

*Petra Tjurin*

# SEDENTARY BEHAVIOR IN MIDDLE-AGED ADULTS

MEASUREMENT METHOD DEVELOPMENT  
AND ASSOCIATIONS WITH LIPID AND GLUCOSE  
METABOLISM

UNIVERSITY OF OULU GRADUATE SCHOOL;  
UNIVERSITY OF OULU,  
FACULTY OF MEDICINE;  
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AGED ADULTS**

Measurement method development and associations  
with lipid and glucose metabolism

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### ***Abstract***

The adverse health effects of sedentary behavior and prolonged sedentary bouts are well-known. However, it is still unknown how physical activity can modify adverse health impacts related to sedentary behavior. The purpose of this study was to develop signal analysis methodology for sedentary behavior and physical activity classification from raw data of a hip-worn accelerometer and to investigate associations of patterns of sedentary behavior with lipid and glucose metabolism.

A machine learning model was developed and validated using acceleration data, which included nine predefined and controlled typical daily activities ranging in intensity from sedentary to vigorous physical activity. Acceleration data was collected from 22 Finnish adults using a triaxial accelerometer attached to an elastic belt on a hip. The data were classified into five categories (lying down, sitting, and light, moderate, and vigorous physical activity). Thirty-six middle-aged Finnish adults wore an accelerometer for 14 days, and their sedentary behavior and sitting characteristics were determined. In addition, associations of sedentary behavior, sitting, and physical activity with glucose and lipid metabolism were investigated in the Northern Finland Birth Cohort 1966 46-year follow-up (n=5,832). Participants completed health and lifestyle questionnaires and attended clinical examinations and two weeks of sedentary behavior and physical activity measurements. Isotemporal substitution modeling was used for investigating time reallocations from sedentary to physical activities.

The developed machine learning model provided acceptable accuracy for sedentary behavior and physical activity classifications. The method can be used for describing characteristics of sedentary behavior and sitting separately. Patterns of SB were more consistently associated with lipid metabolism than those of sitting. Associations between sedentary behavior and cardiometabolic health depended on moderate-to-vigorous physical activity levels. Replacement of sedentary behavior and prolonged sedentary bouts by at least light physical activity improved glucose metabolism. The results of this study can be used for planning evidence-based interventions to decrease sedentary behavior in midlife.

*Keywords:* accelerometer, cardiometabolic health, glucose metabolism, insulin resistance, machine learning, physical activity, sedentary behavior



## **Tjurin, Petra, Paikallaanolo keski-iässä. Mittausmenetelmän kehittäminen ja yhteys rasva- ja sokeriaineenvaihduntaan**

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### ***Tiivistelmä***

Runsas paikallaanolo ja pitkien paikallaanolojaksojen haitalliset vaikutukset terveyteen ovat hyvin tiedossa, mutta edelleen puuttuu tietoa, kuinka fyysinen aktiivisuus voi muokata paikallaanolon haitallisia vaikutuksia terveyteen. Työn tarkoituksena oli kehittää signaalinkäsittelymenetelmä paikallaanolon ja fyysisen aktiivisuuden luokitteluksi lantiolla pidettävän aktiivisuusmittarin raakakiihtyvyyksistä sekä tutkia paikallaanolon piirteiden yhteyksiä rasva- ja sokeriaineenvaihduntaan.

Koneoppimismalli kehitettiin ja validoitiin käyttämällä kiihtyvyydataa, joka sisälsi yhdeksän ennalta määriteltä ja kontrolloitua tyyppistä arkiaktiiviteettiä, joiden intensiteetti vaihteli paikallaanolosta raskaaseen fyysiseen aktiivisuuteen. Kiihtyvyydata kerättiin 22 suomalaisen aikuisen lantiolta elastiseen vyöhön kiinnitetyllä kolmiakselisella kiihtyvyyssanturilla, jonka raakadata luokiteltiin viiteen eri luokkaan (makaaminen, istuminen sekä kevyt, keskiraskas ja raskas fyysinen aktiivisuus). Kolmekymmentäkuusi keski-ikäistä suomalaista käyttivät kiihtyvyyssanturia 14 päivän ajan ja heidän paikallaanolonsa ja istumisensa piirteet määritettiin. Paikallaanolon, istumisen ja fyysisen aktiivisuuden yhteyksiä rasva- ja sokeriaineenvaihduntaan tutkittiin Pohjois-Suomen vuoden 1966 syntymäkohortin 46-vuotistutkimuksessa (n = 5832). Tutkittavat täyttivät terveys- ja elämäntapakyselyitä ja osallistuivat klinisiin tutkimuksiin sekä kahden viikon mittaisiin paikallaanolon ja fyysisen aktiivisuuden mittauksiin. Isotemporaalisella korvausmallilla tutkittiin paikallaanoloajan korvaamista fyysisellä aktiivisuudella.

Kehitetyllä koneoppimismenetelmällä voidaan riittävällä tarkkuudella luokitella paikallaanoloa ja fyysistä aktiivisuutta. Menetelmää voidaan käyttää paikallaanolon ja istumisen piirteiden kuvailussa erikseen. Paikallaanolon piirteet olivat selvemmin yhteydessä rasva-aineenvaihduntaan kuin istumisen piirteet. Paikallaanolon yhteydet rasva-aineenvaihduntaan olivat riippuvaisia keskiraskaan ja raskaan fyysisen aktiivisuuden tasosta. Paikallaanolon ja pitkien paikallaanolojaksojen korvaamisella vähintään kevyellä fyysisellä aktiivisuudella oli suotuisia vaikutuksia sokeriaineenvaihduntaan. Tutkimuksen tuloksia voidaan hyödyntää näyttöön perustuvien keski-ikäisten paikallaanoloa vähentävien interventioiden suunnittelussa.

*Asiasanat:* fyysinen aktiivisuus, insuliiniresistenssi, kiihtyvyyssanturi, koneoppiminen, paikallaanolo, sokeriaineenvaihdunta, sydänterveys





*To my family and friends*



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Hailuoto, April 2023

Petra Tjurin

## Abbreviations

APE	Angle for posture estimation
AUC	Area under the (ROC) curve
BMI	Body mass index
CHAP	Convolutional neural network hip accelerometer posture
CI	Confidence interval
CO <sub>2</sub>	Carbon dioxide
CVD	Cardiovascular disease
DLW	Doubly-labeled water technique
EE	Energy expenditure
ENMO	Euclidean norm minus one
GPAQ	Global Physical Activity Questionnaire
HDL	High-density lipoprotein
<sup>2</sup> H	Hydrogen isotope (deuterium)
<sup>2</sup> H <sup>18</sup> O	Doubly-labeled water
HOMA-B	Homeostasis model assessment of beta cell function
HOMA-IR	Homeostasis model assessment of insulin resistance
IFG	Impaired fasting glucose
IGT	Impaired glucose tolerance
IPAQ	International Physical Activity Questionnaire
IQR	Interquartile range
LDL	Low-density lipoprotein
LDL/HDL	Low-density lipoprotein to high-density lipoprotein ratio
LPA	Light physical activity
MAD	Mean amplitude deviation
MEMS	Micro-electro-mechanical systems
MET	Metabolic equivalent of task
MIMS	Monitor-Independent Movement Summary unit
ML	Machine learning
MPA	Moderate physical activity
MVPA	Moderate-to-vigorous physical activity
NFBC1966	Northern Finland Birth Cohort 1966
O <sub>2</sub>	Oxygen molecule
<sup>18</sup> O	Oxygen isotope
OGTT	Oral glucose tolerance test
PA	Physical activity

R <sup>2</sup>	Coefficient of determination
ROC	Receiver operating characteristics
SB	Sedentary behavior
SD	Standard deviation
Total/HDL	Total cholesterol to high-density lipoprotein ratio
VPA	Vigorous physical activity

## Original publications

This thesis is based on the following publications, which are referred to throughout the text by their Roman numerals:

- I Tjurin, P., Niemelä, M., Huusko, M., Ahola, R., Kangas, M. & Jämsä, T. (2017). Classification of physical activities and sedentary behavior using raw data of 3D hip acceleration. *IFMBE Proceedings*, 65, 872–875. [https://doi.org/10.1007/978-981-10-5122-7\\_218](https://doi.org/10.1007/978-981-10-5122-7_218).
- II Tjurin, P., Niemelä, M., Kangas, M., Vähä-Ypyä, H., Sievänen, H., Jämsä, T. & Korpelainen, R. (2019). Accelerometry-based characteristics of overall sedentary behavior and sitting in middle-aged adults. *Measurement in Physical Education and Exercise Science*, 23(3), 249–257. <https://doi.org/10.1080/1091367X.2019.1613997>.
- III Tjurin, P., Niemelä, M., Kangas, M., Nauha, L., Vähä-Ypyä, H., Sievänen, H., Korpelainen, R., Farrahi, V., & Jämsä, T. (2022). Cross-Sectional Associations of Sedentary Behavior and Sitting with Serum Lipid Biomarkers in Midlife. *Medicine and Science in Sports and Exercise*, 54(8), 1261–1270. <https://doi.org/10.1249/MSS.0000000000002916>.
- IV Tjurin, P., Länsitie, M., Kangas, M., Korpelainen, R., Farrahi, V. & Jämsä, T. (2023). Associations of reallocating time spent in sedentary behaviors and physical activities with glucose metabolism biomarkers in middle-aged adults. Manuscript.

Contributions to research for publications: I participated in the planning of data collection and designing the study, performed accelerometer initialization and accelerometer data handling, cleaning, preprocessing, and analysis, and drafted the manuscript for publication I. In publications II–IV, I participated in the planning and designing the studies, performed data and statistical analysis, and drafted manuscripts using previously collected data.





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# 1 Introduction

The leading causes of death globally are cardiometabolic diseases, such as cardiovascular diseases (CVDs), diabetes, and chronic kidney failure (de Waard et al., 2019; World Health Organization [WHO], 2022). Unhealthy lifestyles, including physical inactivity, an unhealthy diet, obesity, smoking, and the harmful use of alcohol, increase the risk for cardiometabolic diseases. Although the health-enhancing benefits of physical activity (PA) are well-known (Lear et al., 2019), the growing number of adults aged 18–64 years old do not meet the current PA guidelines of at least 150 to 300 minutes of moderate-intensity PA (MPA), at least 75 to 150 minutes of vigorous-intensity PA (VPA), or an equivalent combination of moderate-to-vigorous PA (MVPA) throughout the week (Guthold et al., 2018; WHO, 2020). In addition, adults spend most of their waking time being sedentary (López-Valenciano et al., 2020).

Sedentary behavior (SB) and prolonged uninterrupted bouts of SB are widely recognized as lifestyle risk factors for cardiometabolic diseases and all-cause mortality worldwide (Chastin et al., 2015a; Diaz et al., 2017; Lavie et al., 2019). The recent PA guidelines recommend that adults aged 18–64 sit less and replace sedentary time with any intensity of PA (WHO, 2020). Nevertheless, it is still unclear which is the maximum daily amount of SB and how SB should be interrupted to avoid its unfavorable health effects (Dempsey et al., 2020).

The PA and SB guidelines have traditionally been based on self-reported amounts of total time engaged in MVPA and sitting per day or week. Recently, the use of accelerometers to measure daily PA and SB has markedly increased, and accelerometers have enabled the recording of PA and SB patterns in a free-living environment over the whole 24-h cycle (Owen et al., 2020). Although accelerometers have been stated to be more accurate, reliable, and representative for measuring PA and SB than self-reported methods (Skender et al., 2016), accelerometers have also been associated with limitations, such as the dependency on the attachment site and analysis methods. As a result, the use of raw acceleration signals with a detailed description of the data analysis methods used has been proposed (Wijndaele et al., 2015).

Traditionally, SB has been considered an independent risk factor for unfavorable health conditions despite the amount of PA. Still, recent research has recognized that all PA behaviors have an influence on health, and health-related associations of SB may be modified by PA (Rosenberger et al., 2019; Stamatakis et al., 2019a). For instance, an increase in MVPA may attenuate health risks related

to high volumes of SB (Ekelund et al., 2016). The development of more advanced methods to measure and analyze PA has enabled us to find multidimensional behavioral patterns of PA over the whole 24-h cycle. However, more evidence is needed on the combined relationships between the patterns of SB and PA with cardiometabolic health (Rosenberger et al., 2019).

This study aimed to develop and validate data analysis methodology for classifying SB and PA from raw triaxial accelerometer data and to use this methodology for analyzing associations of characteristics of free-living SB with cardiometabolic health in middle-aged Finnish adults.

## 2 Review of the literature

### 2.1 Definition of sedentary behavior and physical activity

Physical activity is defined as any bodily movement produced by skeletal muscles with energy expenditure (EE) over the resting metabolic rate (Caspersen et al., 1985). PA includes all daily activities and exercises requiring a physical effort with the intensity of at least light physical activity (LPA). Physical inactivity means the lack of the required amount of MVPA described in the health-enhancing PA guidelines (WHO, 2020). In addition, sedentary behavior is defined as any waking time behavior spent in a sitting, reclining, or lying posture with low energy expenditure  $\leq 1.5$  metabolic equivalent of task (MET) (Tremblay et al., 2017). SB and PA can coexist, meaning that the same person can have high amounts of MVPA and still spend most of the day being sedentary (Owen et al., 2010).

The metabolic equivalent of task is widely used for describing the intensity of daily activities. The standard MET is defined as the oxygen consumption of 3.5 ml/kg/min and is equal to 1 kcal/kg/h regardless of body size. One MET corresponds to resting EE while sitting quietly, and a higher MET value describes a higher EE of a physical task. A wide range of typical physical activities have been coded based on their intensity in a Compendium of Physical Activities (Ainsworth et al., 2000; Ainsworth et al., 2011).

Regular PA has several well-known health benefits, such as the reduced risk for chronic disease morbidity and mortality worldwide (Guthold et al., 2018). The recommendations of health-enhancing PA so far have primarily been based on MVPA. The unfavorable effects of excessive SB on health have been widely acknowledged, and SB recommendations have been added to the latest health-enhancing PA guidelines (WHO, 2020). Recent research has also shown that replacing sedentary time even with LPA, such as light-intensity household tasks and slow walking, has favorable effects on health (Chastin et al., 2019; Healy et al., 2007). Especially the most inactive individuals can feasibly achieve health benefits by increasing the amount of LPA at the expense of SB (Van der Berg et al., 2017).

In addition to excessive sedentary time, prolonged bouts of SB have been shown to be detrimental to health (Diaz et al., 2017; Healy et al., 2008; Owen et al., 2020; Saunders et al., 2018). However, a wide range of estimations is used to determine SB bout or break. A sedentary bout is determined as a period of uninterrupted sedentary time typically lasting at least 1–10 minutes and ending with

standing up or any intensity PA (Tremblay et al., 2017). A sedentary break is determined as a non-sedentary bout in between two sedentary bouts and is typically a PA bout or transition from sedentary to standing or stepping with a duration of at least one minute (Husu et al., 2016; Sardinha et al., 2017; Tremblay et al., 2017; van der Velde et al., 2017). In addition, the definition of a prolonged bout of SB varies and is often at least 20 to 60 minutes long (Diaz et al., 2017; Healy et al., 2008; Tremblay et al., 2017). Consequently, there is a lack of consensus on how SB should be interrupted to avoid its detrimental health effects.

## **2.2 Measurement of sedentary behavior and physical activity**

Accurate and reliable measurements of sedentary behavior and physical activity are key factors in determining SB and PA patterns and their associations with health markers. SB and PA can be assessed using subjective or objective methods. Subjective methods are based on the subjects' own estimations of their SB and PA, which usually are collected using questionnaires and diaries. Conversely, objective methods are based on the information given by another person or device, and the information can be collected using direct observation, device-based, or EE-based methods. Device-based methods measure at least one biomechanical or physiological parameter, typically collected using wearable monitors like accelerometers, pedometers, and heart rate monitors. Wearable monitors can contain one type of sensor, or they can be multi-sensor devices. In addition, the EE of PA and SB can be measured using doubly-labeled water (DLW) and indirect calorimetry. (Ainsworth, 2009; Aunger & Wagnild, 2022; Butte et al., 2012; Sylvia et al., 2014)

### **2.2.1 Questionnaires and diaries**

Questionnaires and diaries have traditionally been used as self-reporting methods for assessing SB and PA (Ainsworth, 2009). They can be used both in short-term (e.g., weeks or days) and long-term (participant's usual habits) estimation of SB and PA in large epidemiological samples since they are cost-effective and easy to implement. The advantages of self-reports are that the type and context of the SB can be easily collected (Aunger & Wagnild, 2022). Various questionnaires are validated, have very good reliability and reproducibility, and are accepted measures of SB and PA, such as the International Physical Activity Questionnaire (IPAQ) and

Global Physical Activity Questionnaire (GPAQ) (Bull et al., 2009; Graiq et al., 2003).

However, subjective methods have some limitations. The validity of subjective methods has been questioned in studies that compared self-reporting methods against objective methods. Self-reporting methods have been reported to underestimate the amount of SB and LPA and overestimate the amount of MVPA compared to objective methods (Prince et al., 2008; Steene-Johannessen et al., 2016). In addition, intensive self-monitoring may decrease the amount of participants' SB and self-reporting methods can be burdensome to participants and researchers (Aunger & Wagnild, 2022; Shephard, 2003). The results of self-reporting methods can be affected by recall, social desirability bias, and misinterpretation (Aunger & Wagnild, 2022).

### **2.2.2 Direct observation**

Direct observation is one of the most basic and long-used methods for measuring SB and PA. Currently, the method is typically used to validate other SB and PA measurement techniques, such as accelerometers, since it can accurately differentiate static postures and measure the context of SB and PA (Kozey-Keadle et al., 2011). In addition, the method is feasible for assessing SB and PA in participants with cognitive restrictions since the observation is done by a trained observer without requiring an effort from participants. The observer records predetermined features of a participant's sedentary and physical activity behaviors, e.g., time spent in different postures, SB context, or the number of SB bouts, in real-time or from a video recording. Direct observation does not require expensive equipment. However, some limitations must be noted. The results of direct observation depend on the observer, and continuous observation can change the participant's behavior. In addition, direct observation is associated with limits to measure free-living SB and PA over lengthy periods due to the loss of privacy and high use of time. (Aunger & Wagnild, 2022; Loprinzi & Cardinal, 2011; Sylvia et al., 2014).

### **2.2.3 Energy expenditure-based techniques**

Doubly-labeled water is widely acknowledged as the gold standard technique for measuring energy expenditure in free-living conditions. DLW technique is typically used to calibrate and validate other SB and PA measurement techniques. Doubly-

labeled water is a non-invasive and accurate technique to measure free-living EE over a measurement period. Still, it cannot provide information about patterns or daily fluctuation of SB and PA. In addition, DLW requires the use of expensive isotopes and mass spectrometry.

The first application of DLW in humans was reported in 1982 (Schoeller & van Santen, 1982), and it is well-validated to date (Westerterp, 2017). The technique is based on enriching the body's water with isotopes of hydrogen ( $^2\text{H}$ ) and oxygen ( $^{18}\text{O}$ ) by a dose of ingested doubly-labeled water ( $^2\text{H}_2^{18}\text{O}$ ) and their different turnover rates from the body as a function of carbon dioxide production. The dilution spaces of isotopes are assessed from blood, saliva, or urine samples, collected at the start and end of the measurement period of 1–3 weeks. The length of the measurement period depends on the biological half-lives of the isotopes. It is typically one week in children and endurance athletes, two weeks in adults, and three weeks in older adults (Westerterp, 2017). The samples are analyzed by isotope ratio mass spectrometry.

Indirect calorimetry estimates EE from the measured pulmonary gas exchange ( $\text{O}_2$  and  $\text{CO}_2$ ). During the measurement, the subject can be inside a metabolic chamber or wear a facemask connected to a portable pulmonary gas analyzer. The concentrations of  $\text{O}_2$  and  $\text{CO}_2$  are measured by  $\text{O}_2$  and  $\text{CO}_2$  sensors from expired air and are converted into EE, e.g., one liter of consumed  $\text{O}_2$  equals about 5 kilocalories. (Hills et al., 2014). Indirect calorimetry can accurately determine minute-by-minute energy consumption, and it is currently the most common criterion measure for validating wearable PA monitors (de Almeida Mendes et al., 2018). However, some limitations must be noted. The utilization of indirect calorimetry in long-term free-living measurements is limited since the device is burdensome to wear for a participant. In addition, measuring devices require frequent calibration.

#### **2.2.4 Accelerometer-based devices**

Accelerometer-based activity monitors are the most common wearable monitors for free-living measurements of SB and PA (Strath et al., 2013). They are non-invasive wireless electromechanical devices that mechanically measure the acceleration of motion or gravity and convert it to an electrical signal. Accelerometers can measure and store high-frequency raw acceleration continuously over long periods, which can vary from days to years, depending on the monitor. Therefore, accelerometers can capture more precisely short bouts of



SB and PA than subjective methods and provide more information about SB and PA patterns. Micro-electro-mechanical systems (MEMS) have enabled the availability of inexpensive, small, and light-weight accelerometers (Yang & Hsu, 2010). Accelerometers can be uniaxial (often aligned vertically), biaxial (often aligned vertically and mediolaterally), or triaxial (vertical, mediolateral, and anterior-posterior). Accelerometers can be attached at different body sites. (Aunger & Wagnild, 2022; Troiano et al., 2014).

The operating principle of accelerometers is theoretically described as a spring-mass system based on a combination of Hooke's and Newton's second laws. In brief, the motion of the spring-mass system produces an extending or compressing force on the system, and the spring generates a restoring force (Kavanagh et al., 2008). When the stiffness of the spring and mass are controlled, the resultant acceleration of the mass element can be mathematically determined from its displacement as follows:

$$F = kx = ma, \text{ thus } a = \frac{kx}{m} \quad (1)$$

where  $F$  is force ( $\text{kg}\cdot\text{m}/\text{s}^2$ ),  $k$  is the stiffness of the spring ( $\text{N}/\text{m}$ ),  $x$  is the displacement ( $\text{m}$ ),  $m$  is the mass of the mass element ( $\text{kg}$ ), and  $a$  is acceleration ( $\text{m}/\text{s}^2$ ).

Acceleration can be measured using several techniques, and the most common acceleration sensors are piezoelectric, piezoresistive, and capacitive. Piezoelectric and piezoresistive acceleration sensors are based on similar principles and voltage generation. However, a piezoresistive or cantilever beam sensor consists of a seismic mass attached at the end of a piezoelectric element, and acceleration produces bending in the element. In contrast, a piezoelectric or compression-based acceleration sensor has a seismic mass on top of the piezoelectric element, and acceleration produces compression of the element and further changes the element's shape. Capacitive acceleration sensors consist of fixed electrodes and seismic mass with floating electrodes. Acceleration changes the distance between floating and fixed electrodes and further induces a change in capacitance. Piezoresistive and capacitive acceleration sensors can measure constant acceleration, such as gravity, and therefore are the most common accelerometers in SB and PA measurements (Lowe & ÓLaighin, 2014; Yang & Hsu, 2010).

Although accelerometers are the most popular devices for SB and PA measurements, some limitations must be noted. Accelerometers cannot recognize extra muscle work or carried loads (e.g., hill climbing or lifting heavy weights),

and they do not provide information about the context of the SB and PA. The accelerometer's output depends on the monitor's placement and data analysis methods. As a result, different accelerometer-based activity monitors are not interchangeable with each other and hip-worn accelerometers' ability to accurately recognize body postures, e.g., differentiating sitting from lying down or standing, has been questioned. However, novel analysis methods, such as convolutional neural network hip accelerometer posture (CHAP) and angle for posture estimation (APE), have enabled accurate and reliable posture recognition from hip-worn accelerometers (Aunger & Wagnild, 2022; Butte et al., 2012; Greenwood-Hickman et al., 2021; Matthews et al., 2012a; Troiano et al., 2014; Vähä-Ypyä et al., 2018).

### *Accelerometer placement*

Accelerometer-based activity monitors were used initially for measuring PA, but later, they became popular for measuring SB. Thus, the accelerometers are most often worn on the wrist as a watch or are attached to an elastic belt or a clip and worn on the hip or the waist. The accelerometer attached at the hip has been thought to provide a more accurate measurement of human motion and posture than the accelerometer attached to the wrist due to the close location from the center of mass of the body (Rosenberger et al., 2013). In addition, accelerometers can be placed on the thigh, which has been suggested as the most accurate wear site to detect body postures (Aunger & Wagnild, 2022; Janssen & Cliff, 2015). Nevertheless, the attachment site on the thigh demands the use of adhesives directly on the skin, which may produce dermal irritation and shorten the measurement period. Accelerometers can be worn on different body sites and combined with physiological measures to form multi-sensor devices (Chen & Basset Jr., 2005).

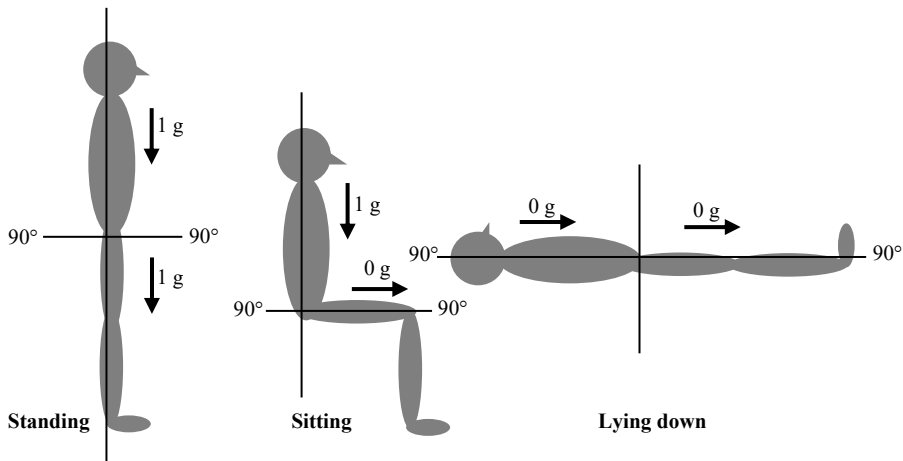
Posture detection has traditionally been based on static accelerations and the inclination of the accelerometer (Lowe & ÓLaighin, 2014). The inclination is typically calculated as follows:

$$\theta = \frac{180}{\pi} \cos^{-1} \frac{a}{g} \quad (2)$$

where  $\theta$  is the angle from the vertical ( $^{\circ}$ ),  $a$  is the acceleration from the sensor ( $\text{m/s}^2$ ), and  $g$  is  $9.81 \text{ m/s}^2$  (Lowe & ÓLaighin, 2014).

The thigh has been thought to be the most accurate attachment site to separate sitting and lying down from standing (Aunger & Wagnild, 2022). Thigh-worn accelerometers may have more homogeneity in the data collection and analysis methods than accelerometers attached to other wear sites (Stevens et al., 2020). In

addition, the use of multisite assessment (e.g., thigh and trunk) has been proposed to improve the accuracy of posture detection (Lowe & ÓLaighin, 2014). When acceleration sensors are attached to both the thigh and the trunk, the different static accelerations can be seen at the thigh and the trunk in different postures. For example, a person is lying down when both sensors are horizontal. The person is sitting when the trunk is vertical and the thigh is horizontal, and the person is standing when both the trunk and thigh are vertical (Figure 1). The magnitude of the measured gravitational force depends on the direction of the acceleration sensor axis and varies ideally between -1 to 1 gravitational units (g, approximately 9.81 m/s<sup>2</sup>). As a result, the accurate detection of sitting, lying down, and standing is possible solely using simple gravitational thresholds of the sensors, and even the uniaxial accelerometers can be used. This enables the use of algorithms that do not require a high computational power meaning lower costs and power consumption requirements (Chen & Basset Jr., 2005; Lowe & ÓLaighin, 2014).



**Fig. 1. Operating principles of posture detection using two accelerometers (modified from Lowe & ÓLaighin, 2014).**

Traditionally, using a single accelerometer has been considered a limitation and the accuracy of the method to detect postures has been questioned (Chen & Basset Jr., 2005; Lowe & ÓLaighin, 2014). However, a single accelerometer attached to the thigh has shown excellent validity against direct observation (Edwardson et al., 2016; Kozey-Keadle et al., 2011), and it can accurately separate sedentary from standing posture (O'Brien et al., 2022). In addition, almost negligible differences in

the duration of PAs and body postures have been observed between different thigh-worn accelerometer brands (Crowley et al., 2019).

Recently, the use of triaxial accelerometers and more advanced data analysis methods have become more popular and enabled more accurate posture detection than the traditional threshold-based posture detection methods (Aunger & Wagnild, 2022; Lowe & ÓLaighin, 2014). Sitting can be reliably separated from standing using an advanced data analysis method with a single triaxial accelerometer, even attached at the hip (Greenwood-Hickman et al., 2021; Vähä-Ypyä et al., 2018) or to the wrist (Rowlands et al., 2016). For instance, the CHAP method which is a machine learning (ML) based posture recognition method for a single hip-worn triaxial accelerometer has offered excellent validity to recognize postures and postural transitions against thigh-worn accelerometer (Greenwood-Hickman et al., 2021).

### **2.3 Accelerometer data analysis**

The measured acceleration signal consists of gravity, body movement, and noise caused by vibrations from the environment or weak attachment of the sensor. Therefore, the acceleration signal needs to be filtered to eliminate the noise from the signal. Typically, human movement causes accelerations that have low frequency and amplitude. The frequencies of the human movement depend on the measurement site, and general frequencies during typical non-impact PAs located close to the center of mass in humans are at the greatest 8 Hz (Chen & Bassett Jr., 2005). Still, some upper limb movements can achieve 25 Hz (Chen & Bassett Jr., 2005). The Nyquist criterion states that the sampling frequency of the accelerometer must be at least twice the highest frequency of human movement to accurately capture human motions (Arvidsson et al., 2019). Thus, the sampling frequencies of accelerometers usually range between 30 Hz to 100 Hz (Migueles et al., 2017). In addition, the measuring range of the accelerometers is typically somewhere between  $\pm 2$ -16 g-units (Sievänen & Kujala, 2017).

Filtering is based on removing certain frequency noise from the acceleration signal. Typically, electrical noise has a high frequency ( $\geq 60$  Hz), and artifacts caused by temperature changes and aging of piezo elements have a very low frequency ( $< 0.1$  Hz) (Chen & Bassett Jr., 2005). The noise and artifacts can be attenuated using a band-pass filter, which allows the frequencies between cut-off limits to pass. The selected cut-off frequencies of the band-pass filter may affect the output of the PA monitor. For instance, an excessively wide bandwidth may

include noises such as external vibrations or electrical artifacts in the signal, and a narrow bandwidth may eliminate part of the human movement from the signal (Chen & Bassett Jr., 2005). In addition, the static accelerations based on the gravitational force can be separated from the dynamic accelerations caused by body movements using high-pass filtering with low frequencies typically lower than 1 Hz (Andreu-Perez et al., 2017). Another method to remove gravity component from the dynamic accelerations is Euclidean norm minus one (ENMO) that first calculates resultant acceleration and then subtracts one gravitational unit from the resultant acceleration at each time point. Negative ENMO values are rounded up to zero and ENMO values can further be classified into PAs by using specific thresholds (Bakrania et al., 2016; van Hees et al., 2013).

Before the acceleration signals can be transformed into more presentative metrics about SB and PA, wear time needs to be detected, and acceleration signals need to be windowed into specific time segments called epochs. The epoch length varies from seconds to several minutes and influences classified PA data. The commonly used epoch lengths are between 1 and 60 seconds (Arvidsson et al., 2019). However, the epoch length of less than ten seconds is considered the most accurate to capture the variation in PA intensity (Matthews et al., 2012a). Wear time detection means that the non-wearing time needs to be eliminated from the acceleration signal. It is usually done by eliminating periods of at least 60 consecutive minutes of zero output with a different allowance of non-zero values (Janssen & Cliff, 2015; Troiano et al., 2008). However, several wear time algorithms are used, recognizing different amounts of SB (Janssen et al., 2015; Janssen & Cliff, 2015; Migueles et al., 2017; Stevens et al., 2020). The actual SB and PA metrics can be calculated from the epochs of the pre-processed acceleration data.

Several data analysis approaches are used for classifying acceleration data into SB and PA parameters. Traditional approaches typically classify acceleration data into, e.g., activity counts or METs using statistical data analysis methods and thresholds, and accelerometers have provided these integrated units as output (Migueles et al., 2017; Troiano et al., 2014). Recently, more advanced data analysis methods, such as mean amplitude deviation (MAD), APE, and ML based approaches, have become alternative data analysis methods for SB and PA classifications. In addition, the use of raw acceleration data has been proposed instead of accelerometers' integrated activity units (Wijndaele et al., 2015).

### **2.3.1 Traditional signal processing techniques**

Several approaches for calculating counts from raw acceleration data have been used, and they can be divided broadly into three categories: time-above-threshold, zero-crossing, and digital integration (Neishabouri et al., 2022). In the time-above-threshold method, the activity count is calculated within an epoch as the amount of time when the acceleration signal is above a predefined threshold, such as a specific g-unit that is thought to indicate motion. In contrast, the zero-crossing method calculates the number of times the acceleration signal crosses the predefined reference point, which can be zero or another threshold describing the low-level activity. The most used analysis method to determine count is digital integration that calculates the area under the activity curve. The digital integration method is the simplest completed by summing the integral values within an epoch (Chen & Bassett Jr., 2005). The digital integration method accounts for the amplitude of the acceleration being an advantage over the zero-crossing and time-above-threshold methods. The advantage of the count-based methods is that they are simple to implement and, therefore, widely used for assessing PA behaviors.

Accelerometers designed for measurements of human physical behavior were originally used to measure PA, and activity counts were transformed into activity intensities using many different sets of cut-points derived from regression analysis (Bassett Jr. et al., 2012). One of the most common sets of cut-points is Freedson's cut-points for hip-worn accelerometers. It classifies activity counts into different categories based on the EE of the activity: SB ( $\leq 1.5$  METs), LPA (1.51–2.99 METs), MPA (3–5.99 METs), and VPA ( $\geq 6$  METs) (Freedson et al., 1998). However, many different cut-points have also been used to classify PAs into intensity categories, e.g., 4-6.99 METs for MPA (Esliger et al., 2011). Typically, sedentary time has been detected from accelerometer data as periods of non-movement using different activity count-based methods (Freedson et al., 1998; Matthews et al., 2008; Trost et al., 2011). Later, the need to separate sitting from standing and lying down emerged, and accelerometers began to be used as inclinometers (Aunger & Wagnild, 2022). More recently, more advanced data analysis methods to detect body posture have been established, and the use of raw acceleration data instead of proprietary integrated activity counts has been proposed (Wijndaele et al., 2015).

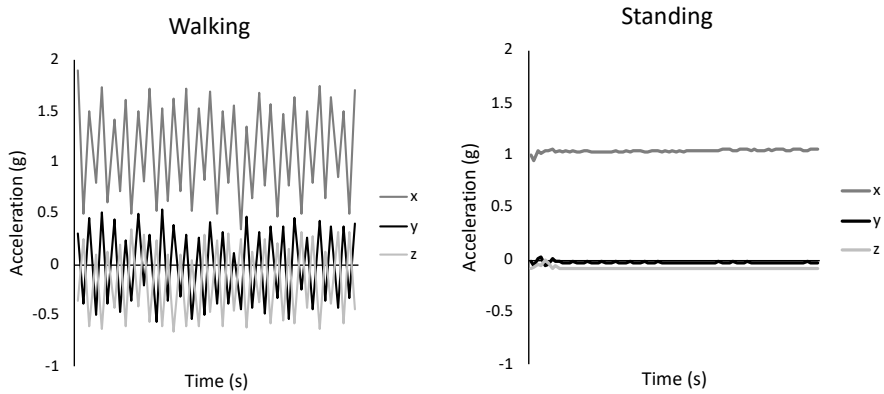
Transition-based posture detection is one of the posture detection methods. Using different parameters (e.g., vertical velocity), it detects the transitions between static postures instead of the postures themselves (Lowe & ÓLaighin, 2014). Sedentary Sphere is another method to detect static postures, and it is

developed for wrist-worn accelerometer data (Rowlands et al., 2016). The method classifies posture as sitting or reclining when the activity level is low and the wrist is elevated higher than  $15^\circ$  below the horizontal. If the wrist is elevated lower than  $15^\circ$  below the horizontal, the arm hangs more vertically, and the posture is classified as standing. Sedentary Sphere can be used for SB classifications from raw accelerations regardless of a wrist-worn accelerometer brand (Rowlands et al., 2016).

In addition, a novel and universal APE method for posture detection from hip-worn accelerometer data has been developed (Vähä-Ypyä et al., 2018). Initially, the method detects the accelerometer's orientation during walking from raw acceleration data and uses it as a reference value. Before setting the reference value for the upright posture within an epoch, the walking is detected based on activity intensity, activity step rate, and movement steadiness. Activity intensity is classified using MAD, which describes the variation in amplitude between the mean value and the data points of the resultant acceleration within an epoch and is calculated as follows:

$$MAD = \frac{1}{n} \sum |r_i - \bar{r}| \quad (3)$$

where  $n$  is the number of samples in the epoch of interest,  $r_i$  is the  $i$ th resultant sample within the epoch, and  $\bar{r}$  is the mean resultant value of the epoch (Vähä-Ypyä et al., 2015). Furthermore, MAD-like parameters are used to determine movement steadiness as previously described elsewhere (Vähä-Ypyä et al., 2018). After the reference value for an epoch is determined, the APE is calculated. APE describes the angle between the measured value (e.g., standing) and reference value (walking) within an epoch (Figure 2). The APE-MAD method can be used for classifying PA and SB from raw triaxial accelerations irrespective of hip-worn accelerometer brand.



$$APE = \cos^{-1} \frac{x_M x_R + y_M y_R + z_M z_R}{\sqrt{x_M^2 + y_M^2 + z_M^2} \sqrt{z_R^2 + y_R^2 + z_R^2}}$$

**Fig. 2.** Angle for posture estimation (APE) and triaxial acceleration data representing walking and standing still. The axis-specific mean values are 1.059, -0.045, and -0.113 g for walking and 1.059, -0.029, and -0.075 g for standing; thus, APE is 2.2° (modified from Vähä-Ypyä et al., 2018).

Monitor-Independent Movement Summary unit (MIMS) is another method to detect postures and PAs from raw acceleration data of triaxial accelerometer irrespective to accelerometer brand. The method first uses digital signal processing techniques to harmonize raw data from different accelerometers with different dynamic range and sampling rates, and then aggregates the raw data to yield MIMS-units that are based on area under the curve calculations to detect human motion and posture. The method enables accurate posture detection, since the MIMS-units are calculated from raw accelerations for each triaxial axes separately rather than computing resultant acceleration (John et al., 2019).

### 2.3.2 Machine learning

Machine learning is a new approach for SB and PA classification with the ability to extract nonlinearities and complex dependencies from the acceleration data. ML-based methods are advanced statistical techniques that can learn to recognize SB and PA patterns from acceleration data using complicated mathematical algorithms (Bassett Jr. et al., 2012; de Almeida Mendes et al., 2018). Compared to traditional statistical approaches, the advantages of ML approaches are that several input features in both time and frequency domains without predetermined thresholds can



be included in the classification model (Preece et al., 2009). The features can describe different acceleration signal characteristics and can be used for predicting activity types, activity intensities, EE, and body postures in the same model (Troiano et al., 2014). In contrast, the traditional statistical approaches typically use one to a few features which are linearly related to EE to determine threshold values (Bassett Jr. et al., 2012).

Although ML models can be used for classifying activity types and body posture, the PA data has primarily been analyzed according to activity intensity categories (SB, LPA, and MVPA) in the previous PA literature. The number of predicted activity classes influences the performance of the prediction models (Ellis et al., 2016). Typically, the performance of the prediction models decreases with the increasing number of activity classes. Therefore, predicting SB and PA data directly into interest categories may be reasonable. In addition, the variations in the performance of the ML models can be influenced by the amounts of signal, noise, activity types, extracted features, and the used prediction model that are most often artificial neural networks, decision trees, support vector machines, and random forests (de Almeida Mendes et al., 2018; Ellis et al., 2016). However, the consensus about the most feasible ML technique and set of features is still missing, although time-domain features have been proposed to be sufficient and provide high accuracy for activity intensity predictions (Chong et al., 2021; Montoye et al., 2018a). The ML models trained with properly selected 20 to 45 time-domain features describing variation and change rate of the acceleration signal may be relevant and provide high performance for activity class prediction (Chong et al., 2021).

The ML approaches have offered improved classification accuracy compared to traditional cut-point methods, and the use of raw acceleration data has enabled the development of accelerometer brand-independent ML methods (Ellis et al., 2016; Kerr et al., 2017; van Hees et al., 2016; Wijndaele et al., 2015). Nevertheless, some limitations concerning ML methods need to be noted. Although ML models are device-independent data analysis methods, accelerometers providing count data have been shown to be more highly comparable than raw data between accelerometers (Montoye et al., 2018b). The output and performance of the ML models are dependent on many factors (e.g., wear site, filtering methods, wear time detection, epoch length, extracted features, prediction model, activity types and classes), which may explain the challenges in the comparability of ML-based studies (Preece et al., 2009). In addition, ML models may be associated with limited generalization capability if the ML model is applied to different populations than

the population used in the model development (Bassett Jr. et al., 2012; de Almeida Mendes et al., 2018). However, the generalization performance of the ML models can be enhanced by using heterogeneous study samples in large training datasets involving a wide range of activities (Farrahi et al., 2020).

## **2.4 Associations of sedentary behavior with cardiometabolic health**

An extensive literature has shown that SB and prolonged SB bouts are unfavorably associated with cardiometabolic health (Bellettiere et al., 2019; Benatti et al., 2015; Brocklebank et al., 2015; Carson et al., 2014; Cavallo et al., 2022; Henson et al., 2013; Patterson et al., 2018; Sjöros et al., 2020; Vaara et al., 2022; Vasankari et al., 2017). Traditionally, SB and prolonged sedentary bouts have been thought to have independent associations with cardiometabolic health despite the amount of PA (Brocklebank et al., 2015; Healy et al., 2008; Matthews et al., 2012b; Owen et al., 2010). However, recent research has recognized that daily PAs and SBs are interrelated (Rosenberger et al., 2019), and associations of SB with cardiometabolic health may be modified by PA (Cavallo et al., 2022; Ekelund et al., 2016; Huang et al., 2021; Stamatakis et al., 2019b)

### **2.4.1 Independent associations**

Several free-living studies have found that total sedentary time and prolonged SB bouts are associated with poorer glucose metabolism independently of MVPA (Biswas et al., 2015; Brocklebank et al., 2015; Carson et al., 2014; Healy et al., 2008). In addition, it has been proposed that independently of total sedentary time and mean intensity of breaks, regular breaks in SB attenuate metabolic risk in adults (Healy et al., 2008). In free-living studies, independent associations have mostly been found using single activity statistical models that do not account for the fact that sedentary and physical activity behaviors form a continuum, and an increase in one behavior causes a decrease in other behaviors (Healy et al., 2008; Matthews et al., 2012b; Owen et al., 2010; Rosenberger et al., 2019). For instance, regression analysis can be done using different models, such as single activity, partition, and isotemporal models. The free-living observational studies using different linear regression models have shown that independent associations of SB with cardiometabolic health markers can be found using partition modeling. Still,

interdependent associations can also be found using isotemporal modeling (Healy et al., 2015).

In experimental studies studying the acute effects of breaking up SB, uninterrupted SB has also been associated with impaired glucose metabolism independently of the subject's PA level (Saunders et al., 2018; Stephens et al., 2011). One day of SB considerably reduced insulin action, whereas limiting SB by participating in daily LPA had a favorable effect on insulin action (Stephens et al., 2011). Interrupting prolonged SB with short bouts of LPA or MPA improved glucose metabolism in obese adults (Dunstan et al., 2012). In addition, interrupting SB every 15 minutes rather than every 30 minutes or 60 minutes with light-intensity walking may provide more favorable effects on glucose metabolism (Paing et al., 2019). Although experimental studies have provided considerable evidence about the favorable effects of breaking up prolonged SB on cardiometabolic health, PA type, intensity, and frequency counteract SB (Benatti et al., 2015). Currently, the evidence about the independent effects of SB is scarce, and the subject's habitual PA level and acute changes in PA may modify the associations of SB with cardiometabolic health (Benatti et al., 2015).

#### ***2.4.2 Interrelation with physical activity***

The recent research has shown that PA may modify associations of SB with cardiometabolic health and independent associations of SB have been questioned (Cavallo et al., 2022; Ekelund et al., 2016; Rosenberger et al., 2019; Stamatakis et al., 2019b). Previous studies have examined the associations between sedentary time and cardiometabolic health at different MVPA levels, and high sedentary time has been shown to be the most adversely associated with cardiometabolic biomarkers when combined with a low MVPA level (Ekelund et al., 2016; Huang et al., 2021; Stamatakis et al., 2019b). Health risks related to high volumes of SB can be attenuated by increasing MVPA, especially among the least physically active adults (Matthews et al., 2015; Mossavar-Rahmani et al., 2020; Stamatakis et al., 2019b; von Rosen et al., 2020). In addition, the importance of LPA on cardiometabolic health has been noted (Chastin et al., 2019; Healy et al., 2015; Länsitie et al., 2021; Swindell et al., 2018). It has been proposed that substituting SB with light-intensity walking and standing could have even more positive effects on insulin and lipid levels than one hour of daily VPA (Duvivier et al., 2013).

More advanced statistical analysis methods, such as traditional isotemporal substitution modeling (Mekary et al., 2009) and compositional data analysis

(Dumuid et al., 2018), have enabled investigating time reallocations between different sedentary and physical activity behaviors. Recent research has shown that SB and PA form a continuum, and an increase in one behavior causes decreases in another (Rosenberger et al., 2019; Dumuid et al., 2019; Mekary et al., 2009). In practice, a decrease in SB needs to be done by increasing PA unless SB is replaced by sleep. (Biddle et al., 2021). The previous studies using traditional isotemporal substitution modeling or compositional data analysis have consistently found that replacing SB with any intensity PA is favorably associated with cardiometabolic health (Cavallo et al., 2022; Del Pozo-Cruz et al., 2018; Farrahi et al., 2021b; Galmes-Panades et al., 2019; Grgic et al., 2018; Healy et al., 2015; Yates et al., 2015). However, a more positive health effect may be achieved when SB is replaced with MVPA compared to LPA (Chastin et al., 2015; Farrahi et al., 2021b).

In addition, previous studies have observed a significant interrelation between free-living sedentary bout duration and total sedentary time (Diaz et al., 2017; Hibbing et al., 2022). A recent systematic review reported that adults with more time spent in prolonged sedentary bouts also have more sedentary time overall than adults with interrupted sedentary profiles (Hibbing et al., 2022). A recent observational study investigated sedentary profiles and showed that profiles with high total sedentary time or with high sedentary bout duration have no different associations with cardiometabolic biomarkers (Farrahi et al., 2021a). In addition, total sedentary time and prolonged sedentary bouts seem to be jointly associated with glucose metabolism (Diaz et al., 2017). Consequently, there is no definite evidence whether the prolonged bouts of SB independently of total sedentary time are associated with cardiometabolic health.

Previous long-term experimental studies have shown that an increase in PA and a decrease in SB combined positively affect cardiometabolic health (Kozey-Keadle et al., 2014; Sjöros et al., 2022). However, separately reducing SB or increasing MVPA showed no changes in insulin action (Kozey-Keadle et al., 2014). It is still unclear how daily sedentary and physical activity behaviors should be distributed to improve cardiometabolic health. More studies using advanced data analysis methods are needed, especially to investigate time reallocations from prolonged SB bouts to short SB bouts.

### **3 Aims of the study**

Physical inactivity and a sedentary lifestyle are global public health problems. Although the guidelines for health-enhancing PA are well-established, accurate recommendations for breaking up sedentary behavior are still missing. There is a need for studies that examine the associations between cardiometabolic health and the accelerometry-based patterns of sedentary and physical activity behaviors in free-living conditions.

This study aimed to develop a method for measuring accumulation patterns of sedentary behavior and sitting separately in free-living conditions and investigating associations between sedentary behavior characteristics and cardiometabolic health in middle-aged Finnish adults. The specific aims of this study were:

1. To develop and validate a machine learning-based method for classifying physical activity and sedentary behavior data among Finnish adults.
2. To determine the characteristics of overall sedentary behavior and sitting among middle-aged Finnish adults using raw data from a hip-worn triaxial accelerometer and a novel machine learning-based signal processing method.
3. To investigate the associations of patterns of accelerometry-based overall SB and sitting in different MVPA categories with serum lipid biomarkers.
4. To study time reallocations from sedentary behavior and prolonged sedentary bouts to LPA, MVPA, and short sedentary bouts and their associations with glucose metabolism.



## 4 Materials and methods

### 4.1 Study design

This thesis consists of four sub-studies utilizing three datasets. Sub-study I developed and validated a machine learning model of physical activity and sedentary behavior. Sub-study II was a pilot study of the 46-year data collection of the Northern Finland Birth Cohort 1966 (NFBC1966) (University of Oulu, 1966). Sub-studies III–IV consisted of the 46-year follow-up data collection of the NFBC1966 study. A summary of the participants, study setup, and methods used in each sub-study is presented in Table 1.

All participants were volunteers who had the right to decline to participate in or withdraw from the study. The participants were given oral and written information about the study and asked to provide written consent to participate. All sub-studies followed the ethical principles for medical research involving human participants in Finland and the Declaration of Helsinki. Personal identity information was replaced with identification codes. The sub-studies II–IV were approved by the Ethical Committee of the Northern Ostrobothnia Hospital District in Oulu, Finland (94/2011).

**Table 1. Study setup, participants, and methods in sub-studies I–IV.**

Sub-study	Study setup	Study sample	Measurements
I	Development and validation of machine learning model for PA and SB	Working-aged adults (n = 22)	Laboratory-based accelerometry, indirect calorimetry, direct observation
II	Accelerometer-based characteristics of overall SB and sitting	A pilot study of the 46-year follow-up of the NFBC1966 study (n = 36)	Free-living accelerometry, anthropometric measurements
III	Cross-sectional associations between patterns of SB and sitting with cardiometabolic health by MVPA category	46-year follow-up study of the NFBC1966 (n = 3,272)	Free-living accelerometry, health and lifestyle questionnaires, clinical examinations
IV	Time reallocations from SB and prolonged SB bouts to LPA and MVPA and their cross-sectional associations with glucose metabolism	46-year follow-up study of the NFBC1966 (n = 2,991)	Free-living accelerometry, health and lifestyle questionnaires, clinical examinations

Abbreviations: PA = physical activity, SB = sedentary behavior, MVPA = moderate-to-vigorous physical activity, LPA = light physical activity, NFBC1966 = the Northern Finland Birth Cohort 1966.

#### **4.1.1 Development and validation study (I)**

The participants of sub-study I were 22 working-age (17–58 years old) healthy volunteers living in Finland. They participated in laboratory-based PA and SB measurements in 2016. Before measurements, the participants abstained from unaccustomed strenuous activity or exercise and alcohol for 24 hours. The gender and age of the participants were inquired about through a questionnaire, and height and body mass was measured prior to measurements. Body mass index (BMI) was calculated by dividing weight in kilograms by height in meters squared from the measured height and weight data. The demographic characteristics of the participants are presented in Table 2.

**Table 2. Demographic characteristics of the participants. Modified from publication I with permission of Springer Nature.**

Variable	Women (n = 11)	Men (n = 11)	Total (n = 22)
Age (years)	26.0 (11.3)	29.0 (11.6)	27.5 (11.2)
Height (cm)	165.8 (3.2)	180.1 (3.5)	173.0 (8.0)
Weight (kg)	66.8 (8.2)	84.5 (6.7)	75.7 (11.7)
BMI (kg/m <sup>2</sup> )	24.2 (2.4)	26.0 (1.6)	25.1 (2.2)

Values are mean (SD). BMI = body mass index.

#### **4.1.2 Northern Finland Birth Cohort 1966 studies (II-IV)**

Initially, the NFBC1966 study included all newborns in the two northernmost provinces in Finland whose expected date of birth was in the year 1966 (n = 12,058 live births). Information about the study participants' health condition, social-economic status, and lifestyle has been recorded regularly through healthcare records, questionnaires, and clinical examinations. The most recent follow-up was conducted in the years 2012–2014, when the participants were approximately 46 years old.

##### ***NFBC1966 pilot (II)***

The 46-year data collection of the NFBC1966 study was piloted in 2012. The study participants of the NFBC1966 pilot study (II) were volunteers 47–49 years old from the city of Oulu and neighboring municipalities (Leinonen et al., 2017). In total, 150 study participants were selected randomly from the national population register and invited to participate in the pilot study. Of these adults, 41 participants agreed



to participate in the baseline visit and free-living PA and SB measurements. In the baseline visit, participants' height and weight were measured, and the accelerometers were given to the participants. The descriptive characteristics of the participants are shown in Table 3.

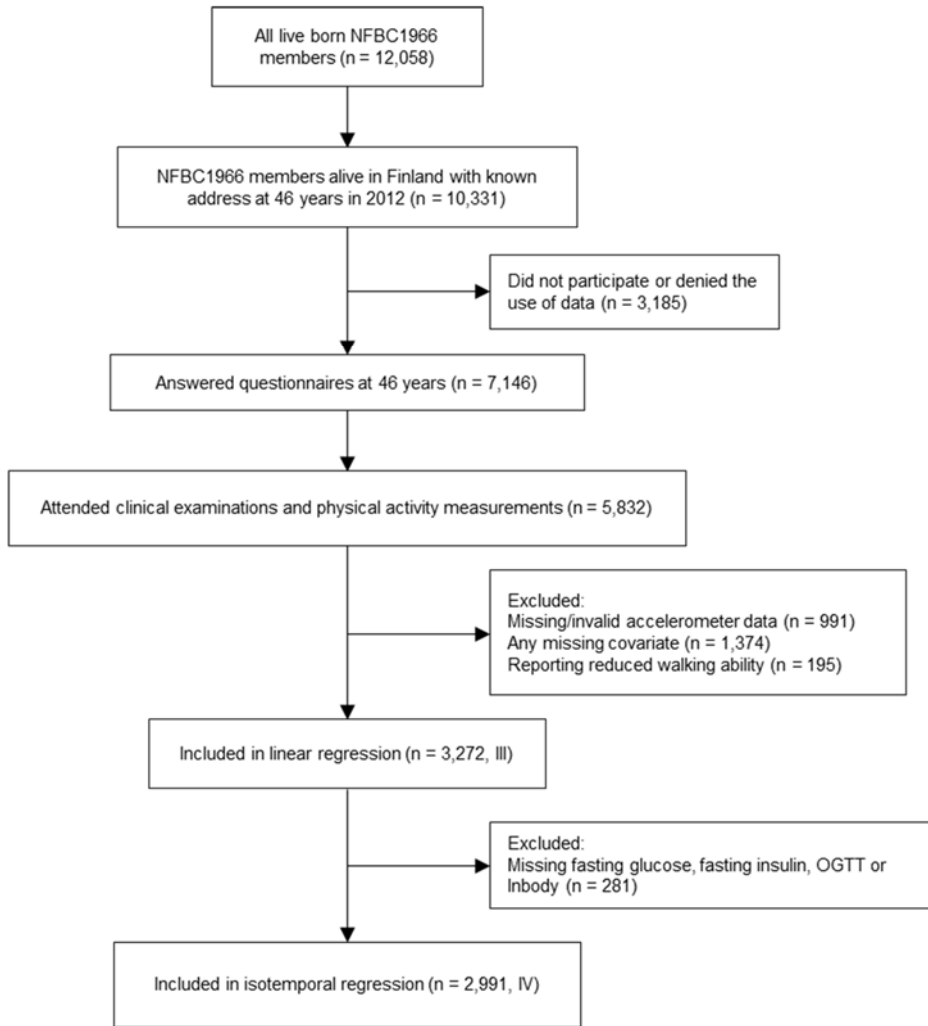
**Table 3. Descriptive characteristics of the participants. Modified from publication II with permission of Informa UK Limited, trading as Taylor & Taylor & Francis Group.**

Variable	Women (n = 24)	Men (n = 12)	Total (n = 36)
Age (years)	47.5 (0.6)	47.8 (0.7)	47.6 (0.6)
Height (cm)	163.2 (6.9)	177.7 (5.8)	168.0 (9.5)
Weight (kg)	72.6 (13.9)	80.1 (10.5)	75.1 (13.3)
BMI (kg/m <sup>2</sup> )	27.2 (4.8)	25.4 (3.0)	26.6 (4.3)

Values are mean (SD). BMI = body mass index.

### *NFBC1966 study (III–IV)*

The study population of the sub-studies III–IV is the 46-year follow-up of the NFBC1966 study (Nordström et al., 2021). The living cohort members in Finland were invited for the follow-up during 2012–2014 (n = 10,331). The data collection included health- and lifestyle-related questionnaires, clinical examinations, and PA and SB free-living measurements (Figure 3).



**Fig. 3. Flowchart of the sub-studies III–IV.**

## 4.2 Methods

### 4.2.1 Physical activity and sedentary behavior measurements (I–IV)

#### *Protocol for development and validation study (I)*

The study protocol included a predefined set of nine controlled and supervised typical daily free-living activities (hanging out on a sofa, sitting at a computer, standing/poster viewing, wiping and setting up the kitchen table, floor cleaning, slow walking, fast walking, soccer passing drills, and jogging). Activities ranged in intensity from sedentary to vigorous and were performed for four minutes each, with a 0.5–4 minute resting period between activities depending on the intensity of the previous activity. Fast walking, soccer, and jogging were conducted on an outdoor track, and the rest were conducted indoors. Fast walking and jogging were performed at a self-selected speed. A trained supervisor controlled the measurements to be conducted according to the predefined study protocol. The participants were instructed orally during the measurements and were not allowed to speak during activities. The participants performed activities wearing a hip-worn triaxial accelerometer (Hookie AM20, Traxmeet Ltd, Espoo, Finland) and an indirect calorimetry device (COSMED K4 b2, Cosmed Ltd, Rome, Italy), which was worn as a vest with a rubber facemask. A Hookie AM20 -accelerometer was worn on the participant's right hip on an elastic belt, and acceleration data were collected in raw mode at 100 Hz with a range of  $\pm 16g$ .

#### *Physical activity and sedentary behavior measurements in NFBC1966 pilot (II) and NFBC1966 study (III–IV)*

Physical activity and sedentary behavior measurements were performed similarly in the NFBC1966 pilot (II) and the NFBC1966 study (III–IV) in 2012 and 2012–2014, respectively. The participants who attended the baseline visit were invited to participate in PA and SB measurements and wear a triaxial accelerometer (Hookie AM20) for 14 consecutive days during all waking hours except during water-related activities. The accelerometers and prepaid-postage padded envelopes for returning the monitors, were given to the participants during the baseline visit. The participants were asked to wear the accelerometer for at least 14 days with an elastic belt on the right posterior side of the hip. Raw triaxial acceleration signals were

collected at a sampling frequency of 100 Hz with a range of  $\pm 16g$ . The accelerometer was used as a datalogger and did not provide feedback to the participants. The criterion for the valid measurements was using the accelerometer for at least four days, including a wear time of at least 600 minutes per day which is a commonly used criterion (Arvidsson et al., 2019).

#### **4.2.2 Questionnaires (III–IV)**

The participants of the NFBC1966 studies (III–IV) filled out postal questionnaires about their health condition, socioeconomic background, lifestyle, and work (Nordström et al., 2021; University of Oulu, 1966). Inquiries were made about their employment, education, marital status, and prevalence of diagnosed diseases and medication. Information about smoking habits was recorded using many questions, and smoking status was dichotomized (current smoker and non-smoker or former smoker). Drinking habits were inquired about using beverage-specific questions on the usual frequencies of consumption and amounts of beer, wine, and spirits per drinking occasion. The average volume of ethanol consumed per day was calculated. The threshold values for heavy users of alcohol were set at  $\geq 40$  g/day for men and  $\geq 20$  g/day for women.

A question about mobility from the 15D instrument was used to determine the participants' ability to walk (Sintonen, 2001). The question included five alternative responses, which were "I am able to walk normally (without difficulties) indoors, outdoors, and on the stairs," "I am able to walk without difficulty indoors, but outdoors and on the stairs, I have slight difficulties," "I am able to walk without help indoors (with or without a device) but outdoors and on the stairs only with considerable difficulty or with help from others," "I am able to walk indoors only with help from others," and "I am completely bedridden and unable to move about." The participants were asked to select one alternative which best describes their current health condition. The normal ability to walk was used as a criterion for inclusion.

#### **4.2.3 Clinical examinations (III–IV)**

The NFBC1966 studies (III–IV) included clinical examinations conducted by a trained study nurse (Nordström et al., 2021; University of Oulu, 1966). The participants' height, weight, and waist circumference from the midway point between the iliac crest and the lowest ribs were measured. The waist circumference

was divided into three equal-sized groups using tertiles as cut points for men and women. The participants' visceral fat area and skeletal muscle mass were measured using the bioelectrical impedance measurement device Inbody 720 (Inbody Co., Ltd., Seoul, Korea).

Venous blood samples were collected after overnight fasting (at least 12 hours) and abstaining from drinking coffee and smoking on the clinical examination day. Total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides, fasting plasma glucose, and fasting serum insulin were analyzed from the collected fasting blood samples as previously described elsewhere (Kiviniemi et al., 2017). On a different day, the participants who were not diagnosed with diabetes and whose fasting glucose was  $< 8.0$  mmol/l measured with a quick test participated in a standardized 75 g oral glucose tolerance test (OGTT) with 0-, 30-, 60-, 90-, and 120-minutes measurement points after overnight fasting (WHO, 2006).

Total cholesterol to high-density lipoprotein (Total/HDL) and low-density lipoprotein to high-density lipoprotein (LDL/HDL) ratios were calculated from the fasting samples to obtain stronger predictors for CVD risk than the isolated lipid biomarkers (Millán et al., 2009; Prospective Studies Collaboration et al., 2007). The serum lipid and lipoprotein biomarkers were dichotomized using the threshold values from the Finnish Current Care Guidelines: triglycerides  $< 1.7$  mmol/l, total cholesterol  $< 5.0$  mmol/l, LDL cholesterol  $< 3.0$  mmol/l, HDL cholesterol for men  $> 1.0$  mmol/l and women  $> 1.2$  mmol/l, total/HDL cholesterol ratio  $< 4$ , and LDL/HDL cholesterol ratio  $< 3$ . Beta-cell function (HOMA-B) and insulin resistance (HOMA-IR) were calculated from the fasting glucose and insulin levels (Matthews et al., 1985; Wallace et al., 2004). The Matsuda index was calculated from the glucose and insulin levels during OGTT with 0-, 30-, 60-, and 120-minute measurement points to obtain insulin sensitivity (Matsuda et al., 1999). The participants were classified for impaired fasting glucose (IFG), impaired glucose tolerance (IGT), and diabetes based on the WHO's recommended threshold values of fasting glucose 6.1–6.9 mmol/l, and 2-h glucose  $< 7.8$  mmol/l for IFG, fasting glucose  $< 7.0$  mmol/l and 2-h glucose 7.8–10.9 mmol/l for IGT, and fasting glucose  $\geq 7.0$  mmol/l or 2-h glucose  $\geq 11.1$  mmol/l for diabetes (WHO, 2006). If the participant was identified for both IGT and IFG, the participant was assigned to the IGT group.

### 4.3 Accelerometer data analysis

#### 4.3.1 Development and validation for machine learning model of physical activity and sedentary behavior (I)

The raw triaxial acceleration data of Hookie AM20 from the nine daily activities were used for developing and validating a machine learning-based prediction model for the classification of PAs and SBs. The data processing was conducted using MATLAB R2016b (The MathWorks, Inc).

The raw acceleration data were transformed into g-units, and the resultant acceleration  $r_i$  was calculated from triaxial acceleration data as follows:  $r_i = \sqrt{acc_x^2 + acc_y^2 + acc_z^2}$  where  $acc_x$  is medio-lateral acceleration (m/s<sup>2</sup>),  $acc_y$  is vertical acceleration, and  $acc_z$  is anterior-posterior acceleration. The acceleration signals were filtered with a 4th-order Butterworth lowpass filter with a cut-off frequency of 20 Hz to filter high-frequency noise from human movement. The resultant acceleration was filtered with a 4th-order Butterworth highpass filter with a cut-off frequency of 0.5 Hz to eliminate the influence of gravity from the signal. The acceleration signals were windowed with a 5 s window size and 2.5 s slide between two adjacent windows.

PA and SB classifications were performed using five different supervised ML classifiers (bagged trees, boosted trees, k nearest neighbors, support vector machines, and linear discriminant analysis), and in total, 21 features (mean, minimum, maximum, zero crossing rate, peak-to-peak amplitude, and MAD (Vähä-Ypyä et al., 2015), extracted in all three axes, and the resultant acceleration except MAD that was extracted only in the resultant acceleration). Direct observation and indirect calorimetry were used as a criterion measures for PA classifications. Based on the movement patterns and METs of activities, the activities were classified into five activity and sedentary behavior classes: lying down (lying on a sofa), sitting (sitting at a computer), LPA (standing/poster viewing, table wiping, floor cleaning, and slow walking), MPA (fast walking), and VPA (soccer and jogging).

Leave-one-subject-out cross-validation was used to validate the prediction models to receive user-independent results and find the most accurate classifier. In brief, each ML model was trained using the accelerometer data from other subjects except one subject whose data was used as test data for validation. The procedure was repeated so many times that the accelerometer data of each subject was used as test data. Total accuracy for models was obtained from confusion matrix by

dividing the number of correct predictions by the total number of predictions. Sensitivity was obtained as the true positive rate and specificity as true negative rate for each classes.

The mean value of MET for each activity was calculated from the steady-state data collected with indirect calorimetry to ensure that activity and sedentary behavior classes align somewhat with the Compendium of Physical Activities (Ainsworth et al., 2000; Ainsworth et al., 2011). The breath-by-breath oxygen consumption data of 12 participants were filtered with a 15 s average filter using the K4 b2 software and transformed to METs using the standard conversion of  $1 \text{ MET} = 3.5 \text{ ml O}_2/\text{min}/\text{kg}$ .

#### **4.3.2 Data analysis in NFBC1966 studies (II–IV)**

The data analysis was performed using MATLAB R2016b (The MathWorks, Inc). Initially, wear time was recognized from the raw acceleration signals by removing non-wear periods, defined as at least 30 minutes of consecutive zero values. One-minute periods from the beginning and the end of the wear time acceleration signals were removed to eliminate the noise caused by dressing and undressing the accelerometer. Light, moderate, and vigorous PA, lying down, and sitting were recognized from the steady-state acceleration signals using the ML model developed in sub-study I. Wear time was limited to a maximum of 20 hours/day to eliminate the error from participants who may have used the accelerometer during sleeping at night. The exceeding wear time was removed from the lying down time. Lying down and sitting bouts were observed from the classified accelerometer data and combined to form SB bouts. A sedentary bout was defined as a minimum of 30 seconds of continuous lying down or sitting with  $EE \leq 1.5$  METs. A break in SB was defined as a PA bout at any intensity with a minimum of 30 seconds between two successive SB bouts. In addition, sitting bouts were analyzed separately and defined as a minimum of 30 seconds of continuous sitting. Several patterns of SB were observed from the extracted sedentary and sitting bouts separately since they are the commonly studied sedentary behaviors. Moderate and vigorous PA were summed up to form MVPA. The analyzed SB, sitting, and PA variables in each sub-study are presented in Table 4.

**Table 4. Physical activity, sedentary behavior, and sitting pattern variables (II–IV).**

Variable	Definition	Sub-study
Wear time (min/d)	The total wear time of the accelerometer per day	II, III, IV
Sedentary behavior and sitting		
Total time (min/d)	Total SB/sitting time per day	II, III, IV
Median bout length (min)	The median length of SB/sitting bouts per day	II
50% median bout length (min)	Length of SB/sitting bout corresponding to half of the daily cumulatively accumulated SB/sitting time when bouts are ordered from the shortest to the longest	II
Maximum bout length (min)	The maximum length of sedentary/sitting bouts per day	II
Number of bouts (bouts/d)	Total number of SB/sitting bouts per day	II
Fragmentation index (number of bouts/h)	The number of sedentary/sitting bouts divided by total hours spent in SB/sitting per day	II
Fraction of the SB/sitting time accumulated in bouts longer than the median bout (%)	Time spent in SB/sitting bouts longer than the median bout divided by total SB/sitting time per day	II
Number of SB/sitting bouts of < 15, 15–29.99, 30–59.99, 60–119.99, and ≥ 120 minutes (number of bouts/d)	Number of SB/sitting bouts per day of < 15, 15–29.99, 30–59.99, 60–119.99, and ≥ 120 minutes	II, III, IV
Total time in SB/sitting bouts of < 15, 15–29.99, 30–59.99, 60–119.99, and ≥ 120 minutes (min/d)	Total time per day accumulated in SB/sitting bouts of < 15, 15–29.99, 30–59.99, 60–119.99, and ≥ 120 minutes	II, III, IV
Breaks in sedentary behavior		
Median break length (min)	The median length of sedentary breaks per day	II
Number of breaks ≥ 1 minute (breaks/d)	Number of at least 1-minute sedentary breaks per day	II
Physical activity		
LPA (min/d)	Total LPA time per day	III, IV
VPA (min/d)	Total VPA time per day	III
MVPA (min/d)	Total MVPA time per day	III, IV

Abbreviations: SB = sedentary behavior, LPA = light physical activity, MPA = moderate physical activity, VPA = vigorous physical activity, MVPA = moderate-to-vigorous physical activity.

#### 4.4 Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics for Windows (IBM Corp., Armonk, USA), version 24.0 (II) or version 25.0 (III–IV). The descriptive characteristics of the participants were presented for categorical variables in counts and proportions, for normally distributed continuous variables



in means and standard deviations (SD), and for skewed continuous variables in medians and 25<sup>th</sup> and 75<sup>th</sup> percentiles or interquartile ranges (IQR). The statistical significance was set to  $p < 0.05$ .

#### **4.4.1 Characteristics of sedentary behavior and sitting (II)**

The average and median values of the SB and sitting pattern variables were calculated through the personal median values of the participants. Statistical differences between men and women were examined using an independent samples t-test (normal distribution) or a Mann-Whitney U-test (non-normal distribution). Histograms were created to describe the mean number of and total time in SB and sitting bouts per day of  $< 15$ ,  $15-29.99$ ,  $30-59.99$ ,  $60-119.99$ , and  $\geq 120$  minutes with 95% confidence intervals (95% CI).

#### **4.4.2 Associations of sedentary behavior and sitting patterns with serum lipid biomarkers (III) and glucose metabolism (IV)**

The NFBC1966 46-year follow-up study participants with valid data from questionnaires, clinical examinations, and PA and SB measurements, and reporting normal walking ability were included in the statistical analyses. For finding a possible interaction between SB and MVPA, the participants were grouped into three categories based on their measured MVPA level: *low activity* (total MVPA time  $< 150$  min/week and total VPA time  $< 75$  min/week), *moderate activity* (total MVPA time =  $150-300$  min/week and total VPA time  $< 150$  min/week or total MVPA time  $< 300$  min/week and total VPA time =  $75-150$  min/week), and *high activity* (total MVPA time  $> 300$  min/week or total VPA time  $> 150$  min/week).

Univariate associations between continuous variables and MVPA categories (III) were analyzed using analysis of variance (ANOVA) with Tukey's post hoc test for normally distributed data or the Kruskal-Wallis test with the Mann-Whitney U-test pairwise comparison for skewed data. Likewise, univariate associations between continuous variables and sexes (IV) were analyzed using the Mann-Whitney U-test for skewed data. For analyzing differences in categorical variables between MVPA categories (III) or sexes (IV), the chi-square ( $\chi^2$ ) test and Z-test with Bonferroni correction for post hoc were used. All serum lipid and glucose metabolism biomarkers and PA and SB variables with non-Gaussian distribution were natural log-transformed prior to regression analyses to obtain a normal distribution. MVPA time and time spent in SB and sitting bouts of  $\geq 30$  minutes

had several zero values, which were eliminated before natural log transformation by adding a constant value of 1.

Multivariable linear regression analyses were conducted between SB and sitting variables and serum lipid biomarkers for the whole study population and in each MVPA category separately (III). The analyzed SB and sitting variables were total SB time (min/day), time spent in SB bouts of 15–29.99 and  $\geq 30$  minutes (min/day), total sitting time (min/day), and time spent in sitting bouts of 15–29.99 minutes (min/day). The linear regression analyses were performed using five models, each including one SB or sitting variable. The linear regression models were adjusted for potential confounders, including sex, education (no professional education, vocational/college level education, university/polytechnic degree), employment status (employed/unemployed/studying/other), marital status (married/cohabiting, divorced/widowed, unmarried), smoking status (non-smoker/current smoker), heavy alcohol consumption (men  $\geq 40$ g/day, women  $\geq 20$  g/day), abdominal obesity (men  $> 102$  cm, women  $> 88$  cm), diagnosis or medication for diabetes or CVD (coronary artery disease, heart failure, myocardial infarction, stroke), accelerometer wear time (min/day), and MVPA (min/day). SB variables that were most significantly associated with serum lipid and lipoprotein levels were entered into receiver operating characteristic (ROC) analyses with dichotomized serum lipids and lipoproteins to determine the threshold values of the SB and sitting variables.

Multivariable associations between SB variables and biomarkers of glucose metabolism were performed using the enter method in linear regression analysis (IV). The analyzed SB variables were total SB time (min/day) and time spent in SB bouts of  $\geq 30$  minutes (min/day). The linear regression models were adjusted for the most significant confounders, including sex, waist circumference in tertiles, accelerometer wear time (min/day), and MVPA (min/day). SB variables, LPA, MVPA, and covariates had a linear relationship with serum lipid and glucose metabolism biomarkers. They had no significant autocorrelation (Durbin–Watson statistics  $1.5 < d < 2.5$ ), multicollinearity (variance inflation factor  $< 5$ ), or heteroscedasticity based on the variance and distribution of residuals.

#### ***4.4.3 Associations of isothermal substitution of sedentary behavior with glucose metabolism (IV)***

Isothermal substitution regression modeling was used to analyze hypothetical time reallocations from SB to LPA or MVPA and from sedentary bouts  $\geq 30$  minutes

to sedentary bouts < 15 minutes, LPA, or MVPA (Mekary et al., 2009). In traditional isotemporal substitution modeling, wear time and all activity behaviors (minutes/day) except the activity that is replaced are entered in the linear regression model. Time reallocations were performed by dividing the activities in minutes by the amount of time replaced and dropping SB or time spent in sedentary bouts  $\geq 30$  minutes out of the model. The non-standardised regression coefficient of the activity represents the estimated change in the outcome variable when that activity replaces the activity excluded from the model. Two models were created, one including wear time, LPA, and MVPA and another including wear time, LPA, MVPA, and sedentary bouts of < 15 minutes and 15-29.99 minutes. The substituted amounts of time for replacing SB and sedentary bouts  $\geq 30$  minutes with LPA or MVPA were 15, 30, 45, and 60 minutes/day and for replacing sedentary bouts  $\geq 30$  minutes with sedentary bouts < 15 minutes were 30, 60, 90, and 120 minutes/day, respectively. The confounding variables in the isotemporal substitution modeling were sex and waist circumference in tertiles.



## 5 Results

### 5.1 Physical activity and sedentary behavior classification using machine learning method (I)

The performance of the prediction models is presented in more detail in sub-study I. In brief, the bagged trees prediction model provided the best results (total accuracy of 96.5%) and was chosen to be used in the final classification process. The specificity and sensitivity of the bagged trees classifier for each activity are presented in Table 5. The mean sensitivity for the model was 95.5%, and the mean specificity was 99.1%. For MVPA, the mean sensitivity was 95.3% and specificity 99.0%. PA classification and METs of different activities are shown in Table 6.

**Table 5. Sensitivity and specificity for detecting physical activity and sedentary behavior. Modified from publication I with permission of Springer Nature.**

Physical activity classification	Sensitivity (%)	Specificity (%)
Lying down	96.4	99.2
Sitting	92.2	99.2
LPA	98.5	99.0
MPA	91.5	99.7
VPA	99.0	98.3

Abbreviations: LPA = light physical activity, MPA = moderate physical activity, and VPA = vigorous physical activity.

**Table 6. Physical activity classification and metabolic equivalents. Modified from publication I with permission of Springer Nature.**

Physical activity classification	Activity	METs	
		Mean	SD
Lying down	Lying on a sofa	-	-
Sitting	Sitting at a computer	1.23	0.16
LPA	Standing/poster viewing	1.51	0.11
	Table wiping	2.85	0.37
	Floor cleaning	3.25	0.37
	Slow walking	2.25	0.26
MPA	Fast walking	5.02	0.54
VPA	Soccer	6.42	1.27
	Jogging	7.53	1.05

Abbreviations: LPA = light physical activity, MET = metabolic equivalent of task, MPA = moderate physical activity, and VPA = vigorous physical activity.

## 5.2 Characteristics of sedentary behavior and sitting (II)

In total, 36 (87.8%) participants wore the accelerometer for at least four days, including at least 600 minutes of wear time per day. The median number of valid days was 13 (IQR 1), and the median wear time of the accelerometer was 804.3 min/d (IQR 116.6). The participants spent 557.6 min/day (69.3%) of waking time in SB, of which 290.8 min/day (52.2%) was performed in a sitting posture (Table 7).

**Table 7. Characteristics of sedentary behavior and sitting among the study participants (n = 36). Modified from publication II with permission of Informa UK Limited, trading as Taylor & Taylor & Francis Group.**

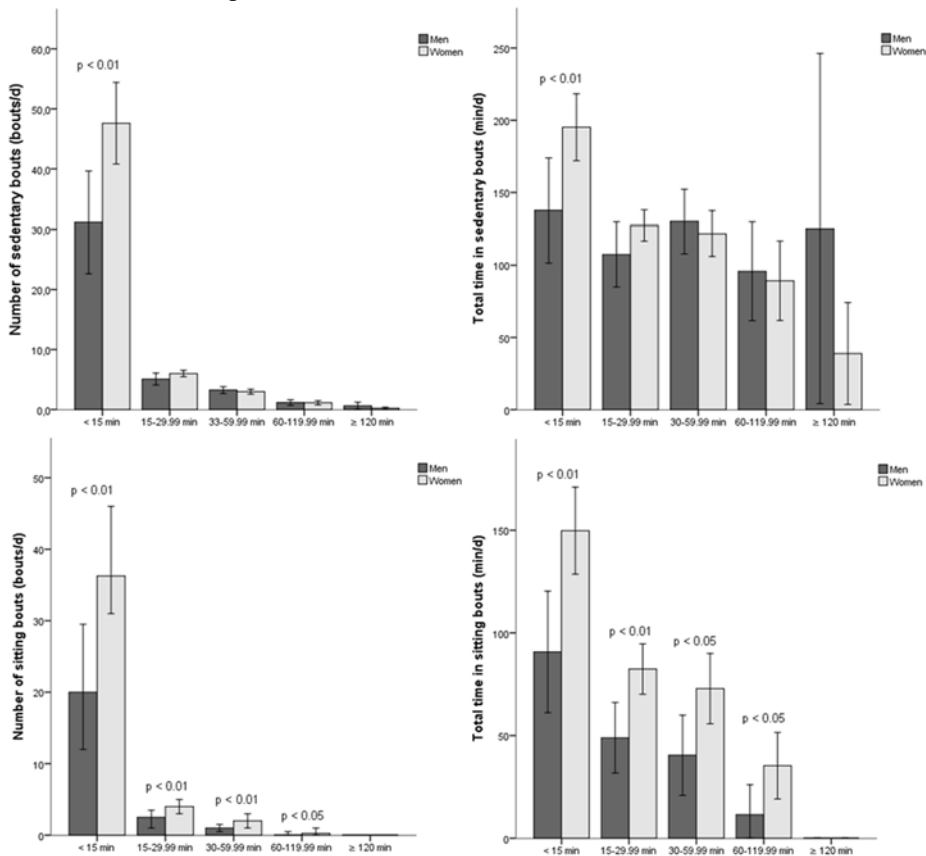
Variable	Women (n = 24)	Men (n = 12)	p-value	All (n = 36)
<b>Sedentary behavior</b>				
Total time (min/d)	537.0 [146.9]	592.0 [125.7]	0.37 <sup>a</sup>	557.6 [143.3]
Median bout length (min)	4.3 [1.5]	5.6 [2.7]	< 0.05 <sup>a</sup>	4.4 [2.1]
50% median bout length (min)	26.4 [12.9]	39.5 [44.9]	< 0.05 <sup>a</sup>	28.9 [22.6]
Number of bouts (bouts/d)	78.8 [50.1]	90.0 [110.0]	0.09 <sup>a</sup>	82.2 [57.0]
Maximum bout length (min)	58.6 (15.2)	42.0 (14.2)	< 0.01 <sup>b</sup>	53.0 (16.7)
Fragmentation index (number of bouts/h)	6.1 (2.3)	4.1 (1.8)	< 0.05 <sup>b</sup>	5.4 (2.3)
Fraction of daily SB time accumulated in bouts > median bout (%)	90.0 [2.5]	91.0 [3.2]	0.30 <sup>a</sup>	90.7 [2.8]
<b>Sitting</b>				
Total time (min/d)	340.4 (112.7)	191.5 (93.9)	< 0.001 <sup>b</sup>	290.8 (127.2)
Median bout length (min)	3.7 [1.6]	3.9 [2.1]	0.62 <sup>a</sup>	3.8 [1.7]
50% median bout length (min)	17.3 [9.4]	18.8 [13.8]	0.92 <sup>a</sup>	17.4 [9.9]
Maximum bout length (min)	58.1 [24.7]	44.0 [27.2]	0.27 <sup>a</sup>	49.4 [25.0]
Number of bouts (bouts/d)	44.1 (15.6)	25.7 (12.2)	< 0.001 <sup>b</sup>	37.9 (16.8)
Fragmentation index (number of bouts/h)	7.6 (2.5)	7.6 (2.4)	0.81 <sup>b</sup>	7.6 (2.5)
Fraction of daily sitting time accumulated in bouts > median bout (%)	88.6 [2.0]	88.0 [3.5]	0.55 <sup>a</sup>	88.4 [2.2]
<b>Breaks in sedentary behavior</b>				
Median break length (min)	2.4 [0.5]	2.5 [0.4]	0.64 <sup>a</sup>	2.4 [0.4]
Number of breaks ≥ 1 minute (breaks/d)	47.1 (14.0)	33.5 (12.4)	< 0.01 <sup>b</sup>	42.6 (14.8)

Abbreviations: SB = sedentary behavior, values are mean (SD) or median [IQR], <sup>a</sup> = Mann–Whitney U-test, <sup>b</sup> = Independent-Samples T-test.

A comparison of the characteristics of SB and sitting between the sexes showed no significant difference in the total amount of daily SB between men and women (592.0 vs. 537.0 min/day,  $p = 0.37$ ). However, women broke up their sedentary time

more often than men (6.1 vs. 4.1 breaks/hour,  $p < 0.05$ ). On average, women had 148.9 minutes more daily sitting ( $p < 0.001$ ) compared to men. However, sitting time was broken up as often in men and women (7.6 breaks/hour).

The number of and total time in a day spent in sedentary and sitting bouts  $< 15$ , 15–29.99, 30–59.99, 60–119.99, and  $\geq 120$  minutes among men and women are shown in Figure 4. Women had a significantly greater number of and total time in sedentary bouts  $< 15$  minutes and sitting bouts  $< 15$ , 15–29.99, 30–59.99, and 60–119.99 minutes compared to men.



**Fig. 4.** The number of (left) and the total time spent (right) in sedentary behavior (upper) and sitting (lower) bouts  $< 15$ , 15–29.99, 30–59.99, 60–119.99, and  $\geq 120$  minutes per day among men and women (II). Data are shown as means with error bars representing 95% CI. Significant differences between men and women are indicated with p-values.

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### 5.3 Associations of sedentary behavior and sitting patterns with serum lipid biomarkers (III) and glucose metabolism (IV)

#### *Characteristics of the participants*

Anthropometric, demographic, and behavioural characteristics of the study participants are presented in Table 8 (n = 3,272).

**Table 8. Characteristics of study participants (n = 3,272). Modified from publication III.**

Variable	All (n = 3,272)
Sex	
Men, n (%)	1,395 (42.6)
Women, n (%)	1,877 (57.4)
Height, cm	170.3 (163.9–177.7)
Weight, kg	75.6 (65.4–86.6)
BMI, kg/m <sup>2</sup>	
<18.5, n (%)	20 (0.6)
18.5–24.99, n (%)	1,372 (41.9)
25–29.99, n (%)	1,319 (40.3)
≥ 30, n (%)	561 (17.2)
Waist circumference, cm	89.5 (80.5–98.0)
Abdominal obesity, n (%)	1,047 (32.0)
Education	
No professional education, n (%)	171 (5.2)
Vocational/college level education, n (%)	2,062 (63.0)
Polytechnic/university degree, n (%)	1,039 (31.8)
Employment status	
Employed, n (%)	3,182 (97.2)
Unemployed, n (%)	28 (0.9)
Studying, n (%)	16 (0.5)
Other, n (%)	46 (1.4)
Smoking	
Nonsmoker, n (%)	2,708 (82.8)
Current smoker, n (%)	564 (17.2)
Alcohol consumption, g/d	4.6 (1.2–13.1)
Heavy user (men ≥ 40 g/d, women ≥ 20 g/d), n (%)	241 (7.4)
CVD or diabetes diagnosis or medication, n (%)	573 (17.5)

Values are median (25<sup>th</sup>–75<sup>th</sup> percentiles) unless otherwise stated. BMI = body mass index, CVD = cardiovascular disease (coronary artery disease, heart failure, myocardial infarction, stroke).



*Accelerometer-measured physical activity and sedentary behavior by physical activity categories (III)*

The mean accelerometer measurement period was 14 days, and the median wear time was 903.4 (25<sup>th</sup>–75<sup>th</sup> percentiles 859.3–945.5) min/day. The mean accelerometer-measured PA, SB, and sitting variables by MVPA categories are presented in Table 9. Daily sedentary time and time spent in sedentary bouts  $\geq 30$  minutes were greater in the low-activity category compared to the moderate or high-activity categories ( $p < 0.001$ ). However, the participants in the high-activity category had more daily sitting time and time spent in sitting bouts  $\leq 30$  minutes than those in the low or moderate-activity categories ( $p < 0.001$ ). No statistically significant difference in LPA time between the activity categories was found.

**Table 9. Accelerometer-measured physical activity and sedentary behavior, and serum lipid biomarkers by moderate-to-vigorous physical activity category (n = 3,272). Modified from publication III.**

Variable	Low activity (n = 1,341)	Moderate activity (n = 1,238)	High activity (n = 693)	p-value
<b>Accelerometer-measured PA and SB</b>				
Wear time, min/d	895.4 (848.3–940.5) <sup>a, b</sup>	904.7 (860.6–945.9) <sup>c</sup>	916.2 (879.2–953.5)	< 0.001
MVPA time, min/d	12.3 (7.4–16.7) <sup>a, b</sup>	29.5 (25.2–34.8) <sup>c</sup>	55.3 (47.8–66.3)	< 0.001
LPA time, min/d	266.1 (198.8–340.0)	270.8 (216.5–338.6)	262.0 (209.1–329.3)	0.084
SB time, min/d	592.8 (520.9–672.1) <sup>a, b</sup>	581.8 (513.0–646.2)	577.6 (507.4–637.0)	< 0.001
Time in SB bouts < 15 min, min/d	190.1 (159.6–223.6) <sup>a, b</sup>	197.0 (171.1–225.5)	195.5 (166.5–227.7)	0.001
Time in SB bouts of 15–29.99 min, min/d	116.1 (95.9–137.8) <sup>a, b</sup>	123.2 (102.5–143.3)	125.1 (105.8–144.5)	< 0.001
Time in SB bouts ≥ 30 min, min/d	206.1 (137.8–293.8) <sup>a, b</sup>	189.5 (120.6–255.5)	184.8 (126.3–249.4)	< 0.001
Sitting time, min/d	345.0 (275.2–422.8) <sup>a, b</sup>	368.3 (295.4–439.7) <sup>c</sup>	378.3 (303.2–453.8)	< 0.001
Time in sitting bouts < 15 min, min/d	145.1 (111.8–175.7) <sup>a, b</sup>	153.4 (121.9–182.4)	152.4 (118.6–183.5)	< 0.001
Time in sitting bouts of 15–29.99 min, min/d	71.3 (52.6–91.8) <sup>a, b</sup>	78.0 (60.7–99.3)	81.0 (62.1–102.6)	< 0.001
Time in sitting bouts ≥ 30 min, min/d	61.6 (36.5–128.1) <sup>a, b</sup>	70.3 (39.9–125.7)	74.5 (40.1–134.3)	0.001
<b>Serum lipid biomarkers</b>				
Triglycerides, mmol/l	1.1 (0.8–1.6) <sup>a, b</sup>	1.0 (0.8–1.4) <sup>c</sup>	0.9 (0.7–1.3)	< 0.001
Total cholesterol, mmol/l	5.3 (4.7–5.9) <sup>b</sup>	5.3 (4.7–5.9) <sup>c</sup>	5.1 (4.6–5.7)	0.008
LDL cholesterol, mmol/l	3.4 (2.8–4.1) <sup>b</sup>	3.4 (2.8–4.0) <sup>c</sup>	3.1 (2.6–3.8)	< 0.001
HDL cholesterol, mmol/l	1.5 (1.2–1.7) <sup>b</sup>	1.5 (1.3–1.8) <sup>c</sup>	1.6 (1.4–1.9)	< 0.001
Total/HDL cholesterol ratio	3.6 (3.0–4.4) <sup>a, b</sup>	3.4 (2.8–4.2) <sup>c</sup>	3.1 (2.6–3.9)	< 0.001
LDL/HDL cholesterol ratio	2.4 (1.8–3.1) <sup>a, b</sup>	2.2 (1.7–2.9) <sup>c</sup>	2.0 (1.5–2.7)	< 0.001

Values are median (25th–75th percentiles). Only significant ( $p < 0.05$ ) pairwise comparison p-values are reported. <sup>a</sup>low activity vs. moderate activity,

<sup>b</sup>low activity vs. high activity, and <sup>c</sup>moderate activity vs. high activity. PA = physical activity, MVPA = moderate-to-vigorous physical activity, LPA = light

physical activity, SB = sedentary behavior, HDL = high-density lipoprotein, and LDL = low-density lipoprotein.

### *Associations of sedentary behavior and sitting patterns with serum lipid biomarkers by physical activity categories (III)*

Sedentary behavior and sitting variables having statistically significant linear associations with serum lipid and lipoprotein levels by MVPA categories are summarized in Table 10. Daily sedentary time and time spent in sedentary bouts  $\geq 30$  minutes were adversely associated with HDL and LDL cholesterol, total/HDL and LDL/HDL cholesterol ratios, and triglycerides in the low-activity category. In addition, time spent in sedentary bouts of 15–29.99 minutes was adversely associated with total/HDL and LDL/HDL cholesterol ratios in the low-activity category. In the moderate-activity category, daily sedentary time had adverse associations with HDL cholesterol and total/HDL cholesterol ratios, and time spent in sedentary bouts of 15–29.99 minutes had adverse associations with HDL cholesterol, total/HDL ratios, LDL/HDL cholesterol ratios, and triglycerides. Daily sedentary time and time spent in sedentary bouts of 15–29.99 and  $\geq 30$  minutes were adversely associated with HDL cholesterol and LDL/HDL cholesterol ratios in the high-activity category. MVPA time was most consistently associated with total/HDL and LDL/HDL cholesterol ratios and triglycerides in the low-activity category. In contrast, MVPA time had no association with lipid and lipoprotein biomarkers in the moderate and high-activity categories.

Based on the linear regression analyses, the total sedentary time (min/day) and the time spent in sedentary bouts  $\geq 30$  minutes (min/day) were most often associated with serum lipid biomarkers and entered into ROC analyses to examine the threshold values for excessive time spent in SBs. The area under the curve (AUC) values of the daily sedentary time and the time spent in sedentary bouts  $\geq 30$  minutes were 0.60 for total/HDL and LDL/HDL cholesterol ratios, and 0.59 for triglycerides. The risk for adverse serum lipid and lipoprotein levels was increased with daily sedentary time exceeding around 582.5 min/day (with 61.1–63.5% sensitivity and 45.0–48.8% specificity), and the time spent in sedentary bouts  $\geq 30$  minutes was approximately 190 min/day (with 62.9–64.0% sensitivity and 48.5–50.6% specificity).

**Table 10. Sedentary behavior and sitting variables significantly associated with serum lipids and lipoproteins by moderate-to-vigorous physical activity category according to linear regression analyses among middle-aged participants (n = 3,272). Modified from publication III.**

Serum lipid and lipoproteins		Low activity (n = 1,341)		Moderate activity (n = 1,238)		High activity (n = 693)	
Sedentary behavior or sitting variables	R <sup>2</sup>	$\beta$ (95% CI)	R <sup>2</sup>	$\beta$ (95% CI)	R <sup>2</sup>	$\beta$ (95% CI)	
<i>HDL cholesterol</i>							
Sedentary time, min/d	0.282**	-0.127 (-0.193, -0.060)**	0.226**	-0.079 (-0.154, -0.004)*	0.257**	-0.160 (-0.259, -0.061)*	
Time in SB bouts of 15–29.99 min, min/d	0.275**	-0.028 (-0.067, 0.010)	0.229**	-0.069 (-0.114, -0.023)*	0.253**	-0.080 (-0.140, -0.019)*	
Time in SB bouts $\geq$ 30 min, min/d	0.278**	-0.025 (-0.042, -0.007)*	0.224**	-0.007 (-0.026, 0.011)	0.250**	-0.029 (-0.057, -0.001)*	
<i>LDL cholesterol</i>							
Sedentary time, min/d	0.131**	0.159 (0.075, 0.243)**	0.125**	0.036 (-0.055, 0.128)	0.149**	0.131 (0.014, 0.249)*	
Time in SB bouts of 15–29.99 min, min/d	0.124**	0.043 (-0.006, 0.092)	0.126**	0.050 (-0.006, 0.105)	0.153**	0.101 (0.029, 0.173)*	
Time in SB bouts $\geq$ 30 min, min/d	0.129**	0.037 (0.014, 0.059)*	0.124**	0.001 (-0.022, 0.024)	0.147**	0.031 (-0.002, 0.064)	
Sitting time, min/d	0.122**	-0.010 (-0.054, 0.033)	0.124**	0.007 (-0.045, 0.058)	0.148**	0.066 (0.003, 0.129)*	
<i>Total/HDL cholesterol ratio</i>							
Sedentary time, min/d	0.362**	0.176 (0.104, 0.248)**	0.316**	0.097 (0.017, 0.176)*	0.324**	0.190 (0.084, 0.296)	
Time in SB bouts of 15–29.99 min, min/d	0.353**	0.046 (0.004, 0.088)*	0.319**	0.082 (0.033, 0.130)*	0.325**	0.121 (0.056, 0.185)**	
Time in SB bouts $\geq$ 30 min, min/d	0.358**	0.037 (0.017, 0.056)**	0.313**	0.007 (-0.013, 0.027)	0.318**	0.038 (0.008, 0.068)*	
Sitting time, min/d	0.351**	0.004 (-0.033, 0.042)	0.315**	0.039 (-0.006, 0.083)	0.317**	0.062 (0.005, 0.119)*	
<i>LDL/HDL cholesterol ratio</i>							
Sedentary time, min/d	0.311**	0.286 (0.177, 0.394)**	0.268**	0.115 (-0.005, 0.236)	0.288**	0.291 (0.001, 0.457)*	
Time in SB bouts of 15–29.99 min, min/d	0.300**	0.072 (0.008, 0.135)*	0.272**	0.118 (0.045, 0.191)*	0.289**	0.181 (0.080, 0.282)**	
Time in SB bouts $\geq$ 30 min, min/d	0.307**	0.061 (0.032, 0.090)**	0.266**	0.008 (-0.022, 0.038)	0.282**	0.060 (0.013, 0.106)*	
<i>Triglycerides</i>							
Sedentary time, min/d	0.322**	0.185 (0.055, 0.315)*	0.267**	0.311 (0.164, 0.458)	0.251**	0.401 (0.213, 0.588)*	
Time in SB bouts of 15–29.99 min, min/d	0.319**	0.060 (-0.015, 0.135)	0.260**	0.109 (0.019, 0.199)*	0.233**	0.068 (-0.047, 0.184)	
Time in SB bouts $\geq$ 30 min, min/d	0.324**	0.060 (0.026, 0.095)*	0.259**	0.036 (-0.001, 0.073)	0.245**	0.092 (0.039, 0.144)**	

<i>Serum lipid and lipoproteins</i>	Low activity (n = 1,341)	Moderate activity (n = 1,238)	High activity (n = 693)
Sedentary behavior or sitting variables	R <sup>2</sup> β (95% CI)	R <sup>2</sup> β (95% CI)	R <sup>2</sup> β (95% CI)

Adjusted for sex, employment status, marital status, smoking, alcohol consumption (heavy user), waist circumference (abdominal obesity), diagnosis or medication for cardiovascular disease (coronary artery disease, heart failure, myocardial infarction, stroke) or diabetes, physical strenuousness of work, accelerometer wear time, and MVPA. SB = sedentary behavior, MVPA = moderate-to-vigorous physical activity, HDL = high-density lipoprotein, and LDL = low-density lipoprotein. \* Significant association at level  $p < 0.05$ . \*\* Significant association at level  $p < 0.001$ .

### *Associations of isothermal substitution of sedentary behavior with glucose metabolism (IV)*

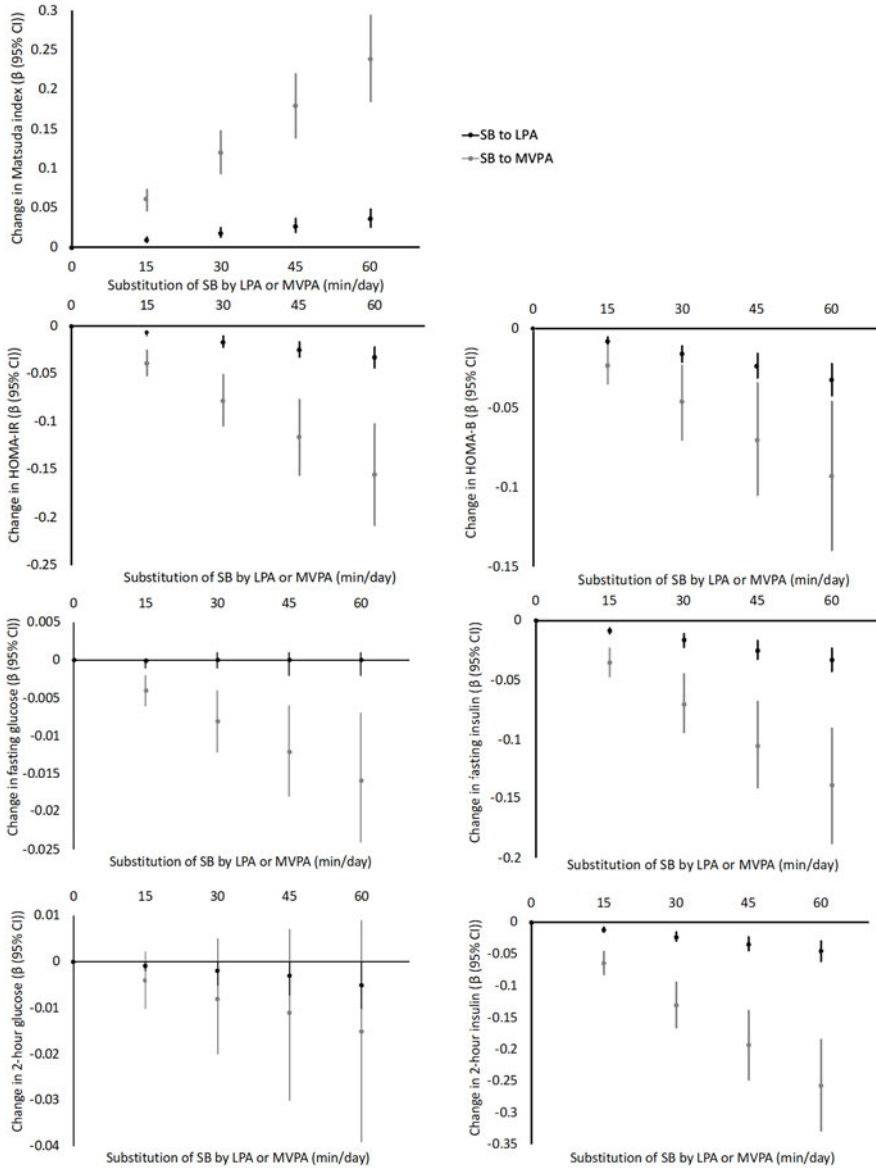
In the linear regression analyses of sedentary behavior with biomarkers of glucose metabolism (IV), 30 minutes more sedentary time and time spent in sedentary bouts  $\geq 30$  minutes were inversely associated with fasting insulin, 2-hour insulin, HOMA-IR, HOMA-B, and the Matsuda index (Table 11). Sedentary time (min/d) and time spent in sedentary bouts  $\geq 30$  minutes (min/d) explained on average 33.5% ( $p < 0.001$ ) of the variance in the Matsuda index showing the highest coefficient of variation. SB variables were not associated with fasting glucose and 2-hour glucose.

**Table 11. Associations of adding 30 minutes of sedentary behavior or time spent in sedentary bouts  $\geq 30$  minutes with biomarkers of glucose metabolism according to linear regression analyses (n = 2,991) (IV).**

<i>Biomarkers of glucose metabolism</i>	<i>R<sup>2</sup></i>	<i>p-value</i>	<i>β (95% CI)</i>	<i>p-value</i>
<i>Sedentary behavior variables</i>				
<i>Fasting glucose</i>				
Sedentary time, min/d	0.210	< 0.001	0.000 (−0.001, 0.001)	0.763
Time spent in SB bouts $\geq 30$ min, min/d	0.211	< 0.001	0.000 (0.000, 0.001)	0.395
<i>Fasting insulin</i>				
Sedentary time, min/d	0.303	< 0.001	0.016 (0.011, 0.021)	< 0.001
Time spent in SB bouts $\geq 30$ min, min/d	0.302	< 0.001	0.013 (0.008, 0.017)	< 0.001
<i>2-hour glucose</i>				
Sedentary time, min/d	0.117	< 0.001	0.002 (0.000, 0.005)	0.075
Time spent in SB bouts $\geq 30$ min, min/d	0.117	< 0.001	0.002 (−0.001, 0.004)	0.166
<i>2-hour insulin</i>				
Sedentary time, min/d	0.200	< 0.001	0.015 (0.009, 0.022)	< 0.001
Time spent in SB bouts $\geq 30$ min, min/d	0.199	< 0.001	0.022 (0.015, 0.030)	< 0.001
<i>HOMA-IR</i>				
Sedentary time, min/d	0.320	< 0.001	0.017 (0.011, 0.022)	< 0.001
Time spent in SB bouts $\geq 30$ min, min/d	0.319	< 0.001	0.013 (0.008, 0.018)	< 0.001
<i>HOMA-B</i>				
Sedentary time, min/d	0.190	< 0.001	0.016 (0.011, 0.021)	< 0.001
Time spent in SB bouts $\geq 30$ min, min/d	0.187	< 0.001	0.012 (0.007, 0.016)	< 0.001
<i>Matsuda index</i>				
Sedentary time, min/d	0.337	< 0.001	−0.018 (−0.024, −0.012)	< 0.001
Time spent in SB bouts $\geq 30$ min, min/d	0.334	< 0.001	−0.012 (−0.017, −0.008)	< 0.001

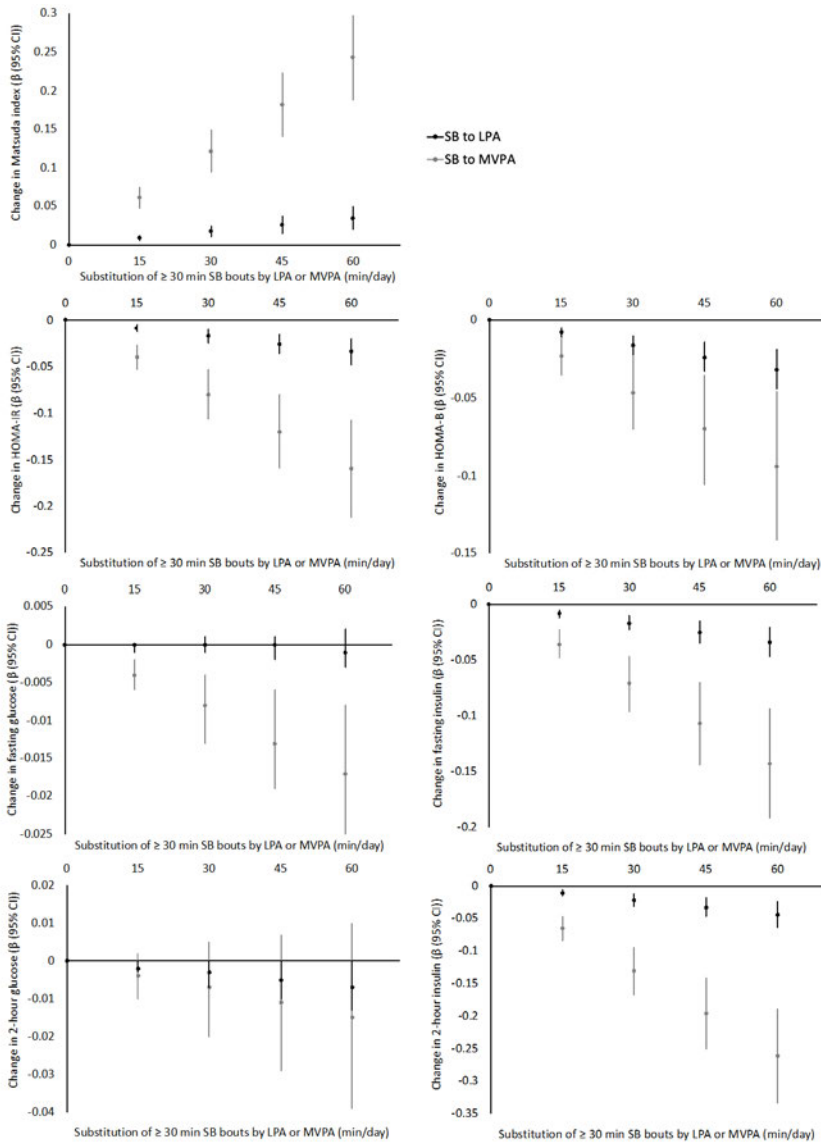
Adjusted for sex, waist circumference tertiles, accelerometer wear time, and MVPA. SB = sedentary behavior, MVPA = moderate-to-vigorous physical activity.

Isotemporal substitution regression modeling was used for examining time reallocations from time spent in sedentary behavior and time in sedentary bouts  $\geq 30$  minutes to LPA and MVPA. The replacement of time spent in SB (Figure 5) and in sedentary bouts  $\geq 30$  minutes (Figure 6) with an equal amount of LPA were associated with lower levels of HOMA-IR, HOMA-B, fasting insulin, and 2-hour insulin and a higher level in the Matsuda index. Furthermore, replacing time spent in SB (Figure 5) and in sedentary bouts  $\geq 30$  minutes (Figure 6) with an equal amount of MVPA were associated with lower levels of HOMA-IR, HOMA-B, fasting glucose, fasting insulin, and 2-hour insulin and a higher level in the Matsuda index. The associations were greater the more time was replaced. In addition, replacing sedentary time or time spent in sedentary bouts  $\geq 30$  minutes with MVPA had more significant associations with all biomarkers of glucose metabolism compared to time reallocations from sedentary time or time spent in sedentary bouts  $\geq 30$  minutes with LPA. In contrast, no significant associations with biomarkers of glucose metabolism were found when time spent in sedentary bouts  $\geq 30$  minutes was substituted by time spent in sedentary bouts of  $< 15$  minutes.



**Fig. 5.** Time reallocations from sedentary behavior with light or moderate-to-vigorous physical activity and the change in glucose metabolism biomarkers among middle-aged participants ( $n = 2,991$ ) (IV). Adjusted for sex and waist circumference tertiles. SB = sedentary behavior, LPA = light physical activity, and MVPA = moderate-to-vigorous physical activity.





**Fig. 6. Time reallocations from sedentary bouts  $\geq 30$  minutes with light or moderate-to-vigorous physical activity and the change in glucose metabolism biomarkers among middle-aged participants ( $n = 2,991$ ) (IV). Adjusted for sex and waist circumference tertiles. SB = sedentary behavior, LPA = light physical activity, and MVPA = moderate-to-vigorous physical activity.**



## 6 Discussion

The present study developed and validated a machine learning-based method for classifying sedentary behavior and physical activity from raw triaxial accelerations measured from the hip. Additionally, the study demonstrated that using the developed machine learning method, SB and sitting patterns could be distinguished in the sample of middle-aged Finnish adults. Finally, the study examined the associations of sedentary behavior and sitting patterns with serum lipid biomarkers at different MVPA levels and the associations of time substitution of SB with PA and their associations with glucose metabolism in the large population-based cohort of middle-aged Finnish adults.

### 6.1 Physical activity and sedentary behavior classification using a machine learning method (I)

A machine learning-based method was developed and validated to classify types of PA and SB from the raw triaxial accelerometer data measured from the hip. The total accuracy of the model was 96.5%, the mean sensitivity for the model was 95.5%, and the mean specificity was 99.1%. Sitting could be recognized with 92.2% sensitivity and 99.2% specificity, and lying down with 96.4% sensitivity and 99.2% specificity, respectively.

The accelerometer data collection was performed simultaneously with indirect calorimetry and using the predefined set of supervised activities as direct observation. The posture of activities was confirmed by direct observation and indirect calorimetry was used to calculate the intensities of the activities to ensure that they are somewhat in line with Compendium of Physical Activities (Ainsworth et al., 2000; Ainsworth et al., 2011). In addition, sitting, lying down, and standing postures were also agreed upon with direct observation.

The results of the present study were in line with other methodology development studies to classify PA and SB from the accelerometer data (de Almeida Mendes et al., 2018; Farrahi et al., 2019). In the previous studies, threshold-based methods perform with high mean values of total accuracy (95.8%), sensitivity (93.7%), and specificity (91.9%) (de Almeida Mendes et al., 2018). In addition, ML-based classification methods performed on average with total accuracy of approximately 85.5% in adults using a hip-worn accelerometer and within the sample validation (Farrahi et al., 2019). However, most of the recent ML-based approaches classified accelerometer data by physical activity types (such as

sedentary, household, and locomotor activities) instead of PA intensity categories, which may explain slight differences in the total accuracies of the models compared to the model developed in the present study (de Almeida Mendes et al., 2018). It can be concluded that the algorithm developed in the present study has the potential for classifications of PAs and SBs from the raw triaxial accelerometer data measured from the hip in working-aged adults.

## **6.2 Characteristics of sedentary behavior and sitting (II)**

For the first time, a comprehensive set of sedentary behavior and sitting parameters was used to describe the characteristics of daily free-living SB and sitting separately in middle-aged Finnish adults. The present study showed that distinctions can be reliably made between the patterns of SB and sitting using an ML-based method in free-living conditions. More detailed information can be achieved when the patterns on SB and sitting are analyzed separately. In the sample studied, men spent their daily sedentary time in prolonged bouts more often than women. However, women sat more but broke up their sitting time as often as men.

The results of the present study about the differences in SB between the sexes were in line with the previous studies in which men had more prolonged bouts of SB (Husu et al., 2016; van der Velde et al., 2017) and more daily sedentary time (López-Valenciano et al., 2020) compared to women. Similarly, a recent study using a wrist-worn accelerometer found that men had more daily sedentary time than women among middle-aged Finnish adults (Niemelä et al., 2019). In contrast, statistically significant differences in total sedentary time or breaks in SB were not found between men and women among type 2 diabetes patients (Sardinha et al., 2017). The agreement between the patterns of sitting with the previous studies cannot be concluded since, to our knowledge, no other study has investigated the patterns of SB and sitting separately. In addition, the results of the previous studies cannot be reliably compared due to the different definitions of sedentary bouts and breaks. In previous studies, an SB bout was defined as a bout of sitting or lying down that ends with standing up (Husu et al., 2016). A break in SB was defined as a PA bout of at least 1 minute with an activity count higher than 100 counts per minute (Sardinha et al., 2017) or a transition from a sitting or lying posture to standing or stepping lasting at least 1 minute (van der Velde et al., 2017).

### **6.3 Associations of sedentary behavior and sitting patterns with serum lipid biomarkers (III)**

The sub-study III showed that sedentary behavior and sitting patterns and their associations with serum lipid biomarkers vary between MVPA categories in a large cohort sample of middle-aged Finnish adults. In all MVPA categories, the accumulation patterns of SB were more significantly associated with lipid biomarkers than sitting. Among adults in the lowest MVPA category (i.e., not meeting the minimum amount of MVPA 150–300 min/week), total sedentary time and time spent in sedentary bouts of 15–29.99 and  $\geq 30$  minutes were most consistently associated with impaired lipid metabolism. In addition, more total sedentary time and time spent in sedentary bouts of 15–29.99 minutes were unfavorably associated with lipid biomarkers among adults in the moderately-active MVPA category (i.e., meeting the lower recommended MVPA limit of 150–300 min/week). Among adults in the highly active MVPA category (i.e., meeting the higher MVPA limit of  $> 300$  min/week), total sedentary time and time spent in sedentary bouts of 15–29.99 and  $\geq 30$  minutes were negatively associated with lipid biomarkers.

The existing literature (Bellettiere et al., 2019; Ekelund et al., 2019; Henson et al., 2013; Patterson et al., 2018; Sjöros et al., 2020; Vaara et al., 2022; Vasankari et al., 2017) has studied chiefly the associations of SB patterns with cardiometabolic health independently of MVPA level. Nevertheless, the results of those studies are in line with the results of sub-study III, showing that the time spent in SB and prolonged sedentary bouts are unfavorably associated with cardiometabolic health. Furthermore, these relationships were dependent on the MVPA category in sub-study III, showing that more total sedentary time and time spent in sedentary bouts of 15–29.99 minutes were inversely associated with lipid biomarkers in all MPVA categories, but time spent in sedentary bouts  $\geq 30$  minutes had inverse associations only in the low and high-activity categories. In addition, more MVPA time was favorably associated with lipid metabolism in the low-activity category but not in the moderate or high-activity categories.

Some previous studies (Ekelund et al., 2016; Huang et al., 2021; Mossavar-Rahmani et al., 2020; Stamatakis et al., 2019b; van der Velde et al., 2018; von Rosen et al., 2020) have investigated the associations daily sedentary time with cardiometabolic health at different MVPA levels. High daily sedentary time was reported to be adversely associated with cardiometabolic health among the least physically active adults (Ekelund et al., 2016; Stamatakis et al., 2019b) or

combined with a low PA level (Huang et al., 2021). On the contrary, one study (van der Velde et al., 2018) reported that high sedentary time was associated with an increased risk for metabolic syndrome and type 2 diabetes. Still, the risk was greatest in participants with low cardiorespiratory fitness and high sedentary time despite their MVPA level. Cardiorespiratory fitness is affected by many factors, such as frequency and intensity of engagement in PA and genetic and environmental factors, and could have mediating effects between SB, PA, and cardiometabolic health. However, previous studies have reported that an increase in MVPA time can attenuate or even eliminate health risks related to high volumes of SB, especially among the least physically active adults (Matthews et al., 2015; Mossavar-Rahmani et al., 2020; Stamatakis et al., 2019b; von Rosen et al., 2020).

Previous research has proposed several thresholds (varying between 6–10 hours/day) for a harmful amount of daily sedentary time (Stamatakis et al., 2019), which supports the results of the present study. In the present study, the risk of unfavorable lipid levels was increased by the daily sedentary time of approximately 582.5 min/day, although this threshold provided limited accuracy. In line with our results, the risk of CVD was increased with high levels (> 10 hours/day) of daily sedentary time after adjustment for other CVD risk factors (Pandey et al., 2016). On the contrary, the risk of CVD mortality has been reported to be higher even in adults with 6–8 hours of daily SB (Patterson et al., 2018).

The results of the present study revealed more consistent associations between the serum lipid biomarkers and the patterns of SB than those of sitting. However, the total time spent in SB was greater and accumulated in more prolonged bouts than sitting, which may explain some of the different associations involving SB and sitting. Nevertheless, previous studies have provided strong evidence of improved cardiometabolic health risk biomarkers when the sitting posture was replaced with standing or ambulatory activities (Graves et al., 2015; Winkler et al., 2018).

#### **6.4 Associations of time reallocations from sedentary behavior to physical activity with glucose metabolism (IV)**

The sub-study IV investigated the impact of time reallocations from sedentary behavior and sedentary bouts  $\geq 30$  minutes to LPA, MVPA, and sedentary bouts < 15 minutes on the associations with glucose metabolism in a large cohort sample of middle-aged Finnish adults. The results showed that reallocating time spent in SB or sedentary bouts  $\geq 30$  minutes to MVPA was associated with healthier glucose metabolism. Substituting sedentary behavior or sedentary bouts  $\geq 30$  minutes with

LPA was also beneficially associated with glucose metabolism. However, no association was found when the time spent in sedentary bouts  $\geq 30$  minutes was substituted with the time spent in sedentary bouts  $< 15$  minutes.

The previous isotemporal substitution modeling studies have shown that time reallocations from SB to LPA, or MVPA, are positively associated with glucose metabolism in adults (Cavallo et al., 2022; Del Pozo-Cruz et al., 2018; Galmes-Panades et al., 2019; Grgic et al., 2018; Yates et al., 2015) which supports the results of the present study. Similarly, a recent study in the same population using compositional data analysis found that reallocating time spent in SB to LPA was associated with favorable glucose metabolism, and a more significant favorable association was found when SB was reallocated to MVPA (Farrahi et al., 2021b). In line with our results, associations were more substantial with insulin-related biomarkers than glucose-related biomarkers (Farrahi et al., 2021b).

In the current study, substituting daily SB with LPA or MVPA increased the Matsuda index, which describes whole-body insulin sensitivity. In addition, substituting daily sedentary time with LPA or MVPA decreased HOMA-IR (describes insulin resistance) and HOMA-B (describes  $\beta$ -cell function). Blood glucose level is regulated by a feedback loop involving insulin secretion in pancreatic  $\beta$ -cells and insulin sensitivity of tissues (Khan et al., 2014). Initially, developing type 2 diabetes increases insulin secretion, and the presence of insulin resistance further increases insulin secretion in  $\beta$ -cells to maintain normal blood glucose levels. PA and resistance training have an essential role in controlling insulin resistance of the whole body and especially muscles (Colberg et al., 2016).

The previous systematic review showed a consistent association between total sedentary time and poor insulin sensitivity in adults (Brocklebank et al., 2015). Furthermore, more time spent in LPA and MVPA was favorably associated, particularly with insulin-related biomarkers in the birth cohort of Finnish older adults (Länsitie et al., 2021). The substitution of SB with LPA has been proposed as an achievable strategy for reducing the risk of type 2 diabetes in the most physically inactive adults (Healy et al., 2015; Van der Berg et al., 2017). In addition, the previous randomized controlled trial showed that substituting 40 minutes of daily SB with non-exercise PA for three months decreased fasting insulin levels in adults with a metabolic disorder (Sjöros et al., 2022).

The results of sub-study IV are somewhat supported by a recent study in the same population, showing that sedentary profiles with high total sedentary time or with high sedentary bout duration have no different associations with glucose metabolism biomarkers (Farrahi et al., 2021a). In sub-study IV, broadly similar

associations were found when PA substituted sedentary behavior or prolonged sedentary bouts. However, the present study results have some inconsistencies one previous study. In adults at high risk of developing type 2 diabetes, replacing time spent in sedentary bouts  $\geq 30$  minutes with time spent in sedentary bouts  $< 30$  minutes was associated with lower fasting insulin (Edwardson et al., 2017). Based on the results of the present study, substituting daily SB or prolonged sedentary bouts with LPA may be an achievable strategy for improving insulin sensitivity and insulin levels, e.g., in physically inactive adults, but substituting daily SB or prolonged sedentary bouts with MVPA provides greater benefits.

## **6.5 Strengths, limitations, the implication of findings, and future research**

The main strengths of the present study were the use of the hip-worn triaxial accelerometer and ML-based signal analysis method to classify SBs and PAs instead of the traditional threshold-based analysis methods (Wijndaele et al., 2015). The hip has been proposed to be one of the most feasible attachment sites of the accelerometer to measure PAs and SBs reliably in large populations over long measurement periods (Aunger & Wagnild, 2022; Matthews et al., 2012a; Rosenberger et al., 2013). In addition, the ML-based model developed in sub-study I was validated against indirect calorimetry and direct observation, which is a definite strength. EE-based techniques in validating PAs and direct observation in validating SBs have been considered the gold standards for validating PA and SB measurement techniques (Aunger & Wagnild, 2022; Hills et al., 2014).

However, some limitations of the ML-based model developed in sub-study I need to be noted. The METs of the activities were calculated from the indirect oxygen consumption using the standard conversion, which may not distinguish the individual variability (e.g., gender, age, and body composition) in metabolic responses (Welk et al., 2012). In addition, standing still was missing from the protocol since standing was measured as a poster viewing that included slight movements. The validation of ML-model in different populations (e.g. children and elderly) will be necessary to conduct before analyzing PA from those populations.

The strength of sub-study II was that using the ML-based approach, the comprehensive set of SB and sitting pattern variables were analyzed separately from the raw triaxial hip acceleration data. In addition, the ML-based model was developed and validated for working-aged adults using the same hip-worn accelerometer. However, the intensity, duration, and frequency of the breaks in SB



or standing still posture were not investigated. Different intensities and activity types (standing or locomotor) of the breaks in SB may also have different health effects. For instance, light-intensity walking during the breaks in SB, but not standing, has been shown to have beneficial effects for postprandial glycemia in adults (Bailey & Locke, 2015). Additionally, the study sample was relatively small, within a narrow range in age and ethnicity. Although sub-study II presented a comprehensive set of the accelerometer-based characteristics of SB and sitting in free-living conditions using ML-based classification, further studies with larger and more heterogeneous populations are needed to characterize the association of SB and sitting parameters with health.

The strengths of sub-studies III and IV were the relatively sizeable population-based study sample, the two-week hip-worn accelerometer measurements of PA and SB, the use of raw triaxial accelerations, the ML-based signal processing method, and the comprehensive range of cardiometabolic biomarkers. In addition, the patterns of SB and sitting were investigated separately in different MVPA categories in sub-study III. Isotemporal substitution modeling was used for time reallocations between SBs and PAs in sub-study IV. Nevertheless, sub-studies III and IV have some limitations. The present study might have some selection bias since participants providing valid PA and SB data smoked less, consumed less alcohol, and had more preferably body compositions and lower rates of CVD or diabetes compared to those not providing valid PA data. The accelerometer was worn during waking hours, which can be considered a limitation due to a possible interconnection between sleep and daily activities (Farrahi et al., 2021b). In addition, all kinds of standing were classified as LPA. MVPA could contain varying amounts of MPA and VPA, and SB's context or behavioral characteristics were not studied. In sub-study IV, the associations of time reallocations between SB and PAs were only theoretically studied. The causal associations of an individual cannot be determined due to the cross-sectional design of these sub-studies. The participants were of the same age and had the same ethnic background, which can be considered a limitation. Nevertheless, the results of this thesis can be used when planning evidence-based interventions to decrease SB in midlife and updating national SB recommendations.

For future studies, it is recommended to investigate joint associations of MPA, VPA, LPA, SB, and prolonged sedentary bouts on cardiometabolic health in longitudinal designs to understand the physiological effects on cardiometabolic health comprehensively. In addition, future studies should analyze sleep and standing still, and the context of SBs should be investigated. Further studies with

more heterogeneous study samples and experimental study designs are needed to understand better the significance of SB's characteristics with cardiometabolic health.

## 7 Conclusions

The present study developed and validated a machine learning-based algorithm measuring accumulation patterns of sedentary behavior and sitting in free-living conditions and indicated that patterns of sedentary behavior have different associations with cardiometabolic health in mid-life depending on the activity level. Based on the aims of this study, it can be concluded that:

1. Physical activity and sedentary behavior classifications can be done from raw triaxial accelerations measured from the hip using a machine learning-based method with high accuracy.
2. Sedentary behavior and sitting distinctions can be reliably made using a machine learning-based method. More detailed information about sedentary behavior can be achieved when overall sedentary behavior and sitting are analyzed separately in free-living conditions.
3. The accumulation patterns of overall sedentary behavior and sitting and their associations with serum lipid biomarkers vary among moderate-to-vigorous physical activity categories. The patterns of overall sedentary behavior are more consistently associated with serum lipid biomarkers than the patterns of sitting.
4. Reallocating daily time spent in sedentary behavior and sedentary bouts  $\geq 30$  minutes with moderate-to-vigorous physical activity is most favorably associated with glucose metabolism, but also reallocating daily time spent in sedentary behavior and sedentary bouts  $\geq 30$  minutes to light physical activity is associated with healthier glucose metabolism.



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## Original publications

- I Tjurin, P., Niemelä, M., Huusko, M., Ahola, R., Kangas, M. & Jämsä, T. (2017). Classification of physical activities and sedentary behavior using raw data of 3D hip acceleration. *IFMBE Proceedings*, 65, 872–875. [https://doi.org/10.1007/978-981-10-5122-7\\_218](https://doi.org/10.1007/978-981-10-5122-7_218).
- II Tjurin, P., Niemelä, M., Kangas, M., Vähä-Ypyä, H., Sievänen, H., Jämsä, T. & Korpelainen, R. (2019). Accelerometry-based characteristics of overall sedentary behavior and sitting in middle-aged adults. *Measurement in Physical Education and Exercise Science*, 23(3), 249–257. <https://doi.org/10.1080/1091367X.2019.1613997>.
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- IV Tjurin, P., Länsitie, M., Kangas, M., Korpelainen, R., Farrahi, V. & Jämsä, T. (2023). Associations of reallocating time spent in sedentary behaviors and physical activities with glucose metabolism biomarkers in middle-aged adults. Manuscript.

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