

Vedtak

Godkjent

REK har gjort en forskningsetisk vurdering av endringene i prosjektet, og godkjenner prosjektet slik det nå foreligger, jf. helseforskningsloven § 11.

Vi gjør samtidig oppmerksom på at etter ny personopplysningslov må det også foreligge et behandlingsgrunnlag etter personvernforordningen. Det må forankres i egen institusjon.

Godkjenningen er gitt under forutsetning av at prosjektendringen gjennomføres slik det er beskrevet i prosjektendringsmeldingen og de bestemmelser som følger av helseforskningsloven med forskrifter.

Med vennlig hilsen

May Britt Rossvoll
sekretariatsleder

Monika Rydland
rådgiver

Søknad om å foreta vesentlige endringer

Dersom man ønsker å foreta vesentlige endringer i forhold til formål, metode, tidsløp eller organisering, skal søknad sendes til den regionale komiteen for medisinsk og helsefaglig forskningsetikk som har gitt forhåndsgodkjenning. Søknaden skal beskrive hvilke endringer som ønskes foretatt og begrunnelsen for disse, jf. hfl. § 11.

Sluttmelding

Søker skal sende sluttmelding til REK nord på eget skjema senest seks måneder etter godkjenningsperioden er utløpt, jf. hfl. § 12.

Klageadgang

Du kan klage på komiteens vedtak, jf. forvaltningsloven § 28 flg. Klagen sendes til REK nord. Klagefristen er tre uker fra du mottar dette brevet. Dersom vedtaket opprettholdes av REK nord, sendes klagen videre til Den nasjonale forskningsetiske komité for medisin og helsefag (NEM) for endelig vurdering.

Appendix D

Ethical approval, Regional Ethics Committee for Medical and Health Research, REC North; changes to include all Tromsø Study Surveys (1974-2016). Reference number 14289, date 19.04.2021.

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK nord	Monika Rydland	77620756	19.04.2021	14289

Deres referanse:

Bente Morseth

14289 Stillesitting og kardiometabolsk helse

Forskningsansvarlig: UiT Norges arktiske universitet

Søker: Bente Morseth

REKs vurdering

Vi viser til søknad om prosjektendring mottatt 12.04.2021 vedlagt forskningsprotokoll revidert 07.04.2021 for ovennevnte forskningsprosjekt. Søknaden er behandlet av sekretariatet i REK nord på delegert fullmakt fra komiteen, med hjemmel i forskningsetikkforskriften § 7, første ledd, tredje punktum. Søknaden er vurdert med hjemmel i helseforskningsloven § 11.

Av endringssøknaden fremgår følgende: *"I henvendelse til REK november 2020 ble det beskrevet at PhD-prosjektet ville bli utvidet med et masterprosjekt i medisin som skal undersøke følgende problemstilling: Examine whether cardiorespiratory fitness mediate the association between physical activity and mortality. I etterkant viser det seg at et annet masterprosjekt ønsker å benytte samme problemstilling. Vi har derfor endret vår problemstilling fra mortality til hjerteinfarkt: Examine whether cardiorespiratory fitness mediate the association between physical activity and myocardial infarction."*

Videre er forskningsprotokollen oppdatert med endringer i metodedelen tilpasset problemstillingene, hvor den essensielle endringer er at prosjektet vil benytte data fra alle Tromsøundersøkelsene, ikke bare Tromsø 7 som beskrevet i den opprinnelige søknaden."

REK har ingen innvendinger til omsøkte endringer. Etter fullmakt er det fattet slikt

Vedtak

Godkjent

REK har gjort en forskningsetisk vurdering av endringene i prosjektet, og godkjenner prosjektet slik det nå foreligger, jf. helseforskningsloven § 11.

Tillatelsen er gitt under forutsetning av at prosjektendringen gjennomføres slik det er beskrevet i prosjektendringsmeldingen og de bestemmelser som følger av

helseforskningsloven med forskrifter.

Med vennlig hilsen

May Britt Rossvoll
sekretariatsleder

Monika Rydland
rådgiver

Klageadgang

Du kan klage på komiteens vedtak, jf. forvaltningsloven § 28 flg. Klagen sendes til REK nord. Klagefristen er tre uker fra du mottar dette brevet. Dersom vedtaket opprettholdes av REK nord, sendes klagen videre til Den nasjonale forskningsetiske komité for medisin og helsefag (NEM) for endelig vurdering.

Appendix E

Detailed descriptions of all questionnaire-based data included in this thesis are found online:

- Tromsø1 (1974), available at: <https://uit.no/research/tromsundersokelsen/project?pid=706181>, accessed 14.10.2022.
- Tromsø2 (1979-80), available at: <https://uit.no/research/tromsundersokelsen/project?pid=706184>, accessed 14.10.2022.
- Tromsø3 (1986-87), available at: <https://uit.no/research/tromsundersokelsen/project?pid=706195>, accessed 14.10.2022.
- Tromsø4 (1994-95), available at: <https://uit.no/research/tromsundersokelsen/project?pid=706779>, accessed 14.10.2022.
- Tromsø5 (2001), available at: <https://uit.no/research/tromsundersokelsen/project?pid=706781>, accessed 14.10.2022.
- Tromsø6 (2007-08), available at: <https://uit.no/research/tromsundersokelsen/project?pid=706783>, accessed 14.10.2022.
- Tromsø7 (2015-16), available at: <https://uit.no/research/tromsundersokelsen/project?pid=706786>, accessed 14.10.2022.
- HAI 2012-19, available at: <https://www.livsmedicin.se/variabellista-hai>, accessed 14.10.2022.
- NNPAS 2008-09, available at: <https://www.helsedirektoratet.no/rapporter/fysisk-aktivitet-kartleggingsrapporter>, accessed 14.10.2022.
- NHANES 2003-04, available at: <https://www.cdc.gov/nchs/nhanes/continuousnhanes/default.aspx?BeginYear=2003>, accessed 14.10.2022.
- NHANES 2005-06: <https://www.cdc.gov/nchs/nhanes/continuousnhanes/default.aspx?BeginYear=2005>, accessed 14.10.2022.

