Targeting sedentary behaviour


LDL
HDL

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an activity tracker approach to combat physical inactivity and improve cardiometabolic health

DISSERTATION

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Chapter 1

General Introduction

Chronic non-communicable diseases (NCDs) such as chronic respiratory diseases, type 2 diabetes mellitus (T2DM), cardiovascular diseases (CVD) and cancer are an important public health concern worldwide [1]. In fact, according to the World Health Organization (WHO), it is estimated that each year more than 41 million people die from NCDs, which is equivalent to 71% of all global deaths [2]. As a result, NCDs now are the leading cause of mortality worldwide and constitute one of the most important challenges for the 21st century [3, 4].

Although the exact aetiology and origin have not yet been identified, their presence appears to be multifactorial arising from a combination of socioeconomic, cultural and environmental determinants, genetic predisposition and modifiable risk factors [5, 6]. The latter are predominantly lifestyle factors such as tobacco use, harmful use of alcohol, unhealthy diet and physical inactivity [5, 6]. Here, physical inactivity is one of the major contributing factors that highly correlates with mortality and hospitalization [7, 8]. Physical inactivity is defined as the absence of sufficient moderate-to-vigorous physical activity (MVPA), often referred as exercise, as recommended by the 2020 WHO guidelines on physical activity and sedentary behaviour [9]. They recommend practicing a weekly volume of 150−300 minutes of moderate intensity (e.g. brisk walking), 75−150 minutes of vigorous intensity (e.g. running) or an equivalent combination of MVPA. This can be performed in different ways as part of work, during leisure time, domestic chores, transportation or participation in exercise or sports activities. However, a recent report from the WHO indicated that 28% of the adult and even 80% of the adolescent population is still physically inactive [10]. As a consequence, any strategy that may improve long-term adherence to adequate daily physical activity and a healthy lifestyle, especially within NCD populations are one of the greatest challenges of the future decades.

Research has mainly focussed on physical activity so far, and it is clear that inactive individuals in general have a worse cardiometabolic health compared to physically active individuals. However, it appears that high levels of MVPA do not always fully protect against cardiometabolic risk factors and NCD development. For example, a person drives to work in the morning, sits behind the desk or computer all day, and spends most of the evening watching television. Although this is a highly sedentary day, it is not an inactive day when he/she is also running

for 30 minutes and, therefore, meets the WHO physical activity recommendations. As such, next to the volume of MVPA, another important key player that appears to determine cardiometabolic health and NCD development is sedentary behaviour.

During the past decade, emerging evidence clearly disclosed that high volumes of sedentary behaviour, typically involving prolonged periods of sitting, are also an important and independent contributor to cardiometabolic diseases and all-cause mortality, even in the presence of regular MVPA [11, 12]. Therefore, both MVPA and sedentary behaviour are clinically relevant targets and major opportunities for interventions to change lifestyle behaviours, improve general health and reduce the risk of developing NCDs. As a result, there is an urgent need to find ways for a healthier balance between sedentary behaviour and physical activity.

Sedentary behaviour

In the past decade, an exponential growth in research regarding the study of 'sedentary behaviour' and its detrimental effects on cardiometabolic health has been observed. Sedentary behaviour (Latin: sedere, "to sit") encompasses any waking sitting, lying or reclining behaviour with low energy expenditure (≤1.5 metabolic equivalents), including sitting during leisure time, transportation and work [13]. For a long time, the terms sedentary behaviour and physical inactivity were used interchangeably. However, since the early nineties public health researchers began to distinguish between these definitions and recognized them as distinct health behaviours [14, 15]. This means that a person can be highly sedentary and highly active at the same time (e.g. a person who sits more than nine hours a day, but also has three training sessions every week). In this regard, a plethora of epidemiologic evidence now shows that high volumes of sedentary behaviour can have adverse impacts on multiple health related outcomes, independently of the amount of MVPA [11, 16-18].

The origins of sedentary behaviour

From a historical perspective, sedentary behaviour is a relatively new phenomenon within the human population. The life of our ancestors evolved to be adapted for regular, moderate amounts of physical activity as a hunter-gatherer due to basic needs as hunger and thirst, or reacting to dangerous threats as

becoming a prey. At the same time, they tended to avoid physical activity for energy saving whenever possible [19, 20]. In contrast, the current society has a predominantly sedentary lifestyle. Technological developments and innovations during the Industrial Revolution in the 18th century changed the way of manufacturing, transportation and communication and, as such, enabled more sedentary behaviour. In the early 19th century, chairs became a social phenomenon and were massively introduced into workplaces, classrooms, train/bus stations and people's houses. Nowadays, it is impossible to imagine a public or private area without sitting opportunities.

These changes have contributed to a predominantly sedentary and unhealthy lifestyle, making this an important global public health concern. It has become clear that there is a mismatch between our contemporary lifestyle and our adaptive biological characteristics or genetic makeup. Our human body is designed to be physically active and not to be sedentary, at least not for prolonged periods of time.

Health Effects of Sedentary Behaviour

The harmful effects of prolonged sitting were first highlighted in the 1950s during the London Busmen Study [21]. Here, J. Morris *et al*. investigated the incidence rates of coronary heart disease within drivers and conductors of the Central ("red") Buses and identified a twofold increase in the risk of a myocardial infarction in bus drivers, who mainly sat during work, compared with physically active bus conductors [21]. In the following 70 years a plethora of research has focused on establishing the associations between MVPA and general health, thereby overlooking the potentially important distinction between sedentary behaviour and physical activity. Objective measures have demonstrated that the average adult in Westernized societies spend between 8 and 10 hours of their day in sedentary pursuits (up to 60% of adult wake time) [18]. A dose-response association between sedentary time and mortality risk increased gradually from 7.5 to 9 hours per day, whereas Patterson *et al*. already found a threshold of 6-8 hours per day of total sitting resulting in increased risks for several important health outcomes [18, 22]. Over the past decade, epidemiologic evidence has revealed that, next to an increased risk for all-cause mortality, sedentary time is also an independent risk factor for several metabolic and cardiovascular health outcomes. Many of these

associations persist even after adjustment for important confounding variables, such as MVPA and adiposity, with the strongest and most persistent associations seen between sedentary time and type 2 diabetes mellitus. Although we now know that prolonged sitting has been associated with various health conditions including, mental health, cognitive impairment, health-related quality of life, regulation of appetite and musculoskeletal functioning, this dissertation will focus on cardiometabolic health in relation to sedentary behaviour.

Cardiometabolic Health, The Metabolic Syndrome and Chronic Diseases

Cardiometabolic health related diseases are strongly associated with a cluster of various common cardiometabolic disturbances, including abdominal obesity, dyslipidaemia, (pre)hypertension and insulin resistance [23]. This cluster of conditions often occur together and is also called the Metabolic Syndrome (MetS), although other terms for the MetS are also used, including syndrome X, the insulin resistance syndrome and the deadly quartet [24]. The exact conditions include (pre)hypertension), hyperglycaemia, excess body fat around the waist, and abnormal blood cholesterol or triglyceride levels. It is generally known that the more conditions are present, the higher the risk to develop complications such as T2DM and CVD [24]. The concept of MetS has existed for at least 80 years and its definition has undergone many revisions [25-27]. The criteria formulated by the National Cholesterol Education Program's Adult Treatment Panel III (NCEP: ATP III) and the European Group for the Study of Insulin Resistance, the ATP III guidelines are mostly used due to its usefulness in clinical practice (Table 1) [28-30]. Nowadays, a continuous cardiometabolic risk score (CCMR) that includes the same five risk factors as the MetS is often used to evaluate cardiometabolic risk. Here, a less favourable CCMR will gradually lead to a less favourable cardiometabolic health profile [31].

There is still much debate regarding the underlying aetiology of the MetS. Although the global prevalence of the MetS is highly dependent upon the used criteria, demographic factors (age, sex and ethnicity) and the environment, the estimates range from 10 to 84% [32]. With regard to these high prevalence rates and the associated health consequences, implementing successful prevention and

management strategies with the aid of lifestyle changes are important in the near future.

Table 1 *Criteria for clinical diagnosis of the Metabolic Syndrome [30].*

Measure	Categorical Cut-off Points
Elevated waist circumference	≥ 102 cm for men or ≥ 88 cm for women
Elevated triglyceride level (drug treatment for elevated triglycerides is an alternate indicator)	≥ 150 mg/dL (1.7 mmol/L)
Reduced HDL-cholesterol level (drug treatment for reduced HDL-cholesterol is an alternate indicator)	< 40 mg/dL (1.03 mmol/L) in males; < 50 mg/dl (1.30 mmol/L) in females
Elevated blood pressure (antihypertensive drug treatment in a patient with a history of hypertension is an alternate indicator)	Systolic ≥ 130 mm Hg Diastolic ≥ 85 mm Hg
Elevated fasting glucose level (drug treatment of elevated glucose, such as insulin or oral agents, is an alternate indicator)	≥ 100 mg/dL (5.6 mmol/L)

Abbreviations: **HDL** = high-density lipoprotein.

Cardiometabolic Health and Sedentary Behaviour

Several epidemiological studies using accelerometer measured sedentary time have reported negative associations between sedentary behaviour and cardiometabolic health (waist circumference, triglyceride levels and blood glucose and insulin concentrations), the MetS and cardiometabolic health related diseases including T2DM [33, 34]. Interestingly, these associations were also found in individuals who reached the recommended levels of MVPA, which suggests that sedentary behaviour is a stand-alone factor in the relationship between physical activity and cardiometabolic health. Several studies have proposed potential physiological mechanisms due to prolonged sitting, including an impaired glucose homeostasis, lipid metabolism and systemic inflammation.

Glucose Metabolism

The interaction between sedentary behaviour and glucose metabolism has been extensively investigated in both experimental and epidemiological studies due to

the adverse effects of hyperglycaemia on the cardiovascular system [35]. However, the exact molecular mechanisms directly linking the detrimental effects of a sedentary lifestyle to an impaired glucose homeostasis should be further elucidated. It has been shown that prolonged periods of sedentary behaviour reduce (insulin-mediated) glucose uptake into skeletal muscles [36]. Here, it is postulated that prolonged sitting rapidly decreases muscle insulin sensitivity in association with an altered activity and expression of important signalling proteins involved in glucose transport and metabolism [37-39]. In this respect, Biensø *et al.* found that bed rest-induced insulin resistance was associated with reduced insulin-stimulated glycogen synthase activity and Akt (protein-kinase B) signalling, as well as decreased protein levels of hexokinase II (HK2) and glucose transporter type 4 (GLUT4) [38]. This may indicate that an impaired glucose uptake during sedentary behaviours occurs as a consequence of both decreased glucose transport/ phosphorylation as well as a decreased non-oxidative glucose metabolism in skeletal muscles. From this, it could be suggested that the absence of muscle use during prolonged sitting leads to lack of stimulation of transcriptional and translational processes normally seen during physical activity [40]. Alibegovic *et al*. also investigated possible mechanisms involved in the development of insulin resistance during prolonged sedentary behaviours [41]. They found an altered gene expression level of more than 4500 genes and 34 downregulated pathways predominantly associated with mitochondrial (dys)function and type II diabetes mellitus. Here, important genes with a reduced expression and involved in these mechanisms were the master regulator peroxisome proliferator-activated receptor-γ coactivator-α (PGC1α) and oxidative phosphorylation (OXPHOS) genes in general. From this, in could be suggested that a reduced oxidative capacity leads to a lower muscle energy turnover, resulting in a higher intramuscular lipid content including triacylglycerol (TAG), diacylglycerol (DAG) and/or ceramides. There is considerable evidence indicating these lipotoxic intermediates as key mediators of insulin resistance due to interference with insulin signalling transduction [42]. Moreover, a reduced HK2 and increased Ras-related associated with T2DM (RRAD) expression were found. Important to mention was the fact that four weeks of training were not enough to completely normalize the expression levels of approximately 20% of all measured genes, including HK2 and RRAD, thereby suggesting independent effects of

sedentary behaviours on cardiometabolic health. Interestingly, these genes are considered as the most prominent down- and up-regulated transcriptional alterations that contribute to an impairment in insulin response and glucose transport within skeletal muscle from people with T2DM. Therefore, it is suggested that sedentary behaviour induces modifications in gene expression levels similar to those observed in people with T2DM. As a result, the insulin concentration may increase to compensate for the reduction in glucose uptake via the signalling transduction pathway, which in turn causes hyperinsulinaemia and a further decline in skeletal muscle insulin sensitivity. In humans, the earliest detectable reduction in insulin signalling (±17 – 35%) following three days of complete bed rest was observed by Lipman *et al*. and these results were later confirmed by other studies, even after only one day of prolonged sitting [43-45]. Therefore, it has been proposed that an impaired insulin signalling is an early metabolic response to prolonged sedentary behaviours. Moreover, due to the large mass of skeletal muscle, a decreased insulin signalling in this tissue is a major contributor to whole-body insulin resistance.

Furthermore, results from Peddie *et al*. suggest that energy surplus plays a key role in the acute metabolic responses to prolonged sitting [46]. An overabundance of particularly fatty acids and glucose inhibits key components with regard to the insulin signalling pathway within skeletal muscle tissue [47, 48]. Other complex mechanisms potentially involved in a reduced insulin action are increased circulating counter-regulatory hormones as glucagon, epinephrine and cortisol [49]. In addition, hemodynamic changes, including a decreased insulin-mediated muscle blood flow and capillary recruitment are possibly involved [36]. In addition, a reduced expression of vascular endothelial growth factor A (VEGFA), an important regulator of capillarization and microvascular flow, and thereby insulin action, was found [41]. As a results, the distribution volumes for glucose and insulin may be decreased and therefore affect glucose clearance [50].

Lipid Metabolism

The habitual degree of a sedentary lifestyle is a moderator of lipid metabolism and especially contributes to hyperlipidaemia [51-53]. Despite the abundance of studies using a prolonged sitting approach to investigate lipid metabolism, both fasting and postprandial plasma lipid responses have been less consistent compared to

glucose and/or insulin responses [45, 54]. It has been shown that prolonged sitting leads to significant higher levels of plasma triglycerides, and atherogenic lipid particles including low-density lipoprotein (LDL) and very low-density lipoprotein (VLDL) cholesterol [55-57]. These changes theoretically may be due to a disproportionately reduced lipoprotein lipase (LPL) activity following 20 days of bed rest in healthy participants [57]. Interestingly, it has been shown that the regulatory mechanisms affecting skeletal muscle LPL activity, and therefore lipid metabolism, during prolonged sitting were distinct from the molecular events during MVPA. Here, reducing normal physical activity levels in rats were found to decrease LPL activity (relative to ambulatory controls) in oxidative skeletal muscle fibers by 55%, whereas voluntary running had no effect on relative LPL activity [58]. This means that sedentary behaviour had a much greater effect on LPL regulation than adding exercise training on top of the normal level of physical activity [59]. Therefore, it could be speculated that MVPA and sedentary behaviour have independent effects on (cardio)metabolic pathways relevant to metabolic health. In physically active individuals, the clearance of plasma triglycerides is directly linked to the lipolysis of triglyceride-rich lipoproteins (i.e. VLDL) by LPL, which is normally attached to the endothelium of adipose tissue, skeletal muscle and the heart [60]. LPL produces precursors of high-density lipoprotein (HDL) particles as a consequence of VLDL lipolysis. However, Yanagibori *et al*. found that long periods of sedentary behaviour led to a decreased LPL activity, which in turn resulted in increased VLDL triglyceride levels and decreased HDL_2 cholesterol and HDL_3 cholesterol levels [57]. These reduced HDL cholesterol concentrations raise the possibility of changes in reverse cholesterol transport, which normally removes cholesterol from peripheral tissues. Although the exact mechanisms responsible for the decline in LPL have not been elucidated yet, it has been proposed that during prolonged sedentary behaviours, an increased apoC-III/apoC-II ratio may impair LPL activity [57]. Here, it has already been shown that apoC-III is a potent inhibitor of LPL, explaining why increased levels of plasma apoC-III levels are associated with impaired lipolysis of VLDL [60]. In addition, other mechanisms as insulin resistance, a decreased capillary perfusion and the influence of other molecular pathways during prolonged sitting are possibly associated with a decline in LPL activity [61, 62]. Despite a reduced LPL activity, Bergouignan *et al*. showed that the release of spill over non-esterified fatty acids (NEFA) was increased after

hydrolysis of VLDL, which was in accordance with a diminished expression of FAT-CD36 and reduced muscle clearance of NEFA [63].
Furthermore, it is hypothesized that the excess of plasma lipids enhances lipid accumulation in visceral adipose tissue and intramuscular and liver ectopic lipid storage on the long-term [64]. This in turn exacerbates the development of insulin resistance. Here, lipid accumulation in the liver stimulates *de novo* lipogenesis and increased synthesis of VLDL particles, as proposed by a recent study in free-living individuals who reduced their physical activity levels [65]. This increased secretion of VLDL further facilitates hyperlipidaemia and ectopic lipid storage.

Inflammation

Chronic low-grade inflammation is indicated by the production of the pro-inflammatory cytokines such as tumour necrosis factor-alpha (TNF-α), interleukin-1 beta (IL1β), interleukin-6 (IL-6) and the hepatocyte-derived C-reactive protein (CRP) [66]. In addition, after the activation of leukocytes or endothelial cells, soluble forms of adhesion molecules including intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), E-selectin and L-selectin have also been implicated in the inflammatory pathway. Interestingly, a chronic low-grade inflammatory state has found to be associated with several cardiometabolic health related diseases and the pathogenesis of insulin resistance and atherosclerosis [67, 68]. Within the context of sedentary behaviour research, independent associations between sitting time and various pro-inflammatory cytokines including CRP, IL-6 and TNF-α have been observed in both healthy individuals and patients with T2DM [69-72]. In addition, 14 days of bed rest in young volunteers activated pro-inflammatory cascade as shown by increased circulating levels of CRP and IL-6 and decreased anti-inflammatory interleukin-10 (IL-10) white blood cell mRNAs [73]. These findings were partially confirmed in a large, representative population-based sample where sedentary time was negatively associated with CRP [74]. Given that pro-inflammatory markers negatively affect insulin sensitivity and are associated with increased risk of cardiovascular diseases, inflammation may be a key pathway through which prolonged sitting has an impact on NCD development. Important to note is that, within the association between sedentary behaviour and inflammatory markers, modifiable risk factors as abdominal obesity are key potential confounders [75-77]. Therefore,

long-term interventions are necessary to examine the exact independent relations between sedentary behaviour and inflammatory markers.

Cardiovascular Health and Sedentary Behaviour

Global leading organizations such as the American Heart Association, the American College of Cardiology, and the European Society of Cardiology emphasize that sedentary behaviour and physical inactivity are major modifiable risk factors for the development of cardiovascular diseases (CVD) as stroke and coronary heart disease. Here, it was even shown that two decades of a sedentary lifestyle were associated with a doubled risk of premature all-cause and cardiovascular death [78]. In light of the independence between sedentary time and MVPA, prospective cohort studies have shown that populations who even meet the recommended physical activity guidelines still display adverse associations between sedentary behaviour and cardiovascular disease risk factors and mortality [16, 79]. In contrast, although Stamatakis *et al*. found that higher sitting times were associated with higher CVD mortality risk, this relation was in most cases restricted to people not meeting the physical activity recommendations of spending 150 min/week in MVPA [80]. In addition, Pandey *et al*. suggested that an increased CVD risk was only independently associated with total sedentary time at very high levels (>10h/d) [81]. From this, it can be concluded that these independent associations are not as strong as observed between sedentary behaviour, physical activity and T2DM. Therefore, the exact dose-response relationship between sedentary time and cardiovascular health and the underlying mechanisms should further be elucidated. Nevertheless, some potential mechanisms have been proposed. First, a direct association between cardiometabolic health, the MetS, vascular dysfunction and CVD has often been observed. Here, hyperglycaemia is a cardiovascular risk factor due to the negative effects on a pro-inflammatory state, endothelial function and carotid intima-media thickness, subsequently leading to the development of CVD [82, 83]. Interestingly, it has been shown that the development of insulin resistance, hypertension, vascular dysfunction and dyslipidaemia occurs simultaneously in response to sedentary behaviours [84]. This suggests that these phenomena might share a common underlying molecular mechanism. It has proposed that both insulin action and activation of endothelial nitric oxide synthase (eNOS) share a common mechanism

including the phosphatidylinositol-3 kinase (PI3K)/Akt and AMP-dependent protein kinase (AMPK) signalling pathway [85-87]. Interestingly, Baron *et al*. revealed that endothelial dysfunction might contribute to the development of insulin resistance due to a reduced blood flow and subsequently decreased peripheral insulin-mediated glucose uptake [88]. Thus, during prolonged sedentary behaviours, an impaired glucose tolerance may be related to a reduced peripheral blood flow. In addition, other potential mechanisms such as a decreased expression of eNOS, due to a reduction in blood flow and local shear stress, and the production of reactive oxygen species and endogenous vasoconstrictors (i.e. endothelin 1) that alter vascular function might also contribute to the development of vascular dysfunction [87, 89-91]. However, more prospective experimental studies are warranted to characterize the exact mechanism accounting for the development of vascular dysfunction during prolonged sitting and whether these effects are independent of physical activity.

Targeting Sedentary Behaviour

Physical Activity and Sedentary Behaviour

The detrimental effects of physical inactivity have been described for a long time, and there is an urgent need for strategies to prevent the emerging global pandemic [92]. It is clear that regular physical activity, mostly performed as MVPA, induces a wide range of direct and indirect physiological adaptations and benefits for human general health [93]. Physical activity is often defined as "any bodily movement produced by skeletal muscles that requires energy expenditure" [9]. This energy expenditure varies on a continuous scale ranging from low to high and is expressed in Metabolic Equivalent of Task (METs). METs represent the ratio of the energy expenditure during a certain physical activity to the energy cost in rest, where 1 MET reflects an resting energy consumption of 1kcal/kg/hour or 3.5ml/kg/min. Physical activity is mostly categorized by intensity, of which low-intensity physical activity (LPA) is defined as activities between 1.5 and 2.9 METs, moderate physical activity contains all physical activity behaviours between 3 and 6 METs and vigorous physical activity (VPA) includes all physical activity intensities above 6 METs (Figure 1) [94]. All these physical activity intensities, when displacing sedentary behaviours, exert different effects on cardiometabolic health with effect

sizes reported in descending order of the physical activity intensity. For example, health effects for LPA were 2 – 4 times lower compared to the same amount of time spent in MVPA [95]. This was found by a study of Migueles *et al.* who showed that reallocating sedentary behaviour to the same amount of either LPA or MVPA were both significantly associated with lower mortality rates and the magnitude of the association was larger as the intensity of the replacement behaviour increased [96].

Light Physical Activity

Light physical activity (LPA) contains all behaviours with lower intensities (1.5 – 3 METs) such as household activities and casual walking during daily living. Interestingly, although a strong inverse relationship exists between sedentary behaviour and total physical activity, the strongest associations are observed for LPA [97]. This highlights a fundamental principle that people tend to spend a greater portion of their day in LPA (4.5 hours per day), which makes it the largest physical activity time component and most of the time spent in sedentary behaviour displaces time spent in LPA. Moreover, LPA may be more accessible to a large part of the population, especially those who are less physically active and fit, which makes it very suitable

for interventions. In the last decade a plethora of studies have investigated the feasibility and cardiometabolic health effects of LPA interventions [98-100].

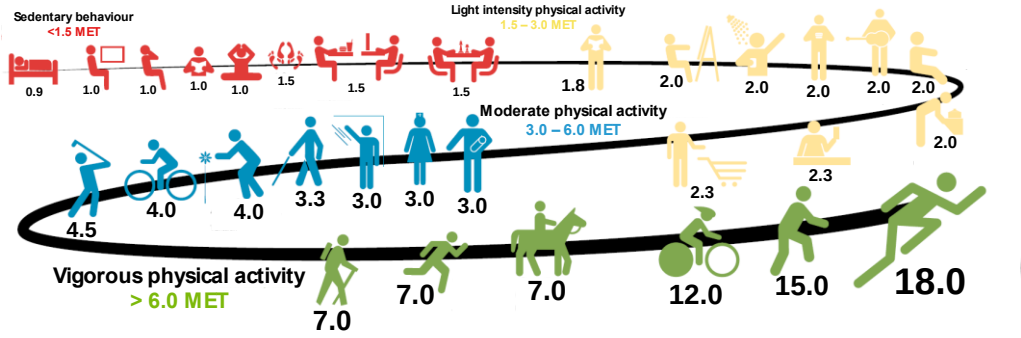

Figure 1 *Physical activity continuum starting with sedentary behaviours and increasing in metabolic equivalents to vigorous physical activity. Abbreviations:* ***MET*** *= Metabolic equivalent of task.*

Here, the association between LPA and cardiometabolic health outcomes points toward acute positive effects on glycaemic control, whereas limited effects on lipid metabolism and cardiovascular risk factors have been observed [98]. Even more beneficial improvements were found when prolonged sitting was interrupted by brief intermittent bouts of LPA [101, 102]. In addition, several researchers indicated that cardiometabolic health markers were positively associated with the reallocation of 30 minutes per day of sedentary behaviours with LPA [103-105]. Furthermore, Duvivier *et al.* showed that, when energy expenditure was matched, replacing sedentary behaviour with LPA of longer duration was more beneficial for cardiometabolic health markers compared to a single continuous bout of MVPA, except for cardiovascular health markers reflected by endothelial function [106, 107]. This means that one hour of physical exercise is not able to compensate the negative health effects of prolonged sitting. In contrast, MVPA was more suitable for microvascular function which rises the hypothesis that MVPA and LPA might have differential effects on cardiometabolic health.

Recently, more research has focussed on dose-response relationships between LPA, general health and all-cause mortality [18, 95]. Here, a curvilinear inverse association was consistently reported with at least 5 hours per day spending in LPA to observe health benefits [18, 95]. Interestingly, optimal risk reductions regarding all-cause mortality were found with spending 6.3 hours per day in LPA [18]. However, greater attention needs to be directed into the dose-response relationships between the LPA volume, frequency and different cardiometabolic health outcomes, and to interactions with other components of physical activity behaviours. This will further optimize health promotion programmes and public health guidelines.

Moderate-to-Vigorous Physical Activity

The vast majority of the evidence concerns the health benefits of moderate-to-vigorous physical activity (MVPA), which is defined as physical activity with intensities of at least 3 METs, on cardiometabolic health and reducing the CVD and all-cause mortality risk [18, 108, 109]. This is also the reason why all existing physical activity guidelines emphasize participation in MVPA to achieve (cardiometabolic) health benefits [9]. Since vigorous physical activity is sporadically reported, most of the time researchers take both moderate and vigorous physical

activity together as MVPA. The association between MVPA, all-cause mortality and cardiometabolic health is well established [18]. It has clearly been demonstrated that MVPA acutely improves glycaemic control, blood lipid profile, inflammation and cardiovascular risk markers [110], and this with smaller time investments compared to LPA. One hundred and five minutes of sedentary behaviour need to be replaced with LPA, while 30 minutes of MVPA already suffice to achieve similar cardiometabolic health effects [111]. In addition, it seems that replacing prolonged sitting time with regular MVPA breaks is more effective than a single continuous bout [46, 100, 112, 113]. Moreover, recent systematic reviews that used (device-based) measures of physical activity and sedentary behaviour reconfirmed the existing evidence of these findings and found an inverse curvilinear dose-response association between MVPA, all-cause mortality, CVD and cardiometabolic diseases [18, 108]. Here, it was shown that optimal risk reductions were found with spending 24 minutes per day in MVPA, which reflects the recommended physical activity levels of 150-300 minutes per week [9]. Interestingly, Ekelund *et al.* have shown that, although the physical activity measures were based on questionnaires, high levels of MVPA (60-75 minutes per day) seem to eliminate the increased risk of all-cause mortality associated with prolonged sitting [114]. However, most of the people are even not able to reach the recommended MVPA levels [111]. Therefore, other strategies are highly warranted as replacing sedentary behaviour with LPA is probably more feasible.

Vigorous Physical Activity

Vigorous physical activity (VPA), defined as physical activity intensities above 6 metabolic equivalents (equivalent in effort to running or jogging), is a potentially time-efficient strategy to reduce sedentary behaviour [115]. Interestingly, performing VPA has even additional health enhancing responses compared to equivalent volumes of MVPA and LPA [116]. However, although the benefits of VPA on cardiometabolic health and mortality are well understood [117-119], only about 20% of the adult population has reported doing any vigorous exercise for at least 15 minutes a month. In addition, in most studies moderate and vigorous physical activity are represented as MVPA since it is not able to measure VPA on its own with the current technology. Although the physical activity guidelines recommend 75 min of VPA per week, little attention has been paid to the contribution of VPA

on reducing sitting time and improving cardiometabolic health. Moreover, the exact frequency and duration of VPA to counteract the negative effects of sedentary behaviours should be elucidated. Recently, Stamatakis *et al.* have proposed a new paradigm which would allow VPA to be more accessible to individuals who are currently physically inactive by means of the regular accumulation of vigorous intermittent lifestyle physical activity (VILPA), or exercise snacking [120]. It is characterised by brief intermittent bursts of VPA performed during activities of daily living, including brisk walking, stair climbing, gardening or carrying children or shopping bags. Nowadays, the health benefits of VILPA are acknowledged by the public health guidelines of the US (2018) and the UK (2019) [121, 122]. Although the research field is beginning to yield promising trials with measurable effects on cardiorespiratory fitness in young adults, it is highly recommended in future research to examine a broad range of VILPA activities in free-living conditions and the subsequent effects on cardiometabolic health.

Steps Per Day

The most important question within this paragraph is: "do we really need to take 10,000 steps per day"? The answer is: NO. A common goal of 10,000 steps per day has been maintained by the lay press when it comes to being fit and healthy. However, the origin of this advice derived from a marketing trick of Yamasa Clock who sold in 1965 a pedometer with the trade name "Manpo-kei", which means "10,000 steps meter". Studies have shown that this step target improved cardiovascular health, mental health, and even lowers T2DM risk, and this could be the reason why a lot of people rely on this arbitrary number [123-125]. Despite this, more research with the aid of prospective cohort studies was warranted by an expert committee who identified a critical gap in knowledge on the dose-response association of steps, (cardiometabolic) health outcomes and all-cause mortality [126]. Recently, Lee *et al.* found that a step volume distribution of 4400 steps per day was associated with a 41% lower risk of mortality, with an optimal reduction up to 7500 steps per day within older women [127]. This was confirmed by other researchers who revealed that participants taking 7000-8000 steps per day or more experienced a lower mortality rate of 50% to 70%, and decreased the risk for CVD and cancer [128, 129]. However, in all studies, no association was

found between step intensity and mortality. Since the number of steps per day are associated with (cardiometabolic) health and all-cause mortality, it is a highly relevant metric for quantifying total daily physical activity levels. In addition, the simplicity, easy use and objective measurements by consumer wearable devices and accelerometers provides an opportunity for population-wide monitoring of steps, which can ultimately be included into public physical activity guidelines.

Patterns of Sedentary Behaviour

In addition to different intensities of physical activity and total sedentary time, the pattern in which sedentary time is accumulated may also play an important role. Here, total sedentary time within a day could be accumulated in prolonged periods of time, or with many short bouts spread throughout the day. Interestingly, breaking up prolonged sitting with short periods of physical activity or standing has been associated with more favourable cardiometabolic health outcomes. Healy *et al.* found in an observational study that frequent interruptions of sedentary time were beneficially associated with cardiometabolic risk factors including blood triglyceride levels and 2-hour plasma glucose concentration, independent of total sedentary time, MVPA and mean intensity of the breaks [130]. Two systematic reviews of intervention studies in laboratory conditions confirmed these findings by showing statistically significant differences between physical activity breaks of any intensity compared to uninterrupted sitting on glucose, insulin and triglyceride concentrations [131, 132]. However, evidence for effects on vascular function was insufficient [132], while Peddie *et al.* reported regular breaks to increase both blood flow and shear stress when sitting timing was interrupted by 2 minutes every 30 minutes [133]. These studies show that not only the total sedentary time matters, but also the manner in which it is accumulated. Therefore, the recommendation to regularly interrupt prolonged sedentary time may be feasible to implement across numerous settings, for instance during television advertising breaks and during long periods of sitting at work. However, more research is necessary to better understand how different patterns of sedentary time affect cardiometabolic health, especially in free-living conditions.

A Combined Physical Activity and Sedentary Behaviour Approach

The associations of sedentary behaviours, LPA, MVPA and VPA (when approached separately) are becoming more and more clear, although there has been proposed to shift towards an integrated and multidimensional research paradigm to examine the composition of all physical activity intensities and sedentary behaviours of the entire day together [96]. This approach mimics a more "real life" approach in which the time is finite during the day (24 hours) and alterations in a certain behaviour necessarily displaces time spent in at least on other behaviour. This simply means that time in each of the various physical activity and sedentary behaviours are co-dependent. This new research field has already a couple of studies in which the combined effect of time spent in sleep, sedentary behaviours and physical activity, that together constitute a composite whole, have been investigated in relation to all-cause mortality and cardiometabolic health [96, 134]. For example, a healthy waist circumference was associated with a time-use composition of 77 min MVPA, 96 min LPA and approximately 13 hours of sedentary behaviour, which could be compared with a typical office worker exercising every day. This same healthy waist circumference was also associated with a composition of 24 min MVPA, about 12 hours of LPA and 2.5 hours of sedentary behaviours, which corresponds to a compositional pattern of someone who does not meet the recommended guidelines, but spends much less time in sedentary behaviours. The most prominent study was recently published by Chastin *et al*. who found that the beneficial association of time spent in MVPA with all-cause mortality depended on the balance of time spent in LPA and SB [17]. Here, the recommended 30 minutes of MVPA a day could decrease all-cause mortality risk by 80% for individuals who spent less than seven hours a day in sedentary behaviours. However, for those who spent 11-12 hours in sedentary behaviours the benefits of MVPA might be completely attenuated and could only reduce the risk if combined with 4−5 hours of LPA [17]. These promising analyses in terms of integrated physical activity profiling might allow us to find whether there is an ideal combination of these behaviours associated with an optimized cardiometabolic health profile.

Interventions to Increase Physical Activity and Reduce Sedentary Behaviour

Although we now know the beneficial health effects of physical activity at different intensities in combination with reducing sedentary time, one third of the adult population is still physically inactive and spend 8 to 12 hours a day in sedentary behaviours. Common cited constraints to engaging in physical activity are lack of time, poor motivation, lack of knowledge, fear of injury and a low long-term compliance to healthy lifestyle interventions [135-137]. Consequently, strategies that aim to improve the long-term adherence to adequately increase physical activity levels and reduce sedentary behaviours are highly warranted. Here, the current literature clearly proposed that goals should be realistic, attainable, specific and measurable [138, 139]. In the past decades the number of efficacious interventions to address the global issue of insufficient physical activity have increased remarkably [140]. However, there is a lack of evidence for interventions in real-world settings since only a small number of successful interventions are translated from research into practice [141]. With regard to physical activity, the International Society for Physical Activity and Health has recently published the 'Eight Investments That Work For Physical Activity, including whole-of-school programmes, active transport, active urban design, healthcare, public education such as mass media, sport and recreation for all, workplaces and community-wide programmes [142].

Nowadays, research from lifestyle interventions and studies focusing on reducing sedentary behaviours are promising. A variety of behaviour change strategies have been applied including the incorporation of environmental (i.e. sit-stand desks or the restructuring outdoor spaces and/or facilities) and/or behavioural approaches on individual and community-based levels to affect behavioural determinants [143]. Systematic reviews found consistent evidence that interventions focusing solely on the reduction of sedentary behaviours led to large and clinically meaningful reductions in sedentary time (22-91 minutes per day) [144-146]. In addition, a comprehensive systematic review and meta-analysis from Nieste *et al.* showed that patients with a clinical condition were able to reduce their sedentary behaviour by approximately one hour following an intervention to reduce prolonged sitting and improved cardiometabolic health in free-living conditions [147]. Here, self-monitoring with the aid of activity trackers or a telephone application in combination with motivational counselling were used as most important

behaviour change interventions. These so-called multicomponent behaviour change interventions were also the most effective strategy to reduce sedentary behaviour within the general population [148]. Despite the promising strategies to reduce sedentary behaviours, more high-quality research is necessary.

Consumer Wearable Activity Trackers to Target Physical Activity and Sedentary Behaviour

During the last decades the use of wearable technologies, including consumer wearable activity trackers (CWATs), has evolved considerably. The popularity of CWATs has increased remarkably, as shown by the large shipping numbers in 2020 (> 445 million devices). These consumer devices are able to track an individual's physical activity behaviour, often via step count measurement with the aid of accelerometry. In addition, CWATs are inexpensive, easy to use and all data is readily available, which make them a user-friendly indicator of overall physical activity volume. Emerging evidence has shown that CWATs are able to encourage physical activity by achieving step goals set by the device [149, 150]. Moreover, Bravata *et al.* showed that the addition of goal setting was even more effective and may be therefore a key motivational factor for increasing physical activity levels [151]. In addition, using CWATs has been shown to be associated with improvements in BMI, blood pressure and metabolic health outcomes [151]. This enable CWATs as an effective tool to increase physical activity levels within the current physically inactive population, especially in people with cardiometabolic conditions. However, until now, research with the aid of activity trackers mainly focused on increasing physical activity instead of reducing sedentary behaviours. Furthermore, more and more measurement options are included such as heart rate, blood pressure, sleep patterns and energy expenditure. These wearables could therefore become a key element in the management and follow up of patients with chronic diseases since it can provide unique insights into people's physiological functions and general health. In the future, a fundamentally different healthcare approach can be applied using CWAT devices. Deviations from an individual's 'normal' baseline physiological measurement could be detected immediately instead of comparing these values with population statistics as done in current practice. In addition, people are provided with immediate feedback and will be confronted with their own health risks and can change their lifestyle in an

early stage of chronic disease development. Interestingly, the potential value of CWATs has become increasingly apparent during the current times of the coronavirus disease 2019 (COVID-19) pandemic. For example, Mishra *et al.* looked at sleep patterns, elevated resting heart rates and increased heart rates relative to the number of steps, where 81% of the participants could be identified as potentially COVID-19 positive [152]. Here, the positive participants showed aberrant physiological signals 4 to 7 days in advance of the onset of symptoms or diagnosis.

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Chapter 2

Objectives and General Outline

Although we know that physical activity in the form of MVPA has a plethora of beneficial (cardiometabolic) health effects, it is far less clear whether high volumes of MVPA are able to improve cardiometabolic health despite spending in high volumes of sedentary time. This stems from the fact that sufficiently active people are also often classified as sedentary. In other words, is it possible to attenuate, or even eliminate, the association between sedentary behaviour and cardiometabolic health with high volumes of MVPA?

Several studies already observed that the associations between sedentary behaviour and all-cause mortality differed depending on how much physical activity was carried out [1]. More and more research is being performed to elucidate a cut-off value of physical activity to compensate the detrimental effects of prolonged sitting on the development of several chronic conditions. Recent large prospective cohort studies reported a MVPA level of at least 60 – 75 min/day, whereas others found that only about 20 – 40 minutes of MVPA a day appears to eliminate the detrimental effects of a high total sitting time on CVD and all-cause mortality [1-3].

This evidence emphasizes the role of MVPA in offsetting the potential harms associated with excessive sedentary time and, therefore, it is suggested that MVPA modifies the associations between sedentary behaviours and all-cause morta

However, most of these studies are based on self-reported levels of MVPA and sedentary time and, therefore, it is unclear whether these associations still exist when these variables are objectively measured with the aid of accelerometers. In addition, only associations between MVPA, sedentary time and all-cause mortality have been found so far. Since cardiometabolic risk factors are a precursor and strongly related to the development of NCDs, it is also important to know if the association between sedentary time and cardiometabolic health related outcomes can be modified by high amounts of MVPA. Therefore, in **Chapter 3** we aim to investigate the modifying effects of MVPA on the inverse association between sedentary behaviour and cardiometabolic health within highly active adults.

For most people these large volumes of MVPA necessary to attenuate or fully eliminate the association between cardiometabolic health and a sedentary lifestyle is challenging, keeping in mind that the majority of the population does not reach the recommended guidelines (150−300 min/week of MVPA). Therefore, other

more pragmatic and time-efficient strategies involving a more holistic 24-hour approach targeting both interacting behaviours are necessary [4]. Here, it is well known that time and motivation are major barriers to the practice of MVPA (i.e. exercise) and, therefore, introducing LPA into daily life activities could be an effective strategy to reduce sedentary behaviours and improve (cardiometabolic) health outcomes.

In addition, current behaviour change strategies to reduce sedentary time are often time consuming, resource intensive, in a clinical setting and difficult to perform by practitioners or health coaches. Therefore, new advanced behaviour change techniques are highly warranted in modern society. In addition, studies that investigated the efficacy of behaviour change techniques to improve sedentary behaviours were often a combination of different techniques. This makes it difficult to examine the exact contribution of each separate technique, or the synergistic effects of the combined techniques. In this respect, the widespread use of consumer wearable activity trackers (CWATs) may be an alternative behaviour change strategy to reduce sedentary behaviours. The self-monitoring, motivational and goal setting properties of these devices support people to better adhere to long-term sedentary behaviour change interventions in free-living conditions. To date, CWATs are predominantly used in sports communities for self-monitoring sport/training performance related parameters. In addition, it has already been shown that CWAT-based multicomponent interventions can increase physical activity levels within healthy adults [5, 6]. This is promising for global public health and potentially reduces the risk of NCD development [6]. Indeed, it has been shown that even small increases in physical activity at a population level could have positive impacts on the risk of NCD development as CVD, T2DM and several cancers [7-9]. Next to the decreased risk, physical activity plays also an important role in the progression and management of people who already have NCDs. Therefore, in **Chapter 4** we systematically review the effect of CWATs on physical activity in populations with NCDs, including chronic respiratory diseases, T2DM, CVD, overweight/obesity, cognitive disorders or sedentary older adults.

Given the fact that both physical activity and sedentary behaviour should be targeted, we subsequently investigate whether these CWAT-based interventions are also capable to reduce sedentary time and improve cardiometabolic health in

healthy sedentary adults. In addition, because CWATs are mostly included as part of a multicomponent intervention, we also wanted to know the efficacy of a monocomponent (CWAT-only) intervention to reduce sedentary time and increase physical activity. This may help to increase the efficiency and quality of health care in the prevention and management of NCDs. We therefore investigate the effectiveness of self-monitoring (CWAT-only) and multiple behaviour change techniques (CWAT + motivational counselling) to reduce sedentary behaviour and increase physical activity. Because patients with chronic diseases have more barriers to engage in physical activity due to a lower self-efficacy and the experience of physical symptoms [10, 11], we will first investigate the efficacy in a healthy sedentary population. This will give more insights into the working mechanism of CWATs as well as the interaction of a multicomponent intervention, consisted of multiple behaviour change techniques, and whether these techniques are efficacious in producing significant and clinically meaningful reductions in sedentary time. In addition, the second aim is to investigate the effectiveness of these behaviour change techniques to improve metabolic (**Chapter 5**) and cardiovascular (**Chapter 6**) health in sedentary adults and to what extent LPA and MVPA affect these parameters (Figure 1).

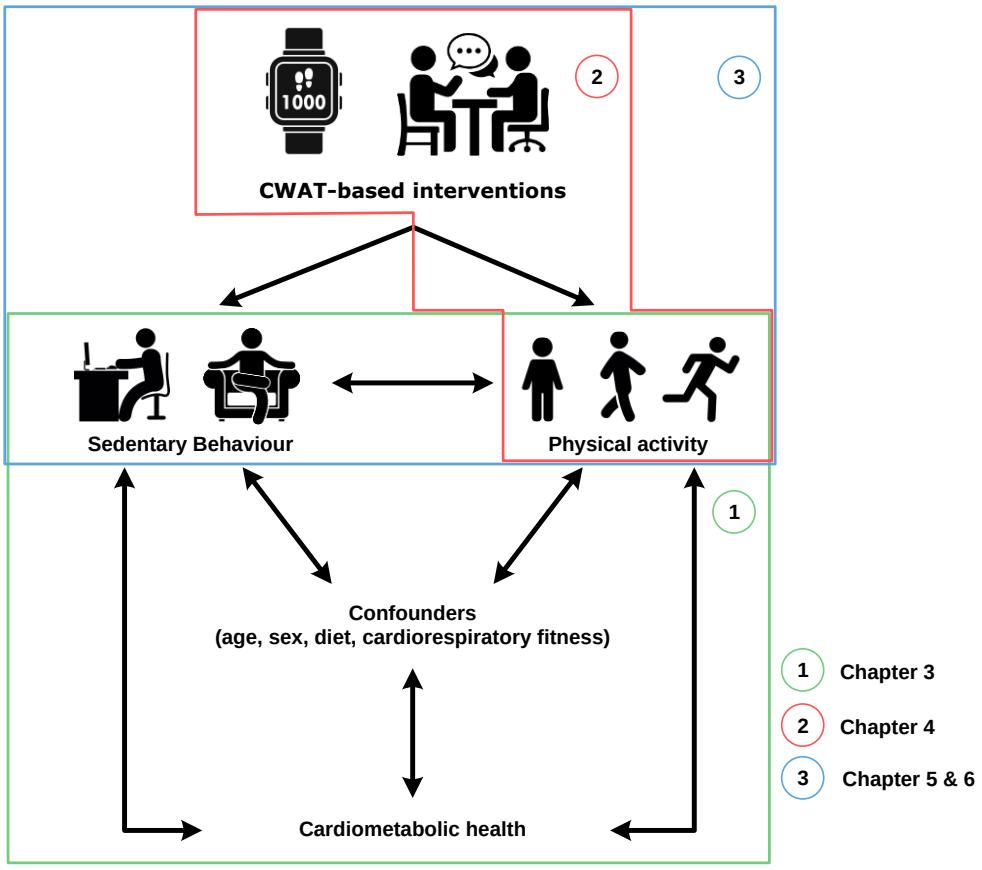

Figure 1 *Schematic representation of all hypothesized associations and mediators discussed in the present dissertation.*

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Chapter 3

The potential harms of sedentary behaviour on cardiometabolic health are mitigated in highly trained athletes

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Submitted

Abstract

Background: Insufficient physical activity and sedentary behaviour are important factors that determines cardiometabolic health and the development of non-communicable diseases. It has been suggested that high levels of moderate-to-vigorous physical activity (MVPA) could beneficially modify the associations between time spent in sedentary behaviour and all-cause mortality. However, the exact amount of MVPA needed to attenuate or even fully mitigate the detrimental effects associated with sedentary behaviour remains unclear. Therefore, the aim of this study was to investigate the modifying effects of MVPA on the association between sedentary behaviour and cardiometabolic health within highly active adults.

Methods: In a cross-sectional design, 61 (male/female: 41/20) highly trained athletes (age: 33.6 ± 10.7 years; BMI: 22.4 ± 2.3 kg/m^2) performed a maximal cardiopulmonary exercise test from which indicators for peak performance were determined. Physical activity (PA) and SB were assessed using the activPAL3™ accelerometer. In addition, anthropometrics, blood pressure, plasma lipids and insulin sensitivity using an oral glucose tolerance test were assessed. These cross-sectional associations between a daily movement behaviour composition and cardiometabolic health parameters were investigated using a compositional data analysis approach.

Results: Participants spent 600 ± 86 min/day in sedentary behaviours and engaged in almost 1.5 hours per day of MVPA. MVPA ($\beta = 8.07 \pm 2.18$; $r^2 = 0.544$; $p < 0.001$) was significantly associated with oxygen uptake, relative to all other remaining behaviours. No associations were found between physical activity behaviours and cardiometabolic health related outcomes.

Conclusion: In highly trained athletes, no association was found between time spent in sedentary behaviour and cardiometabolic health, possibly due to the high amount of time spent in MVPA.

Introduction

Insufficient physical activity is one of the major risk factors for the development of non-communicable diseases (NCD) and has been identified as the fourth leading cause of death worldwide [1]. Insufficient physical activity is defined as not reaching the recommended levels of 150-300 minutes per week spending in moderate-to-vigorous physical activity (MVPA), as stated by the 2020 World Health Organization guidelines [2]. Next to the time recommended to spent in MVPA, it appears that sedentary behaviour also is an important factor that determines cardiometabolic health, NCD development and all-cause mortality [3-5]. Here, sedentary behaviour is defined as 'any waking behaviour characterized by a low energy expenditure (≤1.5 metabolic equivalents), while being in a sitting or reclining posture' [6]. In fact, during the past decade, emerging evidence clearly disclosed that prolonged sedentary behaviour is an interdependent contributor to cardiometabolic diseases and all-cause mortality, even in the presence of regular MVPA [7, 8]. However, several studies have observed that the association between sedentary behaviour and all-cause mortality could be modified, depending on the duration of time spent in MVPA [4]. Interestingly, large cohort studies suggested that spending more than 60 minutes per day in MVPA could beneficially modify (attenuate or even eliminate) the associations between time spent in sedentary behaviour with all-cause and cardiovascular disease mortality [4, 5, 9]. However, conclusions were only based on: 1) a large variety of time spent in MVPA (30-75 minutes per day); 2) the association between sedentary behaviour and all-cause mortality and 3) regression analyses instead of analysing the combined effect of allocating time to different behaviours using compositional data analysis (CoDa). The large variation of time spent in MVPA necessary to mitigate the association between sedentary behaviour and all-cause mortality partly originates from the fact that these studies relied on self-reported data and the use of hip or wrist worn accelerometers to assess MVPA and sedentary behaviour. It is well known that these measurement tools are prone to misclassification and, therefore, more sophisticated and valid instruments such as thigh-worn accelerometers are recommended [10].

Furthermore, although the modifying effects of MVPA on the association between sedentary time and all-cause mortality has been partly investigated, cardiometabolic health is a precursor of and strongly related to the development

of NCDs [11]. Therefore, it is also important to know if the association between sedentary time and cardiometabolic health related outcomes can be modified by spending in high amounts of MVPA. In addition, the majority of studies that examined the association between various movement behaviours (sleep, sedentary behaviour, standing, light-intensity physical activity [LPA] and MVPA) and cardiometabolic health have been performed in isolation by regression analyses, without adjustment for time spent in all other behaviours [4, 5, 9]. Given the finite nature of each day, time spent in one behaviour necessarily affects the time that remains to be spent in at least one other behaviour. Therefore, time spent in sleep, SB, standing, LPA and MVPA are related in a co-dependent manner. To date, new approaches as compositional data analysis have been recommended as a methodological analysis that accounts for this compositional approach [12] and has already been used within the field of sedentary behaviour and physical activity research [13, 14].

To investigate if high amounts of time spent in MVPA are able to beneficially modify the inverse association between sedentary behaviour and cardiometabolic health, recreational athletes would be a suitable study population as their time spent in MVPA is corresponding to the highest physically active group from large cohort studies examining the modifying effects of MVPA on sedentary behaviour and all-cause mortality [4, 9, 15].

Therefore, the aim of this study was to investigate the modifying effects of MVPA on the association between sedentary behaviour and cardiometabolic health using more precise accelerometer-derived measures within highly active adults. Here, a compositional data analyses approach will be used to account for all other movement behaviours such as sleep, standing time and LPA.

Material & Methods

Subjects

Sixty competitive and recreational athletes aged between 18 and 65 years were locally recruited using online and paper advertisements. Subjects exercised ≥ 4 hours per week [16] and different sport types were included based on the classification of Mitchell *et al*. and were restricted to dynamic MVPA as cycling, soccer and running [17].

Exclusion criteria were pregnancy, any known contradiction for physical activity, systolic blood pressure >160 mm Hg, diastolic blood pressure >100 mm Hg, more than 20 alcohol consumptions per week or subjects diagnosed with any known chronic disease or participants with contraindications for cardiopulmonary exercise testing (based on screening visit by general practitioner). All participants were informed in detail and were asked to provide written informed consent. The study was approved by the medical ethical committee of Hasselt University and performed at Hasselt University (Diepenbeek, Belgium) between March 2021 and June 2021 in accordance with the principles of the Declaration of Helsinki. The present study was registered at clinicaltrials.gov (NCT04711928).

Study Design

The study was carried out according to an observational cross-sectional design. During a one-day study visit to Hasselt University the assessment of physical fitness and cardiometabolic health related outcomes including fasting blood samples, an oral glucose tolerance test, anthropometrics and body composition was performed. In addition, 24-hour movement behaviours including sleep, sedentary behaviour and physical activity (standing, LPA and MVPA) were measured. Then associations were examined between sedentary behaviour and MVPA and these cardiometabolic health outcomes, relative to all other remaining behaviours.

Study Procedure

Screening

Following inclusion, participants were screened by their own general practitioner. This was based on a medical examination consisting of medical history and medication use. In addition, cardiovascular status was screened using a resting 12-lead electrocardiogram and resting blood pressure measurement.

Testing Day

After a positive advice of the general practitioner, eligible participants were included for observational measurements during a testing day. Participants were instructed to refrain from strenuous physical exercise two days before the test day, moreover, one day prior to each test day participants were requested not to

consume alcohol. From midnight prior to examination, all subject refrained from consuming food, with the exception of water *ad libitum* to prevent changes on biochemical analysis and exercise physiology. First, in fasted state (at least twelve hours after the last meal) anthropometry and body composition using dual energy X-ray absorptiometry were assessed and venous blood samples were collected. Subsequently, assessment of blood pressure and resting heart rate were performed. Next, an oral glucose tolerance test (OGTT) was performed to assess insulin sensitivity and beta cell function. After a light meal, cardiopulmonary exercise testing (CPET) was performed. Following all measurements, physical activity and sedentary behaviour were assessed using accelerometry (activPAL3™, PAL Technologies Ltd, Glasgow, Scotland) for seven consecutive days.

Measurements

Physical Activity and Sedentary Behaviour

Physical activity and body postures were quantified using the activPAL3™ activity monitor (PAL Technologies Ltd, Glasgow, UK). The device was enclosed with a nitrile sleeve and attached to the anterior mid-thigh of the participants right leg using an adhesive dressing (Tegaderm, 3M, Minnesota, USA). Participants were instructed to wear the device for a period of 7 consecutive days and 24h hours per day. The activPAL™ assesses accurately time spent in sleeping, sedentary behaviours (sitting or lying), standing and physical activity including step count and step cadence (low intensity physical activity and MVPA) [18]. Furthermore, step count and short (< 30 minutes) and prolonged (> 60 minutes) sedentary bouts were identified. All variables were determined from the ActivPAL™ recordings using proprietary software (PALanalysis V8, PAL Technologies Ltd, Glasgow, UK).

Anthropometry and Body Composition

Body height was measured to the nearest 0.1cm using a wall-mounted Harpenden stadiometer, with participants barefoot. Body weight (in underwear) was determined using a digital-balanced weighting scale to the nearest 0.1kg. BMI was calculated from weight and height measurements (weight/height²). Waist and hip circumferences were measured to the nearest 0.1cm using a flexible metric measuring tape with participants barefoot (in light clothes) in standing position.

Waist circumference was measured at the midpoint between the lower rib margin and the top of the iliac crest. Hip circumference was measured at the widest circumference of the hip at the level of the greater trochanter. Waist-to-hip ratio was calculated by dividing waist circumference (cm) by hip circumference (cm). Whole body fat, lean tissue mass and bone mineral density were evaluated using dual energy X-ray absorptiometry (Hologic Series Delphi-A Fan Beam X-ray Bone Densitometer, Vilvoorde, Belgium).

Insulin Sensitivity, Beta Cell Function and Plasma Lipids

After antecubital catheter placement, fasting blood samples were obtained for the measurement of cardiometabolic risk factors. Serum separation and sodium fluoride (NaF) containing BD vacutainer™ tubes (Becton, Dickinson and Company, Franklin lakes, NY, USA) were collected. To obtain plasma, NaF tubes were immediately centrifuged at 1300 x *g* for 15 minutes. Serum tubes coagulated for at least 30 minutes prior to centrifuging at 1300 x *g* for 15 minutes. All centrifugation steps were performed at room temperature (21°C). Supernatants were immediately portioned into aliquots and frozen at −20 °C and subsequently moved to a − 80 °C freezer until analysis. Fasting glucose, insulin, total cholesterol, high density lipoprotein cholesterol (HDL-cholesterol), low density lipoprotein cholesterol (LDL-cholesterol) and triglyceride concentrations were automatically assessed on the Roche Cobas 8000 (Roche Diagnostics International Ltd, Rotkreuz, Switzerland).

A standard 5-point oral glucose tolerance test (OGTT) was performed for assessment of whole body/tissue specific insulin sensitivity and beta cell function. Subjects ingested a solution (250ml) containing 75g dextrose, and venous blood samples were obtained at t=0, 30, 60, 90 and 120min for assessment of venous glucose and insulin concentration. From glucose and insulin concentrations, whole-body insulin resistance was estimated using the homeostatic model assessment for insulin resistance (HOMA-IR) and the Matsuda index. The HOMA-IR was calculated by: fasting glucose (mmol/L) * fasting insulin (µU/mL) / 22.5 [19], and the Matsuda index was calculated as: 10,000/√[fasting glucose (mg/dL) * fasting insulin (µU/mL)) * (mean glucose during OGTT (mg/dL) * mean insulin during OGTT (µU/mL)] [20]. Beta cell function was estimated by calculation of the insulinogenic index (IGI): ratio of increment of insulin (µU/mL) and glucose

(mg/dL) in the first 30 min of OGTT and the HOMA-B: 20 * fasting insulin (µU/mL) / (fasting glucose [mmol/L] – 3.5) [19]. Tissue specific insulin resistance was calculate using the hepatic insulin resistance index (HIRI) and the muscle insulin resistance index (mISI). The HIRI was calculated as the product of the tAUCs for glucose and insulin during the first 30 min of the OGTT (glucose 0 – 30 [tAUC in mg/dL h] * insulin 0 – 30 [tAUC in µU/mL h]) and the mISI was calculated as the rate of decay of glucose concentration during the OGTT divided by the mean insulin concentration during the OGTT in mg/dL/min/ µU/mL). The rate of decay was calculated as the slope of the least square fit to the decline in glucose concentration from peak to nadir, as described by Vogelzangs *et al* [21].The total area under the curve (tAUC) for glucose and insulin for the 2 hour period was calculated using the trapezoidal rule [22].

Blood Pressure

After an initial resting period of 20 min with participants in a seated position in a quiet room with constant temperature (21°C), blood pressure (BP) was measured at least 3 times at 2-min intervals until blood pressure was stabilized using an electronic sphygmomanometer (Omron®, Omron Healthcare, IL, USA) from the left arm and documented as the mean value of the 3 final measurements [23]. Mean arterial pressure (MAP) was calculated as MAP = systolic BP + (2 x diastolic BP) / 3.

Clustered Cardiometabolic Risk Score

A clustered cardiometabolic risk score (CCMR) was computed with the aid of the following variables: waist circumference, triglycerides, HDL-cholesterol, MAP and fasting plasma glucose [24, 25]. The sex specific standardized value of each individual variable was calculated as follows: z-score = [individual value – sample mean]/ standard deviation (SD). Subsequently, HDL-cholesterol z-scores were inverted and z-scores of all variables were averaged to form a CCMR.

Cardiorespiratory Fitness

A cardiopulmonary exercise test was performed up to volitional exhaustion using an electronically braked cycle ergometer (eBike Basic®, General Electric GmbH, Bitz, Germany), controlled by the Metamax (Metalyzer II® 3B Cortex, Leipzig,

Germany) [26]. After a 5-min warm-up phase, an incremental exercise cycling period with an initial workload of 80W for male and 40W for female, and increasing workload of 40W per minute for male and 30W per minute for female was performed. During incremental exercise a cycling frequency of 60 – 70 revolutions per minute (rpm) had to be maintained. The test was ended when the participant failed to maintain a pedal frequency of at least 60 rpm. With the aid of continuous pulmonary gas exchange analysis oxygen uptake ($\dot{V}O_2$), carbon dioxide output ($\dot{V}CO_2$) and the respiratory gas exchange ratio (RER) was collected breath-by-breath and averaged every ten seconds. Heart rate (HR) was continuously monitored and averaged every ten seconds using the H10 Polar heart rate monitor (Polar Electro Oy, Kempele, Finland). All participants were verbally encouraged during exercise testing to achieve maximal effort, based on RER, maximal heart rate (HR) and blood lactate levels (satisfaction of 2/3 of the following criteria: RER >1.15; maximal HR ≥ predicted - 10 beats per minute; post exercise lactate level > 8.0mmol/l).

Data Analyses

Statistical analysis was performed by IBM SPSS® version 27.0 (IBM SPSS Statistics for Windows, Chicago, IL, USA). Data were expressed as mean ± SD. A Shapiro-Wilk test was used to test normality of the data ($p < 0.05$). Three different groups were created according to tertiles of total sedentary time (SB_{slow}, $SB_{intermediate}$ and SB_{high}) to compare cardiometabolic health related outcomes between different amounts of sedentary behaviour. Comparisons between groups (low, intermediate and high sedentary time) were tested using the Fischer's exact test for categorical variables. For continuous variables a one-way ANOVA (Bonferroni post-hoc comparison test) was used for normally distributed data and the Kruskal-Wallis test (Dunn's post-hoc comparison test) for abnormally distributed data.

Variables of sleep, physical activity (standing, LPA and MVPA) and sedentary time were analysed using compositional data analyses (CoDa) approach with the aid of the R package Shiny (Shiny V.1.0.5, RStudio, Boston, USA, 2017), as described before [27]. The CoDa approach is based on the fact that if the time spent in one behaviour is changed, it will inevitably affect the time in at least one other

behaviour within that day. Data with this inherent dependency in a way that they add up to a constant sum are constrained or compositional [28].
Therefore, the composition of the day was defined as the proportions (p) of time spent in five different moment behaviours: sleeping, sedentary behaviour, standing, LPA and MVPA (the method is described in detail by Chastin *et al*. [27]). Here, the compositional mean of all individuals was calculated by normalizing the geometric means of all individual components (sleeping, sedentary behaviour, standing, LPA and MVPA) in such a way they add up to 1 (adjusted for the total day time of 1440 min). Then, the overall geometric ($g_{overall}$) mean for each component was calculated by combining all participants:

$$g_{overall} = 1\ (24h) = p_{sleeping} + p_{sedentary\ behaviour} + p_{standing} + p_{LPA} + p_{MVPA} \quad (1)$$

In addition, the geometric mean was calculated for each component within the subgroups with a low, intermediate and high sedentary time (g_{SBlow}, $g_{SBintermediate}$ and g_{SBhigh} ; $g_{subgroup}$). To characterize the movement behaviours of the individual subgroups relative to the geometric mean of the overall composition the log-ratio of the geometric mean within a group and the overall geometric mean of the individual components was calculated as:

$$\text{Relative difference between subgroups: } log\left(\frac{g_{subgroup}}{g_{overall}}\right) \quad (2)$$

The variability within the data was described as the variability of each behaviour relative to the variability of all other behaviours using a variation matrix. Here, a log-ratio variance close to zero indicated high co-dependence (proportionality) between the behaviours. Here, a value close to zero implies that the two components involved in the ratio are highly proportional (high co-dependence). To treat and interpret the data correctly, information that contains parts of a composition needs to be expressed relative to the other parts as log ratios [28].

Therefore, time spent in sleep, sedentary behaviour, standing, LPA and MVPA were transformed into an isometric log ratio (ILR) coordinates given by the equations 3−6:

$$\text{ILR/ln(SB: other behaviours)} = \sqrt{\frac{4}{5}}\ln\left(\frac{\text{SB}}{\sqrt[4]{\text{Sleep}\cdot\text{Standing}\cdot\text{LPA}\cdot\text{MVPA}}}\right) \quad (3)$$

$$\text{ILR/ln(standing: other behaviours)} = \sqrt{\frac{4}{5}}\ln\left(\frac{\text{Standing}}{\sqrt[4]{\text{Sleep}\cdot\text{SB}\cdot\text{LPA}\cdot\text{MVPA}}}\right) \quad (4)$$

$$\text{ILR/ln(LPA: other behaviours)} = \sqrt{\frac{4}{5}}\ln\left(\frac{\text{LPA}}{\sqrt[4]{\text{Sleep}\cdot\text{SB}\cdot\text{Standing}\cdot\text{MVPA}}}\right) \quad (5)$$

$$\text{ILR/ln(MVPA: other behaviours)} = \sqrt{\frac{4}{5}}\ln\left(\frac{\text{MVPA}}{\sqrt[4]{\text{Sleep}\cdot\text{SB}\cdot\text{Standing}\cdot\text{LPA}}}\right) \quad (6)$$

Thus, these ILRs express the ratio of sedentary behaviour, standing, LPA or MVPA to time in all other behaviours.

Multivariate linear regression analyses were applied to examine the association between the daily composition of time spent in sleep, sedentary behaviour, standing, LPA and MVPA as independent variables with cardiometabolic health related outcomes including body composition (waist circumference and percentage fat mass), blood pressure (systolic and diastolic), physical fitness (maximal oxygen uptake corrected for body weight), lipid profile (total cholesterol, HDL-cholesterol, LDL-cholesterol and triglyceride concentration), insulin and glucose concentrations in a fasting state and after the 2h OGTT, tAUC of insulin and glucose, whole-body insulin sensitivity (HOMA-IR and Matsuda index), beta cell function (IGI and HOMA-B), tissue specific insulin resistance (mISI and HIRI) and the CCMR. Here, the computation of the association between daily time compositions, as an entire multicomponent exposure variable, with cardiometabolic health took into account the codependence and interactions between behaviours making up the composition. Models were also adjusted for potential confounders including sex, age, smoking status, chronic disease and medication. Correction for multiple testing was implemented using the Benjamini-Hochberg false discovery rate (FDR) method, with FDR < 0.05 considered as statistically significant [29]. A *p*-value < 0.05 (2-tailed) was considered statistically significant.

Results

Subject Characteristics and Cardiometabolic Health Related Outcomes

A total of 72 participants were screened for study entry of which 61 individuals effectively participated in the study. Exclusion was due to a spending less than 4 hours per week on structured MVPA (n = 7) and age restrictions (n = 4). Participants had a mean age of 33.6 ± 10.7 years (range: 18.9 – 64.5 years of age), a BMI of 22.4 ± 2.3 kg/m^2 (range: 17.2 – 31.0 kg/m^2) and a maximal oxygen uptake of 53.5 ± 10.0 mL · kg^{-1} · min^{-1} (range: 38.6 – 79.7 mL · kg^{-1} · min^{-1}). Furthermore, the total population consisted of 41 males (67%) and 20 females (33%). Participants spent 452 ± 39 min/day (31%) sleeping, 600 ± 86 min/day (42%) in sedentary behaviours, 219 ± 59 min/day (15%) standing, 83 ± 29 min/day (6%) in LPA and 87 ± 51 min/day (6%) in MVPA. No significant between group differences (low, intermediate and high sedentary time) were found for anthropometrics, body composition, blood pressure (Table 1) and cardiometabolic health outcomes (Table 2 and Figure 1) between groups.

Physical Activity and Sedentary Behaviour

Time spent in sedentary bouts of more than 60 minutes (low: 76 ± 44 vs. high: 243 ± 129; $p < 0.001$) and 30 – 60 minutes (low: 116 ± 39 vs. high: 167 ± 48; $p = 0.002$) was significantly lower in the low sedentary behaviour group compared to the high sedentary behaviour group. Although there was no significant difference between groups with regard to sleeping time (p = 0.057), the difference in sedentary time was due to significant differences in physical activity of all intensities including, standing (low: 267 ± 46 min/day vs. intermediate: 214 ± 48 min/day; $p = 0.003$ and vs. high: 179 ± 48; $p < 0.001$), LPA (low: 109 ± 23 min/day vs. intermediate: 81 ± 21 min/day; $p < 0.001$ and vs. high: 60 ± 19; $p < 0.001$) and MVPA (low: 126 ± 66 min/day vs. intermediate: 77 ± 33 min/day; $p = 0.002$ and vs. high: 59 ± 19; $p < 0.001$), which were significantly higher in the low sedentary behaviour group compared to the intermediate and the high sedentary behaviour group ($p < 0.001$). These higher volumes of physical activity were also reflected by a significantly higher step count in the low sedentary behaviour group, compared to the intermediate ($p = 0.003$) and high sedentary behaviour group ($p < 0.001$).

Table 1 *Subject characteristics.*

General features	Low (n=20)	Intermediate (n=20)	High (n=21)	*p*-value
Age (years)	38.4 ± 8.2	32.1 ± 12.9	34.5 ± 9.4	0.085
Sex (m/f)	14/6	13/6	13/7	0.499
Body weight (kg)	72.6 ± 12.2	69.8 ± 10.4	69.5 ± 10.8	0.627
Body height (cm)	177.3 ± 9.0	177.7 ± 8.1	175.9 ± 8.5	0.764
BMI (kg/m²)	23.0 ± 2.9	22.0 ± 2.1	22.3 ± 2.0	0.397
Waist circumference (cm)	80.4 ± 10.0	77.8 ± 8.5	76.4 ± 6.9	0.327
Hip circumference (cm)	89.8 ± 6.0	87.7 ± 6.6	86.7 ± 6.7	0.306
Waist-to-hip-ratio	0.89 ± 0.07	0.89 ± 0.05	0.88 ± 0.05	0.822
Lean mass (kg)	56.0 ± 6.1	54.1 ± 8.9	54.2 ± 9.8	0.783
Fat mass (kg)	12.5 ± 5.5	11.7 ± 3.6	11.5 ± 4.0	0.733
Fat mass (%)	17.6 ± 6.9	17.2 ± 5.0	17.0 ± 6.0	0.949
Weekly sport hours	9.2 ± 3.6	8.2 ± 2.9	7.9 ± 3.0	0.430
VO_{2max} ($mL \cdot min^{-1}$)	3991 ± 987	3755 ± 869	3619 ± 896	0.429
VO_{2max} ($mL \cdot kg^{-1} \cdot min^{-1}$)	55.0 ± 11.1	53.7 ± 9.5	51.9 ± 9.5	0.610
Sleeping time (min/day)	438 ± 35	468 ± 32	448 ± 45	0.057
Sedentary time (min/day)	501 ± 34	600 ± 24 [a]	695 ± 37 [b, c]	**<0.001**
Standing time (min/day)	267 ± 46	214 ± 48 [a]	179 ± 48 [c]	**<0.001**
LPA (min/day)	109 ± 23	81 ± 23 [a]	60 ± 19 [b, c]	**<0.001**
MVPA (min/day)	126 ± 66	77 ± 33 [a]	59 ± 19 [c]	**<0.001**
Step count	13225 ± 3815	9904 ± 2694 [a]	7714 ± 2563 [c]	**<0.001**
Sitting bouts < 30 min	378 ± 83	376 ± 96	397 ± 134	0.780
Sitting bouts 30 – 60 min	116 ± 39	150 ± 45	167 ± 48 [c]	**0.002**
Sitting bouts > 60 min	76 ± 44	137 ± 61	243 ± 129 [b, c]	**<0.001**
Smoking status (n)				0.638
Current	1	0	0	
Former	3	2	2	
Never	16	18	19	
Chronic disease (n)				0.242
Respiratory	1	0	3	
Cardiovascular	0	0	0	
Medication (n)				0.242
ACE inhibitor	0	1	0	
Bronchodilator	1	0	3	

Data are expressed as mean ± SD. Abbreviations: **ACE** = angiotensin-converting enzyme, **BMI** = body mass index, **LPA** = light intensity physical activity, **MVPA** = moderate-to-vigorous physical activity, **VO_{2max}** = maximal oxygen uptake. [a] $p < 0.05$ low vs. intermediate, [b] $p < 0.05$ intermediate vs. high, [c] $p < 0.05$ low vs. high

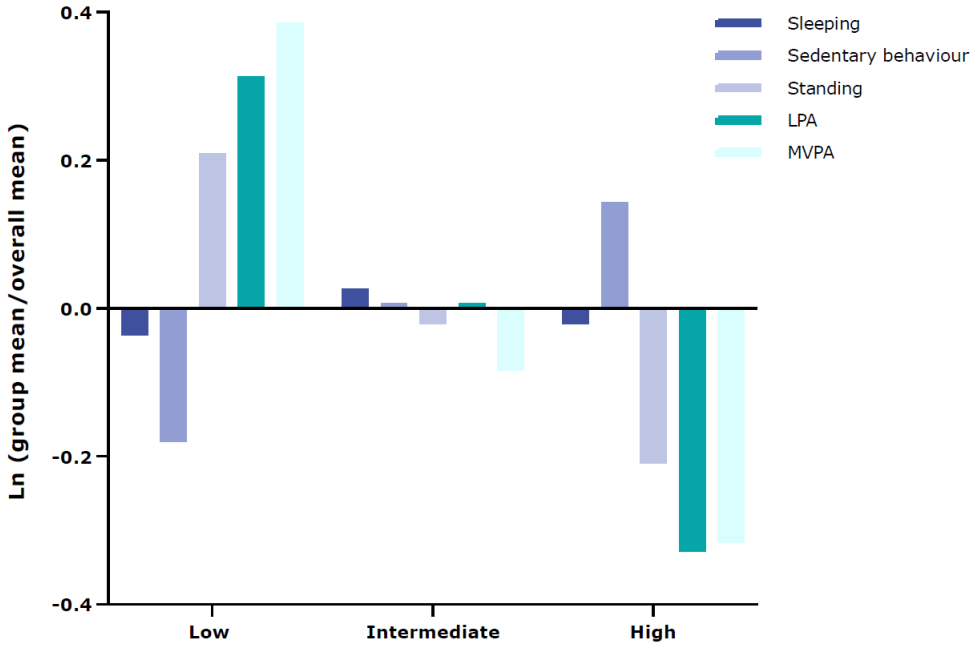

Figure 1 *Compositional analysis of the relative importance of the group (low, intermediate or high) mean time spent in sleep, sedentary behaviour, standing, LPA and MVPA with respect to the overall mean time composition.* Abbreviations: **LPA** = light intensity physical activity, **MVPA** = moderate-to-vigorous physical activity.

The analysis of the daily composition of behaviour categories showed that in the low sedentary behaviour group the proportion of time spent both standing, LPA and MVPA was increased by respectively 21%, 32% and 38% relatively to the overall mean composition, whereas the high sedentary behaviour group reduced their standing (-21%), LPA (-32%) and MVPA (-31%) levels relative to the entire sample (Figure 2). The variation matrix showed the highest log-ratio for sedentary time/MVPA (0.398), reflecting low co-dependence between these behaviours (Table 3). The lowest values were found for the log-ratio of sleeping time in relation to sedentary time (0.025), standing time (0.109) and LPA (0.130), reflecting high co-dependence between sleeping and these behaviours.

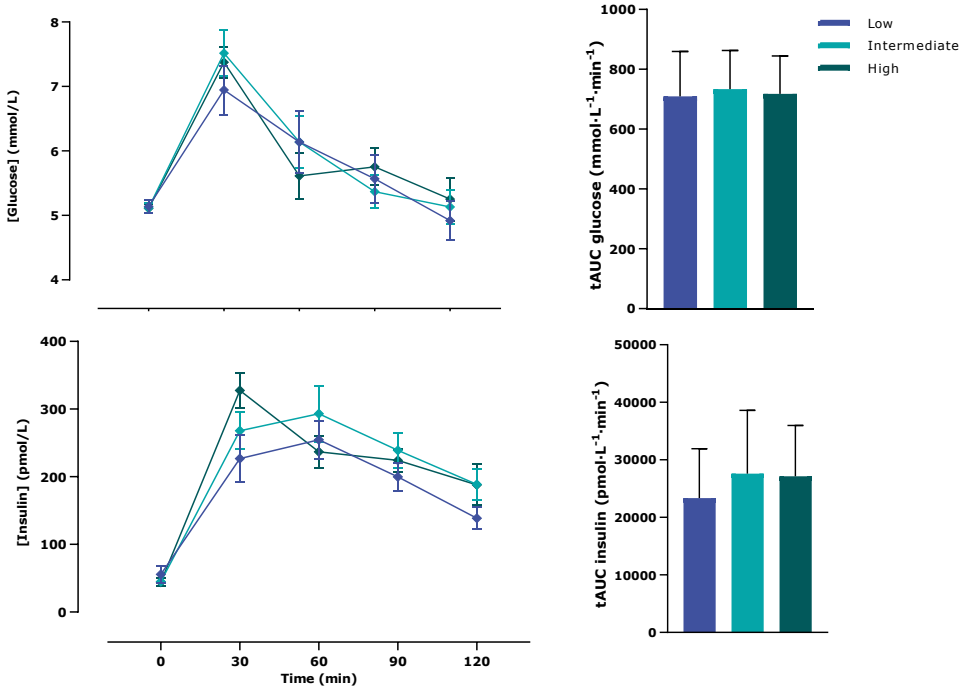

Figure 2 *Glucose and insulin concentrations during a 2-hour oral glucose tolerance test (left hand panel) and the average area under the curve (right hand panel) of the three different groups (low, intermediate and high sedentary time). Data are presented as mean ± standard error of the mean. Abbreviations:* ***tAUC*** *= total area under the curve.*

Table 2 *Cardiometabolic risk factors between groups with low, intermediate and high sedentary time.*

	Low (n=20)	Intermediate (n=20)	High (n=21)	*p*-value
Cardiovascular health				
Systolic blood pressure (mm Hg)	118 ± 10	120 ± 14	118 ± 10	0.818
Diastolic blood pressure (mm Hg)	71 ± 9	73 ± 7	71 ± 7	0.553
Mean arterial pressure (mm Hg)	87 ± 9	89 ± 8	87 ± 7	0.600
Resting heart rate (bpm)	62 ± 6	61 ± 7	59 ± 9	0.129
Total cholesterol (mmol/L)	4.27 ± 0.65	4.22 ± 0.77	4.05 ± 0.82	0.619
HDL cholesterol (mmol/L)	1.61 ± 0.47	1.47 ± 0.28	1.62 ± 0.43	0.402
LDL-cholesterol (mmol/L)	2.30 ± 0.46	2.34 ± 0.75	2.04 ± 0.67	0.446
Triglycerides (mmol/L)	0.75 ± 0.22	0.89 ± 0.27	0.81 ± 0.24	0.190
CCMR	-0.03 ± 0.63	0.12 ± 0.78	-0.09 ± 0.41	0.547
Glucose tolerance				
Fasting glucose (mmol/L)	5.2 ± 0.4	5.1 ± 0.4	5.1 ± 0.3	0.963
Fasting insulin (pmol/L)	56 ± 57	45 ± 20	44 ± 28	0.574
Glucose 120 min (mmol/L)	4.9 ± 1.4	5.1 ± 1.2	5.3 ± 1.5	0.738
Insulin 120 min (pmol/L) [a]	139 ± 70	189 ± 101	188 ± 139	0.511
Matsuda index	8.16 ± 2.89	8.42 ± 3.90	8.47 ± 3.21	0.955
IGI[a]	90 ± 112	80 ± 122	142 ± 76	0.103
HOMA-IR [a]	1.44 ± 0.51	1.49 ± 0.77	1.47 ± 0.98	0.979
HOMA-B (%) [a]	101.3 ± 101.9	80.7 ± 29.5	77.9 ± 42.2	0.468
mISI	0.37 ± 0.24	0.29 ± 0.15	0.33 ± 0.19	0.476
HIRI	21.8 ± 8.2	24.8 ± 6.6	27.0 ± 5.2	0.056

Data are expressed as mean ± SD. Abbreviations: **BP** = blood pressure, **bpm** = beats per minute, **CCRM** = clustered cardiometabolic risk score, **HDL** = high-density lipoprotein, **LDL** = low-density lipoprotein, **AUC** = area under curve, **IGI** = insulinogenic index, **HOMA-IR** = homeostatic model assessment of insulin resistance, **HOMA-B** = homeostatic model assessment of β-cell function, **mISI** = muscle insulin sensitivity index, **HIRI** = hepatic insulin resistance index. * $p < 0.05$. [a] Differences between groups were assessed using the Kruskal-Wallis test due to the abnormal distribution of the data.

Table 3 *Variation matrix of time spent in sleep, sedentary time, standing time, LPA and MVPA.*

	Sleeping time	Sedentary time	Standing time	LPA	MVPA
Sleeping time	0	0.025	0.109	0.130	0.236
Sedentary time	0.025	0	0.207	0.312	0.398
Standing time	0.109	0.207	0	0.048	0.170
LPA	0.130	0.312	0.048	0	0.329
MVPA	0.236	0.398	0.170	0.329	0

Table 4 *Multiple linear regression analyses of the relationship between isometric log-ratio (ilr) coordinates of sedentary time and MVPA and cardiometabolic health related outcomes.*

	ILR/ln(sedentary time: other behaviours)				ILR/ln(MVPA: other behaviours)			
	r^2	B	SE	p-value	r^2	B	SE	p-value
Waist circumference [a]	0.450	-0.015	0.017	0.373	0.447	-0.008	0.011	0.455
Systolic blood pressure	0.452	4.663	4.004	0.249	0.444	-1.814	2.646	0.496
Diastolic blood pressure	0.318	4.252	2.654	0.313	0.282	-3.161	2.144	0.146
Fat mass percentage [a]	0.499	0.062	0.055	0.262	0.492	-0.025	0.036	0.481
Oxygen uptake per kg	0.492	-9.191	3.504	**0.011**	0.544	8.074	2.178	**<0.001**
Fasting glucose	0.160	0.024	0.167	0.885	0.164	-0.057	0.109	0.603
Glucose 120min	0.185	0.806	0.603	0.187	0.206	-0.707	0.394	0.078
Fasting insulin	0.033	-10.592	18.37	0.567	0.028	1.579	12.078	0.896
Insulin 120min	0.314	79.04	44.32	0.080	0.327	-60.27	29.04	**0.043**
Matsuda index	0.151	-0.641	1.621	0.694	0.150	0.351	1.023	0.733
IGI	0.094	240.6	111.4	0.422	0.081	-144.3	73.55	0.055
HOMA-IR	0.142	-0.031	0.100	0.756	0.141	0.006	0.065	0.931
HOMA-B	0.150	-0.103	0.096	0.288	0.139	0.041	0.062	0.510
mISI	0.155	-0.112	0.091	0.227	0.135	0.034	0.062	0.583
HIRI	0.150	8.775	3.173	**0.008**	0.110	-4.708	2.128	**0.031**
tAUC insulin	0.222	0.054	0.014	0.134	0.201	-0.085	0.044	0.061
tAUC glucose	0.157	63.58	60.46	0.298	0.149	-31.45	40.18	0.437
Total cholesterol	0.321	0.396	0.301	0.194	0.322	-0.268	0.197	0.180
Triglycerides	0.058	0.136	0.116	0.247	0.128	-0.177	0.073	**0.019**
HDL-cholesterol [a]	0.273	0.062	0.046	0.186	0.273	0.04	0.03	0.182
LDL-cholesterol	0.278	0.105	0.267	0.697	0.320	-0.317	0.17	0.068
CCMS	0.374	0.099	0.228	0.667	0.412	-0.311	0.154	0.094

All models were adjusted for sex, age, smoking status, chronic disease and medication. Abbreviations: **CCMS** = clustered cardiometabolic risk score, **ILR** = isometric log-ratio, **B** = unstandardised beta coefficients, **SE** = standard error, **MVPA** = moderate-to-vigorous physical activity, **kg** = kilogram, **IGI** = insulinogenic index, **HOMA-IR** = homeostatic model assessment of insulin resistance, **HOMA-B** = homeostatic model assessment of β-cell function, **mISI** = muscle insulin sensitivity index, **HIRI** = hepatic insulin resistance index, **tAUC** = total area under curve, **HDL** = high-density lipoprotein, **LDL** = low-density lipoprotein. Significant associations are shown in bold. [a] Variables were log-transformed due to the abnormal distribution of the data.

Associations Between Physical Activity, Sedentary Behaviour and Cardiometabolic Health

Increased sedentary time was associated with increased HIRI (β = 8.78 ± 3.17; r^2 = 0.150; *p* = 0.008), whereas a negative association was found with the maximal oxygen uptake (β = -9.19 ± 3.50; r^2 = 0.492; *p* = 0.011), relative to all other remaining behaviours (Table 4). After correcting for multiple testing, no association remained statistically significant. Increased time spending in MVPA was associated with an increased maximal oxygen uptake (β = 8.07 ± 2.18 ; r^2 = 0.544; *p* < 0.001) and a decreased insulin concentration after 120 minutes of the OGTT (β = -60.27 ± 29.04; r^2 = 0.327; *p* = 0.043), HIRI (β = -4.71 ± 2.13; r^2 = 0.110; *p* = 0.031) and triglyceride concentration (β = -121 ± 0.073 ; r^2 = 0.128; *p* = 0.019), relative to all other remaining behaviours. After adjustments for multiple testing, only the association between MVPA and oxygen uptake remained statistically significant. No associations between sleeping time, standing time or LPA and markers of cardiometabolic health were found, relative to all other remaining behaviours.

Discussion

In the current study, we aimed to investigate the modifying effects of MVPA on the association between sedentary behaviour and cardiometabolic health in highly active adults. Participants included in this study were highly active, by engaging in almost 1.5 hours per day of MVPA. This far exceeds the 30 minutes per day as recommended by the current physical activity guidelines. However, despite these high levels of MVPA, they engaged in different amounts of sedentary behaviours ranging from 7 to 13 hours a day. We found that the cardiometabolic health risks attributed to these high amounts of sedentary time could fully be mitigated by the high levels of MVPA and possibly by high levels of cardiorespiratory fitness (CRF). This was confirmed by multivariate linear regression analyses showing that the CRF, reflected by the maximal oxygen uptake, was positively associated with MVPA.

Despite the well-established health benefits of daily MVPA, increasing evidence suggests that sleep, SB and LPA also have important consequences for (cardiometabolic) health [30-32]. Although it has been shown that spending 9 hours per day in sedentary behaviours is associated with the risk of all-cause mortality

[4, 33], in the present study no significant differences in cardiometabolic health related outcomes were found between the low (126 min of MVPA), intermediate (77 min of MVPA) and high sedentary (60 min of MVPA) groups. This suggests that 60 minutes of MVPA per day (high sedentary behaviour group) mitigates the detrimental effects of prolonged sedentary behaviour (11.5 hours/day, of which 4 hours were spent in bouts > 60 minutes). This is similar to a previous meta-analysis of Ekelund *et al*. who found that between 60 and 75 minutes per day of leisure time physical activity of moderate intensity was necessary to eliminate the risk of mortality associated with sedentary behaviour [9]. However, their results were based on self-reported data. Other harmonized meta-analyses based on accelerometer measured physical activity found that 30−40 minutes of MVPA on a daily basis were enough to attenuate the risk of all-cause mortality [15, 34]. However, Chastin *et al*. showed that at high sedentary time (> 11 hours) the benefits of these lower MVPA levels, compared to the 60 minutes of our study, might have been completely attenuated [34].

In contrast, intervention studies have found that 60 minutes of daily physical exercise could not compensate the negative effects of sedentary behaviour on cardiometabolic health when the rest of the day was spent in sitting pursuits [35, 36]. From this, it could be suggested that the beneficial effects from exercise are fully blunted due to physical inactivity, a phenomenon termed "exercise resistance" [36]. However, in comparison with our study population in which participants already performed exercise for at least the past 2 years, the conclusions of Duvivier and Coyle were based on relatively short-term interventions (4 days). In addition, their 60-minutes training was performed at 65% of maximal heart rate, which means training at moderate physical activity intensity. In our study it was only possible to measure MVPA instead of moderate and vigorous physical activity (VPA) as separate intensities. Therefore, no conclusions could be made based on the contribution of these intensities as a stand-alone factor. Nevertheless, it has been shown that athletes spent more time in VPA compared to the normal population [37, 38], and therefore, it could be assumed that in the current study the proportion of time spent in VPA was higher than the population studied by Duvivier *et al.* Here, it is possible that physical activity at higher intensities can counteract the effects of prolonged sedentary behaviour. Recent research has proposed that the proportion of time spent in VPA,

compared to moderate intensity, might be more important for reducing the (cardiovascular disease) mortality risk [39, 40]. Therefore, replacing sedentary behaviour with physical activity of higher intensities on the longer-term could be an important contributor to the beneficial effects of MVPA on cardiometabolic health within these highly trained athletes.

No differences on cardiometabolic health related outcomes were found between groups, which was also confirmed by the multivariate regression analyses. This is in contrast with Zheng *et al.* who found that total sedentary time and prolonged sedentary bouts were positively associated with several cardiometabolic biomarkers within highly active young males [41]. However, the associations should be interpreted with caution since multiple linear regression analyses have performed, which may lead to the results being coincidental, as shown in the current study. Furthermore, no associations were found between cardiometabolic health, standing time and LPA which indicates that the time spend in these behaviours is far less important when a certain threshold of MVPA is reached.

MVPA was positively associated with maximal oxygen uptake, relative to all other remaining behaviours. Although it has been shown that there is a strong interrelationship between sedentary time, MVPA and CRF, these factors might have an independent association with cardiometabolic health [42]. Indeed, Van der Velde *et al*. showed that even individuals with a higher CRF may be at increased risk for metabolic diseases due to prolonged sitting and that both sedentary time and CRF were independently associated with the metabolic syndrome and type 2 diabetes mellitus [43]. However, this study was performed in the general population, in which parameters of CRF were lower compared to athletic populations as included in the current study. Interestingly, it has already been shown that CRF may modify the association between sedentary behaviour and cardiometabolic health [44-46]. Nauman *et al.* found that high levels of CRF compensated the deleterious health consequences related to engaging in sedentary behaviour for > 7 hours per day [45]. Indeed, in the current study, despite the fact that we found equal high CRF levels across the groups engaging in different levels of sedentary behaviour, no differences were found in cardiometabolic health related outcomes. This suggests that sedentary behaviour may be a less important determinant of cardiometabolic health in persons with adequate CRF. It has been shown that high levels of CRF fully eliminated the detrimental effects of sedentary behaviour, even

when they did not meet the current PA recommendations of 150 – 300 minutes per week engaging in MVPA [45, 47]. Therefore, it could be suggested that people with a high CRF may provide favourable effects against the deleterious consequences of prolonged sitting. This might also explain why no associations between LPA, standing and markers of cardiometabolic health were found. Indeed, McCarthy *et al.* demonstrated less metabolic benefit from LPA breaks in individuals with a CRF (± 58 mL · kg^{-1} · min^{-1}) comparable to that in the present study [48]. This supports the concept that individuals with higher CRF gain less pronounced health benefits from reducing sedentary behaviour [48].

Although, to our knowledge, this was the first study that investigated associations between sedentary behaviour and cardiometabolic health with CoDa within highly active adults, several limitations could be addressed in future research. Firstly, the cross-sectional nature of our study limited the ability to infer causality. Prospective longitudinal studies are highly recommended to investigate the direct association between these variables. Secondly, although the ActivPAL™ is the gold standard for measuring sedentary behaviour [10, 49], discriminating between moderate and vigorous intensity physical activity is not possible. In this population, it is assumed that VPA was more performed compared to MPA, which could explain why no more associations were found between sedentary time and cardiometabolic health. To further unravel the direct associations between moderate and vigorous physical activity and cardiometabolic health, measurement tools which can perfectly distinguish between these movement behaviours are warranted. Third, food intake was not considered in this study, a factor that may also relate to cardiometabolic health and the development of NCDs [50]. In addition, although we corrected for sex in our statistical analyses, it is warranted in future research to discriminate between males and females to better understand sex differences across the various movement behaviours.

Taken together, it can be concluded that, despite the high levels of sedentary behaviour, high levels of MVPA are able to eliminate the inverse association between sedentary behaviour and cardiometabolic health. It seems that engaging in at least 60 minutes of MVPA may be viable to protect the potential harms of prolonged sitting.

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LDL
HDL

Chapter 4

Can consumer wearable activity tracker-based interventions improve physical activity and cardiometabolic health in patients with chronic diseases? A systematic review and meta-analysis of randomised controlled trials

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Abstract

Background: To date, it is unclear if consumer wearable activity track (CWATs), with or without behaviour multi-component strategies, effectively improve adherence to physical activity and health outcomes under free living conditions in populations with chronic diseases. Therefore, we systematically evaluated the efficacy of CWAT-based interventions to promote physical activity levels and cardiometabolic health in populations with chronic diseases.

Methods: Randomised controlled trials were collected from five bibliographic databases (PubMed, Embase, Web of Science, The Cochrane Central Register of Controlled Trials and CINAHL). Studies were eligible for inclusion if they evaluated a CWAT-based counselling intervention versus control intervention among patients with chronic respiratory diseases, type 2 diabetes mellitus, cardiovascular diseases, overweight/obesity, cognitive disorders, or sedentary older adults. Data were pooled using a random-effects model.

Results: After deduplication 8147 were identified of which 35 studies met inclusion criteria (chronic respiratory diseases: 7, type 2 diabetes mellitus: 12, cardiovascular diseases: 6, overweight/obesity: 3, cognitive disorders: 1, sedentary older adults: 6). Compared to control groups, CWAT-based interventions significantly increased physical activity by 2123 steps per day (95% confidence interval [CI], [1605-2641]; $p<0.001$). In addition, CWAT-based interventions in these populations significantly decreased systolic blood pressure (-3.79 mm Hg; 95% CI: [-4.53, -3.04] mm Hg; $p<0.001$), waist circumference (-0.99 cm; 95% CI: [-1.48, -0.50] cm; $p<0.001$) and low-density lipoprotein cholesterol concentration (-5.70 mg/dl; 95% CI: [-9.24, -2.15] mg/dl; $p=0.002$).

Conclusion: CWAT-based interventions increase physical activity and have beneficial effects on important health-related outcomes such as systolic blood pressure, waist circumference and LDL cholesterol concentration in patients with chronic diseases.

Introduction

Chronic diseases such as chronic respiratory diseases, type 2 diabetes mellitus (T2DM), cardiovascular diseases (CVD) and cognitive disorders are an important public health concern worldwide [1]. In fact, recent data indicate that the prevalence of chronic diseases has increased considerably to 40 million global deaths in 2015. As a result, chronic diseases now are the leading cause of mortality worldwide and as such constitute one of the most important challenges for the 21st century [2, 3]. Physical inactivity is one of the major contributing factors for the development of chronic diseases and is highly correlated with mortality and hospitalization [4, 5]. On the other hand, it is well known that increased physical activity has significant health benefits and is associated with the prevention and delayed onset of many chronic diseases [4, 6]. Given the important role of physical activity in the prevention and management of chronic diseases, it is crucial to promote physical activity. Hence, to date, a multitude of physical activity recommendations and many supervised training interventions and rehabilitation programs are available to encourage physical activity in the global population [7, 8]. Nevertheless, a recent report from the World Health Organization (WHO) indicates that 23% of the adult and 80% of the adolescent population is still physically inactive [9]. Here, very poor long-term compliance to adequate physical activity and a healthy lifestyle appears to be one of the main factors explaining this discrepancy. Consequently, any strategy that improves long-term adherence to adequate daily physical activity and a healthy lifestyle, especially in a population with chronic diseases, is worthwhile investigating. The use of structured behaviour change interventions (e.g. telephone counselling, group sessions, provision of written information materials or individual education sessions) is reported to be effective in increasing physical activity, subsequently leading to a reduced progression of chronic diseases [10-13]. In addition, although Bravata *et al*. showed that goal setting may be a key motivational factor for increasing physical activity, this conclusion was based on observational studies and healthy individuals [14]. However, these strategies are often resource-intensive and time-consuming, factors that limit long-term adherence and usually not feasible in routine clinical care [15]. In this respect and following the recent use of pedometer and accelerometer-based remote monitoring of physical activity in patients with chronic diseases, consumer wearable activity trackers (CWATs) may be an alternative strategy to increase

physical activity levels. CWATs are electronic devices used for monitoring and recording daily physical activity, although nowadays the term is also used for wearable fitness gadgets. These CWATs are consisted of pedometers (e.g. Omron and Yamax), which provide direct feedback on the level of physical activity in terms of number of steps per day, and activity trackers (Polar, Fitbit, Garmin and Apple Watch) which often include goal setting and can monitor physical activity and fitness related metrics including the amount and intensity of physical activity, sedentary behaviour and heart rate. Initially, CWATs have predominantly been applied in the sports community for self-monitoring sport/training performance-related parameters [16-18]. To date, they are widely used to quantify physical activity and monitor fitness. Possibly, the self-management, motivational and goal setting properties of these commercially available devices may also help patients with chronic diseases to better adhere to long-term physical activity under free-living conditions in a home-based setting. Surprisingly and despite the widespread use of these wearables, their feasibility and efficacy on physical activity (compliance) and cardiometabolic health including anthropometric measurements, systemic blood pressure, lipid profile and glycemic index, especially in patients with chronic diseases, is not fully clear. Although recent reviews have shown that CWATs have potential to increase physical activity, they included only one type of chronic disease [19, 20] or solely pedometers [14, 21]. In addition, conclusions are not based on randomised controlled trials [14, 22] and most of reviews did not (or partly) report a cardiometabolic risk profile [15, 19, 20, 23].

Therefore, this study aims to systematically evaluate the efficacy of CWAT-based interventions, as CWATs being either the primary components of an intervention or as part of a multi-component intervention, to promote physical activity levels and cardiometabolic health in populations with chronic diseases including chronic respiratory diseases, T2DM, CVD, overweight/obesity, cognitive disorders or sedentary older adults. A better understanding whether CWATs improve adherence to physical activity and hereby affect cardiometabolic health outcomes may help to increase the efficacy and quality of health care in populations with chronic diseases.

Methods

This systematic review, including an explorative meta-analysis, was registered in the PROSPERO international prospective register of systematic reviews (registration number: CRD42019124126) and was performed in accordance with The Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) statement [24, 25].

Data Sources and Search Strategies

Studies were collected (from inception until March 2019) using computer-based searches in the PubMed, Embase, Web of Science, The Cochrane Central Register of Controlled Trials (CENTRAL) and CINAHL electronic databases. Database specific search strategies were developed with the guidance of a professional clinical librarian. The database searches were performed using four main concepts: chronic diseases or sedentary older adults, CWATs, behaviour change and cardiometabolic health measures. For each main concept relevant related terms and keywords were included in the sensitive search (details presented in Appendix). The systematic search was limited to the English, German and Dutch language.

Eligibility Criteria

Inclusion criteria to select studies were: 1) Study population: adult (aged 18 or older) patients with main chronic diseases including chronic respiratory diseases, T2DM, CVD, overweight/obesity and cognitive disorders, or sedentary older adults (>55 years; high risk population); 2) Types of studies: peer-reviewed randomised controlled trials regarding a CWAT-based behaviour change intervention compared to a control intervention or usual care comparison group. The behaviour change intervention could be a CWAT-only intervention or a multi-component intervention consisting of a CWAT in combination with lifestyle data platforms, applications to change lifestyle behaviour or coaching sessions. In addition, physical activity should be measured objectively; 3) Primary outcome: physical activity expressed in number of steps per day and 4) Secondary outcomes: cardiometabolic health outcomes including physical fitness, exercise capacity, anthropometric measures (body weight, body mass index (BMI), waist circumference and percentage fat mass), systolic and diastolic blood pressure

(BP), resting heart rate, lipid profile (blood total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol and triglyceride concentrations), blood glycated haemoglobin concentration (HbA1c) and the fasting glucose and insulin concentration. Studies that included dietary interventions or had an intervention duration of less than 6 weeks were excluded.

Study Selection

Studies were independently screened in three different steps by two authors (W.M.A.F. and J.S.). Firstly, duplicates were removed using the de-duplication method from Bramer *et al.* [26] and a first selection was performed based on titles and abstracts to identify relevant studies. Then, articles were screened and systematically excluded when they did not meet the pre-specified inclusion criteria. In addition, reviews, editorials, congress abstracts and validation studies were also excluded. Disagreements between authors were resolved by consensus with a third reviewer (B.O.E).

Data Extraction

Data were independently extracted by two of the reviewers (W.M.A.F. and J.S.). Data extraction was performed with the aid of a predesigned data collection form, adapted from the extraction form of the Cochrane Collaboration (Appendix). For each study, the reviewers extracted information with respect to study characteristics (type of study, population description, focused disease or condition, types of outcome measures); study participants (sample size, demographics); methods (study aim, study design, intervention duration, type and frequency, CWAT type, blinding, amount of intervention groups, number of included participants, dropouts and the number of individuals that were randomised and analyzed); outcome variables (outcome definition, unit of measurement, time points measured and reported, statistical method used). If a study consisted of two or more study arms of which one of the intervention arms did not meet the inclusion criteria, data were only extracted from the study arms that met the inclusion criteria. Continuous data including, means, standard deviations and the sample size numbers were extracted. When mean differences were not available, authors of the included studies were contacted to request additional data. Without availability of standard deviations, measures of variance

were estimated from the standard error of a mean, confidence intervals or p-values according to the Cochrane Handbook for Systematic Reviews of Interventions the Cochrane Collaboration (Version 5.2, chapter 7) [27]. In addition, when data were presented as median and interquartile range, the mean and standard deviation were estimated using the formula from Hozo *et al*. [28]. Blood parameters were converted to the same unit (from mmol/l to mg/dl), including triglycerides (divide by 0.0112), total cholesterol, HDL cholesterol, LDL cholesterol (divide by 0.02586) and glucose (divide by 0.05551) concentration [29].

Study Quality Assessment

The risk of bias of the included studies was assessed by one reviewer (W.M.A.F.) as recommended by Higgins *et al.* (Cochrane 'Risk of Bias' assessment tool, the Cochrane Collaboration). Here, the following methodological criteria were assessed: sequence generation, allocation concealment, blinding of participants, personnel and outcome assessors, incomplete outcome data, selective outcome reporting and other potential threats to validity [27]. Each of these criteria were judged and classified as 'low risk', 'high risk' or 'unclear risk' of bias.

Statistical Analysis

Statistical analyses were performed using R version 3.6.0 (The R foundation for Statistical Computing, Wien, Austria) [30]. The mean differences (post-intervention parameter – pre-intervention parameter) with 95% confidence intervals were calculated and pooled effect estimates were obtained using a random-effects model due to the large heterogeneity among the studies (different populations, age, intervention type). Some studies used multiple intervention groups, or the same intervention and control groups were measured at multiple time intervals. Therefore, an extension of the standard meta-analysis models was applied on these data, in order to take correlations of effect estimates coming from the same study into account. The influence of population (age, sex proportion [% male] and populations with various chronic diseases) and study characteristics (intervention type [only CWAT use, or a CWAT in combination with behaviour change strategies including goal setting, telephone support and/or individual or group counselling] and intervention duration) on the intervention effect was evaluated using a mixed effects meta-regression analysis. Here, the effects of these covariates were

studied as fixed effects in the model. Tests for overall effect as well as pairwise comparisons among populations were performed. For the latter, adjustments for all other effects and corrections for multiple comparisons were used. Studies with missing values regarding the covariates were not included into the analysis. The beta estimate refers to the change in number of steps per day for a unit change in the characteristics. Sensitivity analyses were performed to assess heterogeneity of the studies and to evaluate the robustness of the results. Each study was individually removed to evaluate the effect of that study on the summary estimates. Publication bias was assessed using funnel plots and the Egger test (Appendix, Figure S1). The effect of heterogeneity of each summary effect size was quantified using a chi-squared test and the I^2 statistic, in which the boundary limits 25%, 50%, and 75% were designated as a low, moderate, and high heterogeneity value [31].

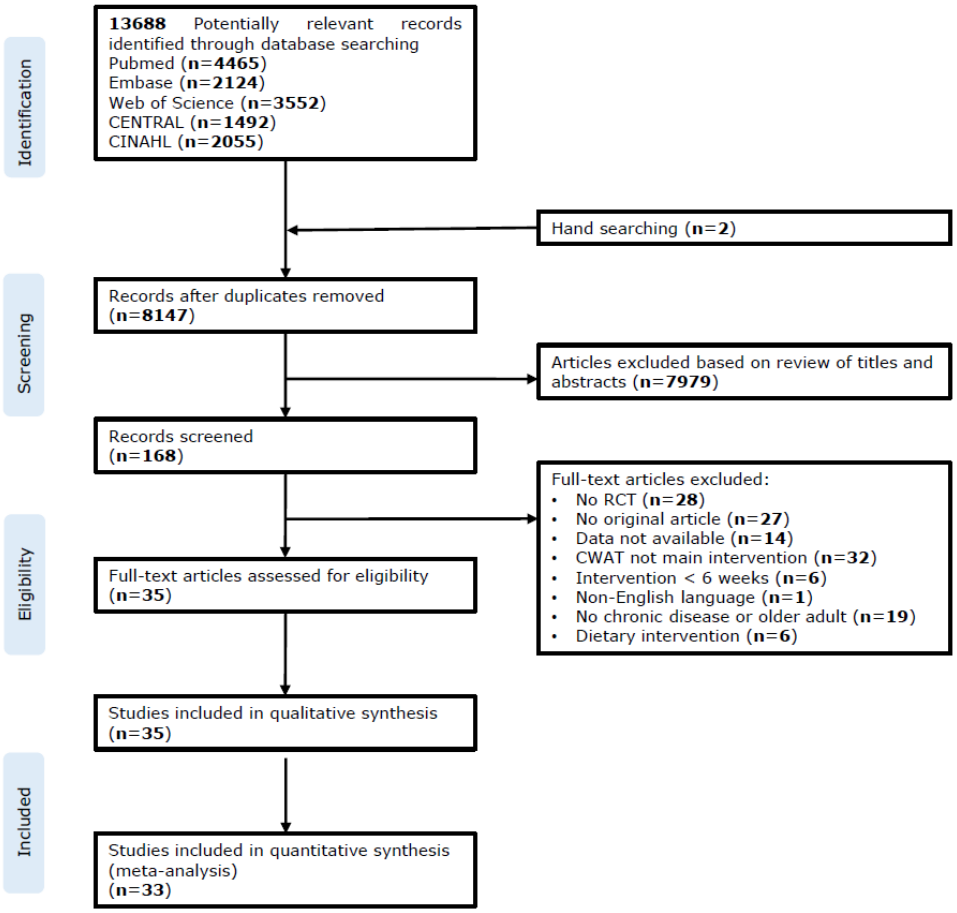

Figure 1 *Flow diagram of the study selection process.*

Table 1 *Characteristics of included studies.*

Study	Population	Intervention duration (wk)	Dropout rate (%)	No. of participants	Intervention	CWAT type	Outcome parameter
Altenburg 2015	COPD (62 ± 1 years; sex m/f: 102/53)	64	30	78	I: Goal setting, motivational interviewing techniques (five individual 30 min counselling sessions) and pedometer use for feedback and motivation	Yamax Digiwalker SW-200	Physical activity: - Steps/day
				77	C: Usual care		
Araiza 2006	T2DM (50± 10 years)	6	0	15	I: Pedometer use and instructed to walk 10.000 steps/day on 5 or more days of the week	Yamax Digiwalker SW-701	Physical activity: - Steps/day Cardiometabolic risk: - Body mass index - Waist circumference - Body fat percentage - Systolic BP - Diastolic BP - HbA1c - Fasting glucose - Fasting insulin - HOMA-IR - Triglycerides - Total cholesterol - HDL cholesterol - LDL cholesterol
				15	C: Pedometer use and instructed to maintain normal activity habits		

Table 1 *Characteristics of included studies (continued).*

Study	Population	Intervention duration (wk)	Dropout rate (%)	No. of participants	Intervention	CWAT type	Outcome parameter
Armit 2009	Sedentary older adults (50-59 years: n=78, 60-70 years: n=58; sex m/f: 40/51)	12	0	46	I: Physical activity advice provided during a 30min behaviour change counselling session (Transtheoritical model) and three follow-up telephone calls, pedometer use, goal setting and motivational interviewing techniques	-	Cardiometabolic risk: - Body mass index - Systolic BP - Diastolic BP - Resting heart rate
				45	C: Usual care (3-5min of brief verbal physical activity advice and written information)		
Baker 2008	Overweight/Obesity (49.3±8.8 years; sex m/f: 63/16)	12	20	39	I: Pedometer-based walking program with consultations based on the Transtheoretical Model of exercise behaviour change, goal setting (3000 steps/day above baseline)	Omron HJ-109E Step-O-Meter	Physical activity: - Steps/day Cardiometabolic risk: - Body weight - Body mass index - Waist circumference - Hip circumference - Waist-to-hip ratio - Body fat percentage - Systolic BP - Diastolic BP - Resting heart rate - Total cholesterol - HDL cholesterol - LDL cholesterol
				40	C: Maintain usual activity levels		

Table 1 *Characteristics of included studies (continued).*

Study	Population	Intervention duration (wk)	Dropout rate (%)	No. of participants	Intervention	CWAT type	Outcome parameter
Bjorgaas 2008	T2DM (58.9±10.5 years; sex m/f: 31/17)	26	31	23	I: Pedometer use, goal setting, physical activity calendar, encouraged to increase targeted number of steps	Yamax Digiwalker ML AW-320	Cardiometabolic risk: - Body weight - Systolic BP - Diastolic BP - HbA1c - Fasting glucose - Triglycerides - Total cholesterol - HDL cholesterol - Peak oxygen uptake
				25	C: Encouraged to increase daily time spent walking		
Bond 2014	Overweight/Obesity (46.0±8.9 years; sex m/f: 10/65)	6	6	40	I: Individual face-to-face counseling sessions (6 sessions lasted 30-45 minutes) based on theoretical constructs from the Transtheoretical Model, Theory of Planned Behaviour, Social Cognitive Theory, and Self-Determination Theory; goal setting, pedometer use, problem solving, action planning, review of progress	-	Physical activity: - Steps/day
				35	C: Standard preoperative care. Surgeons and members of the surgical team advised participants to adopt an active lifestyle and engage in walking exercise and other similar activities		

Table 1 *Characteristics of included studies (continued).*

Study	Population	Intervention duration (wk)	Dropout rate (%)	No. of participants	Intervention	CWAT type	Outcome parameter
Butler 2009	CVD (63.8±10.8 years; sex m/f: 83/27)	26	26	55	I: Pedometer use, step calendar, four telephone calls, behavioural counselling, goal setting, generic physical activity information brochures	Yamax Digiwalker 700B	Cardiometabolic risk: - Body mass index - Waist circumference
				55	C: Generic physical activity information brochures		
Coelho 2017	Asthma (45.9±16.7 years; sex m/f: 5/32)	12	19	20	I: Individual standardized educational session, Pedometer use, step based physical activity prescription, goal setting (steps taken during the previous week plus 1000 steps)	Yamax Digiwalker SW-200	Physical activity: - Steps/day
				17	C: Individual standardized educational session		

Table 1 *Characteristics of included studies (continued).*

Study	Population	Intervention duration (wk)	Dropout rate (%)	No. of participants	Intervention	CWAT type	Outcome parameter
Croteau 2007	Sedentary older adults (72.9±8.8 years; sex m/f: 32/115)	12	14	79	I: Behaviour change counselling session (Social cognitive theory), pedometer use, goal setting, select strategies for increasing daily step counts, review pedometer usage and discuss procedures for keeping a step calendar and monthly group sessions	Yamax Digiwalker SW-200	Physical activity: - Steps/day
				68	C: Instructed to continue usual activity habits		
De Blok 2006	COPD (64.1±11.1 years; sex m/f: 9/12)	10	24	10	I: Behaviour change counselling programme and pedometer use for feedback and motivation	Yamax Digiwalker SW-200	Physical activity: - Steps/day
				11	C: Usual care (regular pulmonary rehabilitation programme)		

Table 1 *Characteristics of included studies (continued).*

Study	Population	Intervention duration (wk)	Dropout rate (%)	No. of participants	Intervention	CWAT type	Outcome parameter
De Greef 2010	T2DM (35-54 years: n=6, 55-75 years: n=35; sex m/f: 28/13)	12	10	20	I: cognitive-behavioural group programme (5 sessions of 90 min), pedometer use	Yamax Digiwalker SW-200	Physical activity: - Steps/day Cardiometabolic risk: - Body weight - Body mass index - Systolic BP - Diastolic BP - HbA1c - Total cholesterol
				21	C: Usual care and one single group education on the effects of physical activity on diabetes care		

Table 1 *Characteristics of included studies (continued).*

Study	Population	Intervention duration (wk)	Dropout rate (%)	No. of participants	Intervention	CWAT type	Outcome parameter
De Greef 2011 (1)	T2DM (67.4±9.3 years; sex m/f: 47/20)	12	4	21	I1: Pedometer and diary use, goal setting, three 90min group counselling sessions (based on the cognitive behavioural therapy, the Diabetes Prevention Program, the First Step Program and motivational interviewing) by a clinical psychologist	Yamax Digiwalker SW-200	Physical activity: - Steps/day Cardiometabolic risk: - Body mass index - Waist circumference - HbA1c - Fasting glucose - Total cholesterol
				22	I2: Pedometer and diary use, goal setting, three individual 15min face-to-face consultations with a clinical psychologist		
				24	C: General care from the general practitioner		
De Greef 2011 (2)	T2DM (62±9 years; sex m/f: 64/28)	26	4	60	I: Face-to-face session (based on the cognitive behavioural therapy, the Diabetes Prevention Program, the First Step Program and motivational interviewing), pedometer and diary use, 24-week telephone support programme	Yamax Digiwalker SW-200	Physical activity: - Steps/day
				32	C: General care from the general practitioner		

Table 1 *Characteristics of included studies (continued).*

Study	Population	Intervention duration (wk)	Dropout rate (%)	No. of participants	Intervention	CWAT type	Outcome parameter
Diedrich 2009	T2DM (54.2±11.6 years sex m/f: 18/35)	12	38	27	I: Diabetes Self-Management Education Program, *Manpo-Kei* book; pedometer use, record pedometer readings according to instructions in the book	Yamax Digiwalker SW-200	Cardiometabolic risk: - Body fat percentage - Systolic BP - Diastolic BP - HbA1c
				26	C: Diabetes Self-Management Education Program		
Duscha 2018	CVD (62.3±8.3 years; sex m/f: 19/6)	12	22	16	I: CWAT use, exercise prescription by daily step count, health coaching (health related recommendations, planning, motivation and sending educational material via email and text messages)	Fitbit Charge	Physical activity: - Steps/day Cardiometabolic: - Peak oxygen uptake
				9	C: Usual care		

Table 1 *Characteristics of included studies (continued).*

Study	Population	Intervention duration (wk)	Dropout rate (%)	No. of participants	Intervention	CWAT type	Outcome parameter
Hospes 2009	COPD (62.2±8.6 years; sex m/f: 21/14)	12	10	18	I: Customized exercise counselling programme (5 sessions), goal setting and pedometer use	Digiwalker SW-200	Physical activity: - Steps/day
				17	C: Usual care		
Houle 2011	CVD (58.5±8.5 years; sex m/f: 51/14)	52	22	32	I: Pedometer use, diary, physical activity, goal setting (target of 3000 steps per day increment in physical activity counselling (social cognitive theory) by a clinical nurse specialist	Digiwalker SW-200	Physical activity: - Steps/day Cardiometabolic: - Waist circumference - Systolic BP - Diastolic BP - Resting heart rate - Fasting glucose - Triglycerides - LDL cholesterol - HDL cholesterol
				33	C: Usual care		
Kaminsky 2013	CVD (56.0±9.2 years; sex m/f: 14/4)	8	36	10	I: Recommended to obtain a minimum of 30-40 minutes/day moderate-to-vigorous physical activity on days they did not attend cardiac rehabilitation, daily step count goals to increase by 10% of baseline step per day	NL-1000 New-lifestyles	Physical activity: - Steps/day
				8	C: Usual care		

Table 1 *Characteristics of included studies (continued).*

Study	Population	Intervention duration (wk)	Dropout rate (%)	No. of participants	Intervention	CWAT type	Outcome parameter
Kawagoshi 2015	COPD (74.6±8.4 years; sex m/f: 24/3)	52	31	12	I: Multidisciplinary home-based physical rehabilitation program, pedometer use, goal of 8000 steps per day, staff gave verbal reinforcement	Kenz Lifecorder EX	Cardiometabolic: - Body mass index
				15	C: Multidisciplinary home-based physical rehabilitation program		
Kempf 2018	Overweight/obese (45.4±10.0 years; sex m/f: 81/99)	12	16	58	I1: Pedometer use, weekly care calls from trained coaches (information about overweight or obesity-related diseases like type 2 diabetes, healthy diet, physical activity, and coping strategies for lifestyle changes), participants were motivated to achieve individual goals using mental motivation program	SmartLAB walk P+	Cardiometabolic risk: - Body weight - Body mass index - Waist circumference - Systolic BP - Diastolic BP - HbA1c - Triglycerides - Total cholesterol - HDL cholesterol - LDL cholesterol
				61	I2: Pedometer use		
				61	C: Routine care		
Kooiman 2018	T2DM (56.4±11.3 years; sex m/f: 38/34)	13	8	40	I: Usual care, activity tracker and access to online self-tracking (eHealth) program	Fitbit Zip	Cardiometabolic risk: - Body weight - Body mass index - Waist circumference - Hip circumference - Waist-to-hip ratio - HbA1c
				32	C: Usual care		

Table 1 *Characteristics of included studies (continued).*

Study	Population	Intervention duration (wk)	Dropout rate (%)	No. of participants	Intervention	CWAT type	Outcome parameter
Rowley 2017	Sedentary older adults (67.3±6.3 years; sex m/f: 135/35)	12	24	51	I1: Pedometer use, given the goal to increase daily step count by 10% each week, when 10.000 steps per day were reached they were instructed to maintain 10.000 steps per day, incentives	Omron HJ-720ITC	Physical activity: - Steps/day
				62	I2: Pedometer use, interactive website with key strategies to increase PA systematically in older adults including education and goal setting, self-regulation, and frequent feedback and rewarding, incentives		
				57	C: Maintain usual activity levels		
Mendoza 2015	COPD (68.7±8.5 years; sex m/f: 62/40)	12	5	52	I: Pedometer use, diary with step count, goal setting	Tanita PD724 Triaxial pedometer	Physical activity: - Steps/day
				50	C: Counselling to increase physical activity (to walk at least 30 min/day)		
Nolan 2017	COPD (68±9 years; sex m/f: 110/42)	26	26	76	I: Usual care (physical rehabilitation programme), pedometer use, goal setting and step count diary	Yamax Digiwalker CW700	Physical activity: - Steps/day
				76	C: Usual care (physical rehabilitation programme)		

Table 1 *Characteristics of included studies (continued).*

Study	Population	Intervention duration (wk)	Dropout rate (%)	No. of participants	Intervention	CWAT type	Outcome parameter
Suboc 2014[1]	Sedentary older adults (63.1±7.3 years; sex m/f: 71/36)	12	6	41	I1: Pedometer use, goal setting (10% above baseline each week to reach 10.000 steps/day)	Omron HJ-720ITC	Physical activity: - Steps/day Cardiometabolic risk: - Body weight - Body mass index - Waist circumference - Systolic BP - Diastolic BP - Resting heart rate - Fasting glucose - Fasting insulin - Triglycerides - Total cholesterol - HDL cholesterol - LDL cholesterol
				36	I2: Pedometer use combined with interactive website intervention (frequent feedback, motivational messages, self-regulation, goal setting, education and practice in realistic behavioural change strategies, rewarding)		
				30	C: Maintain usual activity levels		

Table 1 *Characteristics of included studies (continued).*

Study	Population	Intervention duration (wk)	Dropout rate (%)	No. of participants	Intervention	CWAT type	Outcome parameter
Suboc 2014[2]	Sedentary older adults (63.0±7.3 years; sex m/f: 35/67)	12	6	35	I1: Pedometer use, goal setting (10% above baseline each week to reach 10.000 steps/day)	Omron HJ-720ITC	Physical activity: - Steps/day Cardiometabolic risk: - Body weight - Body mass index - Waist circumference - Systolic BP - Diastolic BP - Resting heart rate
				28	I2: Pedometer use combined with interactive website intervention (frequent feedback, motivational messages, self-regulation, goal setting, education and practice in realistic behavioural change strategies, rewarding)		
				39	C: Maintain usual activity levels		
Ter Hoeve 2018	CVD (59.0±8.5 years; sex m/f: 260/64)	64	34	161	I: Pedometer use, 3 face-to-face group PA counseling sessions consisted of information about health behavior, self-monitoring, goal setting, feedback, barrier identification and relapse prevention	Digiwalker SW-200	Physical activity: - Steps/day
				163	C: Usual care		

Table 1 *Characteristics of included studies (continued).*

Study	Population	Intervention duration (wk)	Dropout rate (%)	No. of participants	Intervention	CWAT type	Outcome parameter
Tudor-Locke 2004	T2DM (52.7±5.2 years; sex m/f: 26/21)	16	22	24	I: First Step behavioural modification program: Behaviour modification program based on the theoretical principles of self-efficacy and social support, the common clinical practices of goal setting, pedometer use and a calendar for self-monitoring and feedback	Digiwalker SW-200	Physical activity: - Steps/day Cardiometabolic: - Body weight - Body mass index - Waist circumference - Hip circumference - Systolic BP - Diastolic BP - Resting heart rate - HbA1c - Fasting glucose - Fasting insulin - Triglycerides - Total cholesterol - LDL cholesterol - HDL cholesterol
				23	C: Usual care		
Van Dyck 2013	T2DM (62±9 years; sex m/f: 63/29)	52	0	60	I: Pedometer use, face-to-face session, telephone support and goal setting.	Digiwalker SW-200	Physical activity: - Steps/day Cardiometabolic: - Body weight - Body mass index - Waist circumference - Systolic BP - HbA1c - Fasting glucose - Triglycerides - Total cholesterol - LDL cholesterol - HDL cholesterol
				32	C: Usual care		

Table 1 *Characteristics of included studies (continued).*

Study	Population	Intervention duration (wk)	Dropout rate (%)	No. of participants	Intervention	CWAT type	Outcome parameter
Vidoni 2016	Cognitive impairment related to Alzheimer's disease (72.3±5.2 years; sex m/f: 12/9)	16	43	9	I: Pedometer use, goal setting (increase goal steps 20% each week and maintaining in weeks 7 and 8), bi-weekly phone calls to encourage physical activity	Fitbit Zip	Physical activity: - Steps/day
				12	C: Masked pedometers		
Vogel 2017	CVD (62.8±9.5 years; sex m/f: 29/0)	12	0	13	I: Pedometer use, goal setting	Polar loop	Cardiometabolic: - Work rate
				16	C: Usual care		
Yamada 2012	Sedentary older adults (75.7±6.8 years; sex m/f: 42/40)	26	6	40	I: Pedometer-based behavioural change program consisted of goal setting (increase daily steps by 10% each month), self-monitoring and feedback	Yamax Powerwalker EX-510	Physical activity: - Steps/day
				42	C: Maintain usual activity levels		
Yates 2009	Impaired glucose tolerance (65.5±9.0 years; sex m/f: 37/21)	52	18	29	I: Group-based education program (PREPARE program), pedometer use, goal setting (increase activity levels by at least 3000 steps/day)	Digiwalker SW-200	Physical activity: - Steps/day Cardiometabolic: - Fasting glucose
				29	C: Usual care		

Table 1 *Characteristics of included studies (continued).*

Study	Population	Intervention duration (wk)	Dropout rate (%)	No. of participants	Intervention	CWAT type	Outcome parameter
Yates 2010	Impaired glucose tolerance (65.0±8.9 years; sex m/f: 33/17)	52	24	24	I: Single session group-based education program (PREPARE program), pedometer use, goal setting (increase activity levels by at least 3000 steps/day)	NL-800 New-lifestyles	Physical activity: - Steps/day Cardiometabolic: - Body weight - Body mass index - Fasting glucose - Triglycerides - Total cholesterol - HDL cholesterol
				26	C: Usual care		

Abbreviations: **BP** = blood pressure, **COPD** = chronic obstructive pulmonary disease, **CVD** = cardiovascular disease, **CWAT** = consumer wearable activity tracker, **T2DM** = type 2 diabetes mellitus.

Results

The search strategy identified 13688 potentially relevant studies of which 8147 after deduplication (Figure 1). Thirty-five full-text articles fulfilled the inclusion criteria and were included in qualitative (n=35) and quantitative (n=33) synthesis (Table 1). Studies included were published over a 14-year period from 2004 to 2018. All studies were written in English and performed in 13 different countries predominantly originating from the United States (n=10). The included studies consisted of populations with various chronic diseases including chronic respiratory diseases (n=7) [32-38], impaired glucose tolerance or T2DM (n=12) [39-50], CVD (n=6) [51-56], overweight/obesity (n=3) [57-59], cognitive disorders (n=1) [60] and sedentary older adults (n=6) [61-65].

Risk of Bias

Among the 35 included studies, several increased risks of bias were assessed. Fifteen studies met five (n=5) [37, 42, 57, 59, 65] and four (n=10) [18, 33, 38, 41, 49, 53, 55, 58, 64, 66] of the six risk of bias criteria. Eighteen studies met three criteria [32, 34-36, 39, 40, 43-45, 47, 50-52, 56, 60-63] and two studies met only two criteria [48, 54]. Although all studies reported appropriate random sequence allocation, insufficient information regarding the procedures used to conceal the allocation of the different trial arm(s) was provided in 21 of the 35 studies (Figure 2). The largest risk of bias was with regard to the performance bias (lack of blinding of participants and personnel) and detection bias (minimal blinding of those assessing outcomes). All included studies were unable to blind the participants and the study personnel/physicians (n=18) or to adequately report blinding (n=17). Only eight studies blinded the outcome assessors, whereas the majority of the studies did not adequately report blinding of the outcome assessors (n=22). Most of the studies provided complete outcome data (n=31), whereas three studies had a high risk of attrition bias [38, 54, 60] due to incomplete outcome data and only one study reported insufficient information [48].

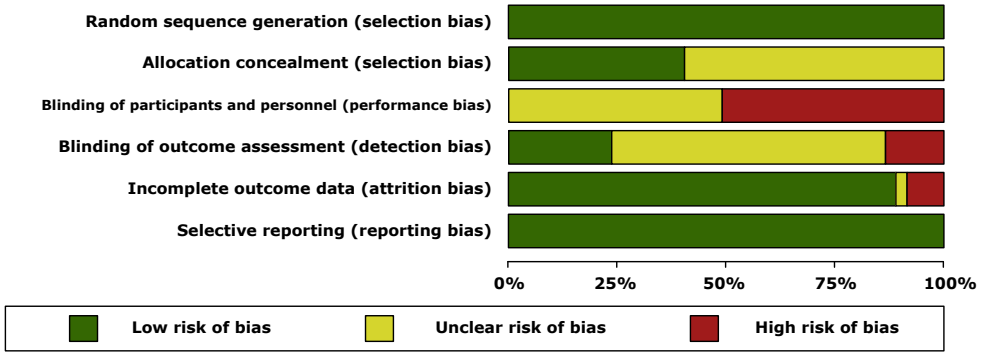

Figure 2 *Risk of bias graph for included studies (n=35).*

Study Characteristics

The CWAT-based interventions evaluated in the included studies varied considerably in intervention duration (mean ± SD; 22 ± 17 weeks; range: 6-64 weeks). In addition, various studies evaluated the effect of a multi-component intervention on physical activity and cardiometabolic health, such as CWAT use with individual counselling and goal setting (n=10) and CWAT use with group counselling (n=3) [41, 49, 50]. The majority of the interventions consisted of CWAT use and individual counselling (n=22) of which five interventions also used additional telephone calls [48, 51, 59-61]. Control conditions varied between studies and consisted of usual care (n=21) [32, 34-36, 38, 41-43, 46-50, 52-56, 58, 59, 61], maintaining normal physical activity levels (n=7) [39, 57, 62-66], encouragement to increase daily physical activity (n=2) [37, 40], generic information brochures (n=1) [51], education sessions (n=2) [33, 44], coaching sessions (n=1) [45] and one control group wore masked CWAT devices (n=1) [60]. Furthermore, the average dropout rate among the studies was 17% (range: 0-43%) of which four studies had a 100% participants completion rate.

Population Characteristics

The included studies evaluated a total of 2858 participants (intervention: n=1567; control: n=1291) of which 529 participants with chronic respiratory diseases (492 with chronic obstructive pulmonary disease; COPD), 704 participants with T2DM, 571 participants with CVD, 334 participants with overweight/obesity, 21 participants with Alzheimer's disease and 699 sedentary older adults. Their mean age was 61.3±7.3 years (range: 45.4-75.7 years) whereas two studies did not

provide information of the average population age [41, 61]. Overall, 60% (range: 13-89%) of the participants were male and one study included only male participants. Twenty-five studies reported daily step counts and most of the participants in the intervention (5105±2591 steps/day; range: 2031-9003 steps/day) and control (5149±2751 steps/day; range: 2334-7539 steps/day) groups were relatively physically inactive at baseline.

Physical Activity

Thirty-three of the studies included data on mean differences of physical activity, expressed as steps per day, and were included in the meta-analyses. Overall, participants with chronic diseases assigned to an intervention group significantly increased their physical activity (step count) by 2123 steps per day more than individuals from control groups (95% confidence interval [CI]: [1605, 2641] steps/day; $p<0.001$). Subgroup analyses showed a significantly increased physical activity above baseline in all groups with a chronic disease, including chronic respiratory diseases (+1314 steps/day; 95% CI: [203, 2426] steps/day; $p=0.020$), T2DM (+2693 steps/day; 95% CI: [1804, 3581] steps/day; $p<0.001$), CVD (+1300 steps/day; 95% CI: [370, 2230] steps/day; $p=0.006$), overweight/obesity (+2405 steps/day; 95% CI: [1232, 3577] steps/day; $p<0.001$) and sedentary older adults (+2568 steps/day; 95% CI: [1396, 3740] steps/day; $p<0.001$), compared to the control groups. However, these results were statistically heterogeneous with respect to the overall effect ($Q=375.2$, $p<0.001$; $I^2=92$) as well as the results from individual subgroups including chronic respiratory diseases ($Q=75.9$, $p<0.001$; $I^2=97$), T2DM ($Q=95.3$, $p<0.001$; $I^2=86$), overweight/obesity ($Q=4.4$, $p=0.037$; $I^2=77$) and sedentary older adults ($Q=58.9$, $p<0.001$; $I^2<82$). In addition, significant publication bias was found in subgroup analyses for patients with CVD ($p=0.012$), overweight/obesity ($p=0.037$) and sedentary older adults ($p=0.004$). Since only 1 study was found regarding cognitive diseases, this study was not included into the meta-analysis. No significant improvement in physical activity was found in patients with Alzheimer's disease after an 8-week intervention period.

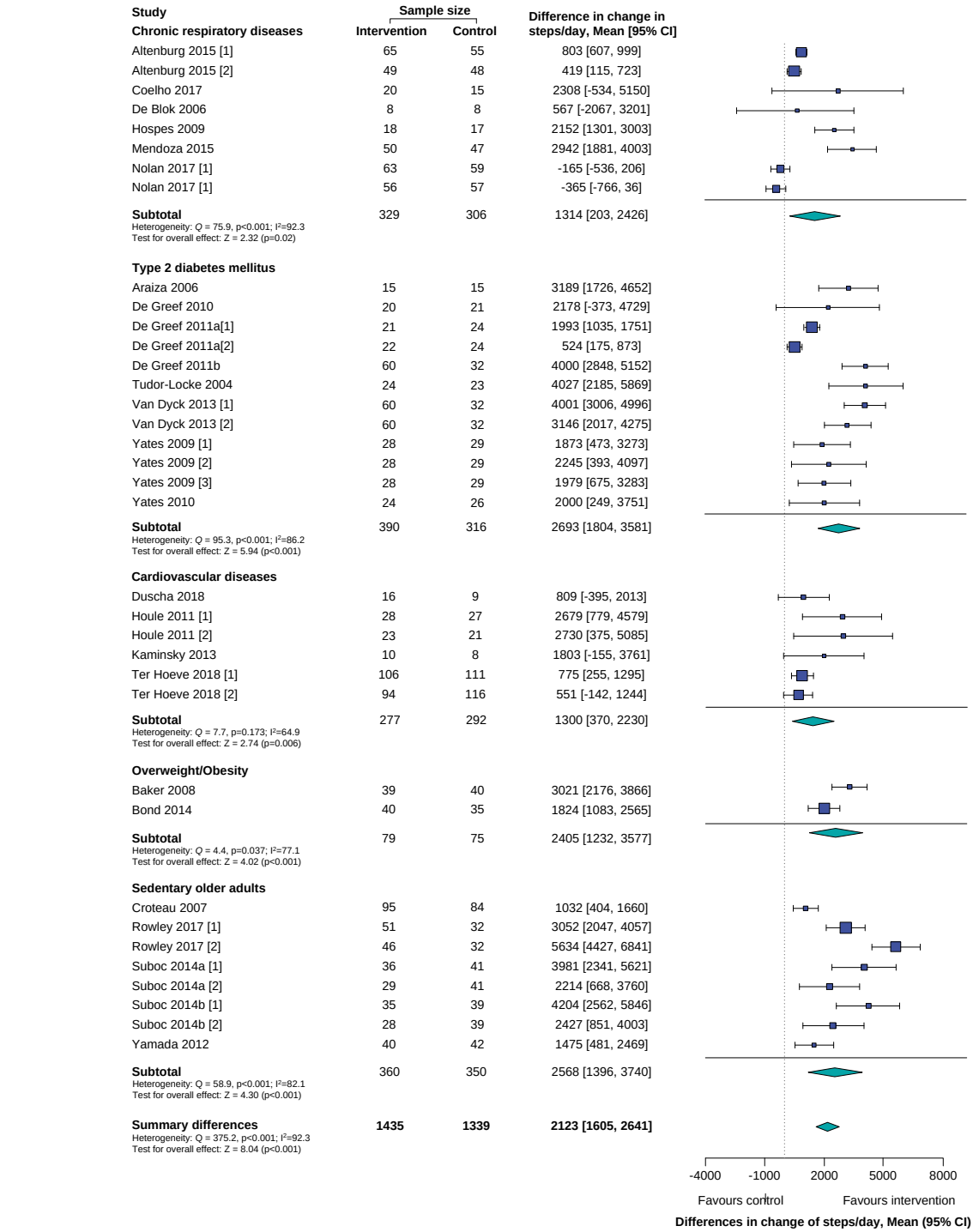

Figure 3 *Forest plot of mean differences of physical activity (steps/day) from CWAT-based behaviour change interventions, compared to control groups. Abbreviations: CI: confidence interval, I^2: the variation in pooled effect size attributable to heterogeneity within that group.*

Table 2 *Effects of CWAT-based behaviour change strategies on cardiometabolic health including anthropometrics, cardiovascular health and biochemical parameters.*

Characteristics	No. of studies	No. of participants (intervention/control)	Preintervention mean (SD)		Mean change (95% confidence interval)	*p*-value
			Intervention	Control		
Anthropometrics						
Body weight (kg)	11	582/570	90.6 (18.3)	88.4 (18.3)	-0.35 [-0.84, 0.13]	0.15
Body mass index (kg/m^2)	16	730/733	30.2 (4.9)	30.5 (5.6)	-0.05 [-0.20, 0.11]	0.56
Waist circumference (cm)	13	715/715	103.6 (13.4)	103.3 (14.7)	-0.99 [-1.48, -0.50]	**<0.001**
Cardiovascular						
Systolic blood pressure (mm Hg)	13	655/654	133.1 (20.0)	131.7 (18.2)	-3.79 [-4.53, -3.04]	**<0.001**
Diastolic blood pressure (mm Hg)	12	535/590	77.3 (13.9)	77.4 (12.0)	0.12 [-1.23, 1.46]	0.87
Resting heart rate (bpm)	6	295/320	68.5 (11.6)	67.4 (10.5)	-1.92 [-3.96, 0.13]	0.07
Biochemical						
HbA1c (%)	11	462/424	7.0 (1.4)	7.1 (1.4)	-0.07 [-0.16, 0.01]	0.08
Fasting glucose (mg/dl)[a]	9	471/431	124.1 (40.1)	116.9 (37.3)	-1.67 [-5.82, 2.49]	0.43
Triglycerides (mg/dl)[a]	8	452/414	151.7 (96.6)	149.0 (103.1)	-1.11 [-8.03, 5.81]	0.75
Total cholesterol (mg/dl)[a]	11	483/459	183.9 (44.2)	187.6 (49.4)	-1.48 [-7.48, 4.51]	0.63
HDL cholesterol (mg/dl)[a]	9	484/448	46.7 (16.1)	48.0 (18.0)	0.29 [-1.13, 1.72]	0.69
LDL cholesterol (mg/dl)[a]	6	408/364	98.4 (39.8)	102.8 (45.3)	-5.70 [-9.24, -2.15]	**0.002**

Abbreviations: **HbA1c** = Haemoglobin A1c, **LDL** = low-density lipoprotein, **HDL** = High-density lipoprotein.
[a]Blood parameters were converted to the same unit (from mmol/l to mg/dl), including triglycerides (divide by 0.0112), total cholesterol, HDL cholesterol, LDL cholesterol (divide by 0.02586) and glucose (divide by 0.05551) concentration.

Association Between Physical Activity and Participant and Intervention Characteristics

Meta-regression analysis showed that all participant characteristics were significantly associated with increased physical activity among individuals from the intervention groups. With respect to the participant characteristics, sex proportion (β=41.0; p=0.039) and CWAT users of a younger age (β=-189.3; p=0.007) were significantly associated with a higher increase in physical activity. In addition, patients with chronic respiratory diseases or CVD had a significantly lower increase in physical activity, compared to other populations with chronic diseases (p<0.001). Furthermore, no significant association was found between the intervention duration (β=-7.2; p=0.951), intervention type (β=-424.4; p=0.528) and physical activity.

Physical Activity and Cardiometabolic Health

Participants from the intervention groups significantly decreased their waist circumference (-0.99 cm; 95% CI: [-1.48, -0.50] cm; p<0.001), systolic BP (-3.79 mm Hg; 95% CI: [-4.53, -3.04] mm Hg; p<0.001) and LDL cholesterol concentration (-5.70 mg/dl; 95% CI: [-9.24, -2.15] mg/dl; p=0.002) more than individuals from the control group (Table 2). In addition, both waist circumference (Q=20.0, p=0.40; I^2=12), systolic BP (Q=7.5, p=0.98; I^2<0.001) and LDL cholesterol concentration (Q=9.0, p=0.44; I^2<0.001) were all homogeneous results and no significant publication bias was found. Furthermore, the study by Vogel *et al.* evaluated changes in physical fitness after a 6-week post-rehabilitation period and showed a significant increased peak workload in the CWAT intervention group (from 185±55 to 192±54 Watt [+27 Watt]; p<0.001), compared to the control group (from 186±52 to 169±44 Watt [-17 Watt]).

Discussion

This review systematically evaluated the efficacy of CWAT-based interventions to promote physical activity levels and improve cardiometabolic health in sedentary older adults and patients with chronic diseases, including chronic respiratory diseases, T2DM, CVD, overweight/obesity and cognitive disorders. To the best of our knowledge, this is the first systematic review and meta-analysis that evaluates the impact of CWATs on physical activity and cardiometabolic health in populations

with various chronic diseases. In addition, these results are solely based on randomised controlled trials and objectively measured physical activity (number of steps per day). In general, individuals with a CWAT increased their physical activity level and this may be associated with improvements in cardiometabolic health including waist circumference, systolic BP and LDL cholesterol concentration.

Physical activity levels increased by 2123 steps per day. This is comparable to 20 minutes or 1.5 km of walking. These results are consistent with findings from other meta-analyses showing an increased physical activity among outpatient adults (+2500 steps/day) [14] and patients with T2DM (+1822 - 2042 steps/day) [21, 22]. In addition, de Vries *et al*. showed that behavioural phyical actvity interventions with an activity monitor increase physical activity (both steps/day and moderate-to-vigorous physical activity) in adults with overweight and obesity [20]. Armstrong *et al*. found that pedometer-based physical activity promotion increased steps per day (+1000 steps/day) when it is used as an intervention alone or alongside pulmonary rehabilitation [67]. These studies all confirm that a CWAT-only, or included in a multi-component intervention, have a positive effect in favor of the interventions groups. Here, Dwyer *et al.* and Jefferis *et al*. both found an association between all-cause mortality and step count where every increment of 1000 steps per day led to a 6% and 14% risk reduction, respectively [68, 69]. In addition, the NAVIGATOR study, which consisted of 9000 individuals with high cardiovascular risk or impaired glucose tolerance, has shown that for every additional 2000 steps/day the risk of developing cardiovascular events decreased by 10%, T2DM by 5.5%, and the metabolic syndrome risk score redcued by 0.29 *z*-score [70-72]. In general, CWAT-users included in this meta-analysis increased their step count from 5100 steps per day at baseline to 7200 after the intervention period. Consequently and in accordance with Lee *et al*., who obeserved that hazard ratios of all-cause mortality declined progressively with higher mean steps per day until approximately 7500 steps/day after which they leveled in older adult women [73], this could indicate a substantial reduction in all-cause mortality risk and the development of chronic diseases. As such, our findings are relevant for the general population and for those who cannot participate in high-intensity physical activities.

Meta-regression analysis showed that both patients with COPD and CVD exhibited the lowest increase in physical activity among all populations with chronic diseases included in this systematic review. This might be due to airflow and cardiac limitations and most of these studies were performed after a rehabilitation period where baseline physical activity levels were reduced. These findings were also found by Amstrong *et al.,* who showed that COPD patients with greater baseline physical activity levels (>4000 steps/day) had greater improvements in steps per day. These results can be confirmed by our results since the baseline physical activity levels of COPD patients in our meta-analysis were 3335 steps per day. In addition, meta-regression analysis showed no additional effect of behaviour change strategies (goal setting, group counselling, individual counselling or telephone support) on physical activity levels. This is in contrast with a systematic review that showed a positive effect for CWATs, even when interventions were separated into CWAT-only and multifaceted interventions [74]. However, a larger effect size for interventions that were multifaceted was found compared to CWAT-only interventions. This suggests that CWATs can be effective on their own, but when combined with other behaviour change strategies, such as telephone support or group-based counselling, the improvement in physical activity is greater. However, it must be outlined that Brickwood *et al.* only included healthy adults and there was only a small number of studies in our meta-regression that included both a CWAT-only and CWATs as part of a multi-component intervention group. Therefore, more studies are warranted which include both a CWAT-only and a multi-component intervention group. Furthermore, patient characteristics were all independently associated with an increased number of step, which possibly explains the heterogeneity of the overall effect and subgroup analyses. For example, the obese population was younger of age compared to other populations and, as a result, propably showed a higher increase in physical activity. Therefore, caution is warranted when interpreting these results.

The increment of physical activity was associated with improvements in several cardiometabolic health parameters. The systolic BP was significantly decreased in the intervention groups. This finding is consistent with previous systematic reviews with respect to physical activity and blood pressure among outpatient [14] and healthy sedentary adults [75, 76]. It has been shown that a change of -10 mm Hg in systolic BP reduces the risk of developing CVD by 17% and overall mortality

by 13% [77]. In addition, a decrease in systolic BP of 2 mm Hg is associated with a reduction of 10% in stroke mortality and a 7% reduction in mortality originating from CVD [78]. Furthermore, a significantly reduced LDL cholsterol concentration was found when physical activity levels were increased among individuals with CWATs. A meta-analysis from The Cholesterol Treatment Trialists' Collaboration showed that with the aid of statins the 5-year incidence of major vascular events reduced by about 20% and all-cause mortality by 12% per 40mg/dl in LDL cholesterol concentration. However, since we showed a reduction of 6mg/dl, medication has probably more beneficial effects rather than increasing physical activity [79]. In addition, most data regarding physical activity and serum lipids seem to indicate that regular physical activity or exercise training does not reduce LDL cholesterol concentration in a clinically relevant way [80, 81]. However, it has been suggested that regular physical activity may change the LDL cholesterol particle size, even when total LDL concentrations remain constant [82, 83]. We also found a significantly decreased waist circumference with the same magnitude (-1.19 cm; 95% CI: [-1.79, -0.59] cm) as found in another published meta-analysis in which the effect of physical activity and dietery interventions on waist circumference was evaluated [11]. De Koning *et al.* have shown that a decrease of 1 cm in waist circumference reduces the relative risk of a CVD event by 2% [84]. In this way, CWAT devices can improve health related outcomes which are closely related to CVD.

Several limitations of the included studies were observed. First, studies with relatively small sample sizes and different intervention durations were included in the meta-analyses. In addition, this review reflected heterogeneous study designs which consisted of multiple components including CWAT use, goal setting, telephone calls, diary use, individual or group counselling, different therapists, face-to-face or written motivation and the frequency of the sessions. Therefore, the independent contribution of any of these components, or a combination of these factors, is difficult to establish. This probably explains the high heterogeneity of the physical activity results ($Q=375$, $p<0.001$; $I^2=92$). However, since clinical and methodological diversity is always present in meta-analysis statistical heterogeneity is inevitable. Moreover, Higgens *et al*. reported that almost one third of meta-analyses have moderate to considerable heterogeneity [85]. Secondly, only eleven studies evaluated physical activty (steps/day) in

combination with one or more of the cardiometabolic risk factors. In this way, no direct associations between increased physical acitivities (steps/day) and cardiometabolic risk factors could be made and no minimal amount of steps per day to improve cardiometabolic health could be determined. Thirdly, various CWAT devices were both used to objectively measure physical activity and as a motivational instrument. As a result, this may affect the control group by increasing their physical activity by the thought that they were being monitored. Finally, all studies only measured physical activity but did not take into account sedentary time. It has been shown that sedentary behaviour is a risk factor for cardiometabilic health and all-cause mortality, indepently of the amount of physical activity [86, 87]. Therefore, we recommend to include sedentary time, next to physical activity, in future studies.

Conclusion

These results suggest that populations with chronic diseases significantly increase physical activity using CWATs only, or as part of a multi-component intervention, and improve their cardiometabolic health such as a reduced waist circumference, systolic BP and LDL cholesterol concentration.

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Appendices

Literature search

NCD Population

"Cardiac Rehabilitation"[MeSH] OR "Cardiovascular Diseases"[MeSH] OR "Chronic Disease"[MeSH] OR Aortic Stenoses[tiab] OR Aortic valve disease*[tiab] OR Aortic Valve Stenos*[tiab] OR Arteriosclerosis[tiab] OR Atherogenesis[tiab] OR Atherosclerоses[tiab] OR Atherosclerosis[tiab] OR Cardiac Disease*[tiab] OR Cardiac dysfunction*[tiab] OR Cardiac rehabilitation*[tiab] OR Cardiomyopath*[tiab] OR Cardiovascular disease*[tiab] OR Cardiovascular rehabilitation*[tiab] OR Cardiovascular risk*[tiab] OR Cardiovascular Stroke[tiab] OR CHF[tiab] OR Chronic disease*[tiab] OR Chronic Illness*[tiab] OR Coronary Disease*[tiab] OR CVD[tiab] OR Heart Attack*[tiab] OR Heart Disease*[tiab] OR Heart dysfunction*[tiab] OR Heart Failure*[tiab] OR Heart Valve Disease*[tiab] OR Myocardial Disease*[tiab] OR Myocardial Failure*[tiab] OR Myocardial Infarction*[tiab] OR Myocardial Ischemia*[tiab] OR Myocardiopath*[tiab] OR Peripheral Angiopath*[tiab] OR Vascular Disease*[tiab] OR Ventricular outflow obstruction*[tiab] OR Arrhythm*[tiab] OR Atrial flutter*[tiab] OR Tachycard*[tiab] OR Tachyarrhythm*[tiab] OR Arterial disease*[tiab] OR "Lung diseases"[MeSH] OR Chronic Airflow Obstruction*[tiab] OR Chronic bronchitis[tiab] OR Chronic Obstructive Airway Disease*[tiab] OR Chronic obstructive pulmonary disease*[tiab] OR Chronic respiratory disease*[tiab] OR COAD[tiab] OR COPD[tiab] OR Emphysema*[tiab] OR Lung disease*[tiab] OR "Glucose Metabolism Disorders"[MeSH] OR Diabetes[tiab] OR Glucose Intolerance*[tiab] OR Glucose metabolism disorder*[tiab] OR Glucose tolerance*[tiab] OR Glucose Metabolic Disorder*[tiab] OR IDDM[tiab] OR Impaired fasting glucose[tiab] OR Prediabetes[tiab] OR Pre-diabetes[tiab] OR Prediabetic State*[tiab] OR "Dyslipidemias"[MeSH] OR Dyslipidemia*[tiab] OR Dyslipoproteinemia*[tiab] OR Dysmetabolic Syndrome X[tiab] OR Elevated Cholesterol*[tiab] OR High Cholesterol Level*[tiab] OR Hypercholesteremia*[tiab] OR Hypercholesterolemia*[tiab] OR Hyperlipemia*[tiab] OR Hyperlipidaemia[tiab] OR Hyperlipidemia*[tiab] OR Hypertriglyceridemia*[tiab] OR Lipemia*[tiab] OR Lipidemia*[tiab] OR Metabolic Cardiovascular Syndrome*[tiab] OR High Cholesterol[tiab] OR High Blood

Pressure[tiab] OR Hypertension[tiab] OR Hyperglycemia*[tiab] OR Hyperinsulinemia[tiab] OR Insulin resistance[tiab] OR Insulin sensitivity[tiab] OR Metabolic syndrome*[tiab] OR "Overweight"[MeSH] OR Obes*[tiab] OR Overweight*[tiab] OR "Cerebrovascular Disorders"[MeSH] OR Apoplex*[tiab] OR Brain Infarction*[tiab] OR Brain Vascular Accident*[tiab] OR Cerebrovascular Accident*[tiab] OR CVA[tiab] OR Stroke*[tiab] OR Cerebrovascular disease*[tiab] OR Cerebral Ischemia*[tiab] OR Brain ischemia*[tiab] OR "Multiple sclerosis"[MeSH] OR Disseminated Scleros*[tiab] OR MS[tiab] OR Multiple Scleros*[tiab] OR "Neurocognitive disorders"[MeSH] OR Alzheimer Disease*[tiab] OR Alzheimer's Disease*[tiab] OR Cognition Disorder*[tiab] OR Cognitive Decline*[tiab] OR Cognitive Dysfunction*[tiab] OR Cognitive Impairment*[tiab] OR Cognitive defect*[tiab] OR Dement*[tiab] OR Neurocognitive Disorder*[tiab] OR Neurological Disorder*[tiab]

Sedentary older adult population

"Postmenopause"[MeSH] OR "Adult"[MeSH] OR Septuagenarian*[tiab] OR Nonagenarian*[tiab] OR Octogenarian*[tiab] OR Octagenarian*[tiab] OR Centenarian*[tiab] OR Centarian*[tiab] OR Supercentenarian*[tiab] OR Elder*[tiab] OR frail*[tiab] OR geriatri*[tiab] OR old age*[tiab] OR oldest old*[tiab] OR senior*[tiab] OR senium[tiab] OR very old*[tiab] OR older people[tiab] OR older subject*[tiab] OR older patient*[tiab] OR older age*[tiab] OR older adult*[tiab] OR older man[tiab] OR older men[tiab] OR older male*[tiab] OR older woman[tiab] OR older women[tiab] OR older female*[tiab] OR older population*[tiab] OR older person*[tiab] OR adult*[tiab] OR postmenopaus*[tiab]

Consumer wearable activity tracker

((((("Telemedicine"[MeSH] OR "Telerehabilitation"[MeSH] OR "Wearable electronic devices"[MeSH] OR Telemedicine[tiab] OR Telerehabilitation[tiab] OR remote rehabilitation[tiab] OR Mobile Health[tiab] OR mHealth[tiab] OR m-health[tiab] OR Pedometer*[tiab] OR Acceleromet*[tiab])))) AND ((Rehabilitation[tiab] OR Treatment*[tiab] OR Intervention*[tiab] OR Prevention[tiab]))) OR (((Fitness Tracker*[tiab] OR Activity Tracker*[tiab] OR Smart wearable*[tiab] OR Activity monitor*[tiab] OR Remote patient monitoring[tiab] OR Fitness device*[tiab] OR SenseWear[tiab] OR BodyMedia Fit[tiab] OR DirectLife[tiab] OR Fitbit[tiab] OR

Garmin[tiab] OR Vivosmart[tiab] OR Jawbone[tiab] OR MisFit Shine[tiab] OR Nike FuelBand[tiab] OR Polar[tiab] OR Withings[tiab] OR Yamax[tiab] OR Bodybugg[tiab] OR Tomtom[tiab] OR Fitbug[tiab] OR Wahoo[tiab] OR Omron[tiab] OR Apple Watch[tiab] OR Actiwatch[tiab] OR Smart watch*[tiab] OR Smart wristband*[tiab])))

Behaviour change

"Health behavior"[MeSH] OR "Health promotion"[MeSH] OR "Leisure activities"[MeSH] OR "Motor activity"[MeSH] OR Physical Activit*[tiab] OR Health Behavior*[tiab] OR Healthy Behavior*[tiab] OR Health Behaviour*[tiab] OR Healthy Behaviour*[tiab] OR Health Promotion*[tiab] OR Leisure Activit*[tiab] OR Physical Exercis*[tiab] OR Measure activit*[tiab] OR Behavior modification*[tiab] OR Behaviour modification*[tiab] OR Behavioral modification*[tiab] OR behavioural modification*[tiab] OR Behavior change*[tiab] OR Behaviour change*[tiab] OR Motor Activit*[tiab] OR Sedentary[tiab] OR Leisure time[tiab] OR lifestyle modification*[tiab] OR lifestyle change*[tiab]

Cardiometabolic health outcomes

"Physical fitness"[MeSH] OR "Exercise tolerance"[MeSH] OR "Blood pressure"[MeSH] OR "Heart rate"[MeSH] OR "Body weights and measures"[MeSH] OR "Body constitution"[MeSH] OR "Cholesterol"[MeSH] OR "Fat body"[MeSH] OR "Anthropometry"[MeSH] OR Oxygen uptake[tiab] OR Oxygen consumption[tiab] OR VO2[tiab] OR Physical Fitness[tiab] OR Exercise tolerance[tiab] OR Weight[tiab] OR Blood Pressure[tiab] OR Diastolic Pressure[tiab] OR Systolic Pressure[tiab] OR Pulse Pressure[tiab] OR Steps[tiab] OR Step count[tiab] OR MVPA[tiab] OR Moderate to vigorous activit*[tiab] OR Moderate to vigorous intensit*[tiab] OR Energy Expenditure[tiab] OR Heart Rate*[tiab] OR Pulse Rate*[tiab] OR Walking distance[tiab] OR Body Composition*[tiab] OR Body Constitution*[tiab] OR Lipid profile*[tiab] OR Cholesterol[tiab] OR LDL[tiab] OR HDL[tiab] OR Insulin[tiab] OR Glucose[tiab] OR Body fat[tiab] OR Waist Circumference*[tiab] OR Body Measure*[tiab] OR Waist-Hip Ratio*[tiab] OR Waist-to-hip ratio*[tiab] OR Anthropometr*[tiab] OR Metabolic health[tiab] OR Health outcome*[tiab] OR BMI[tiab] OR body mass index[tiab]

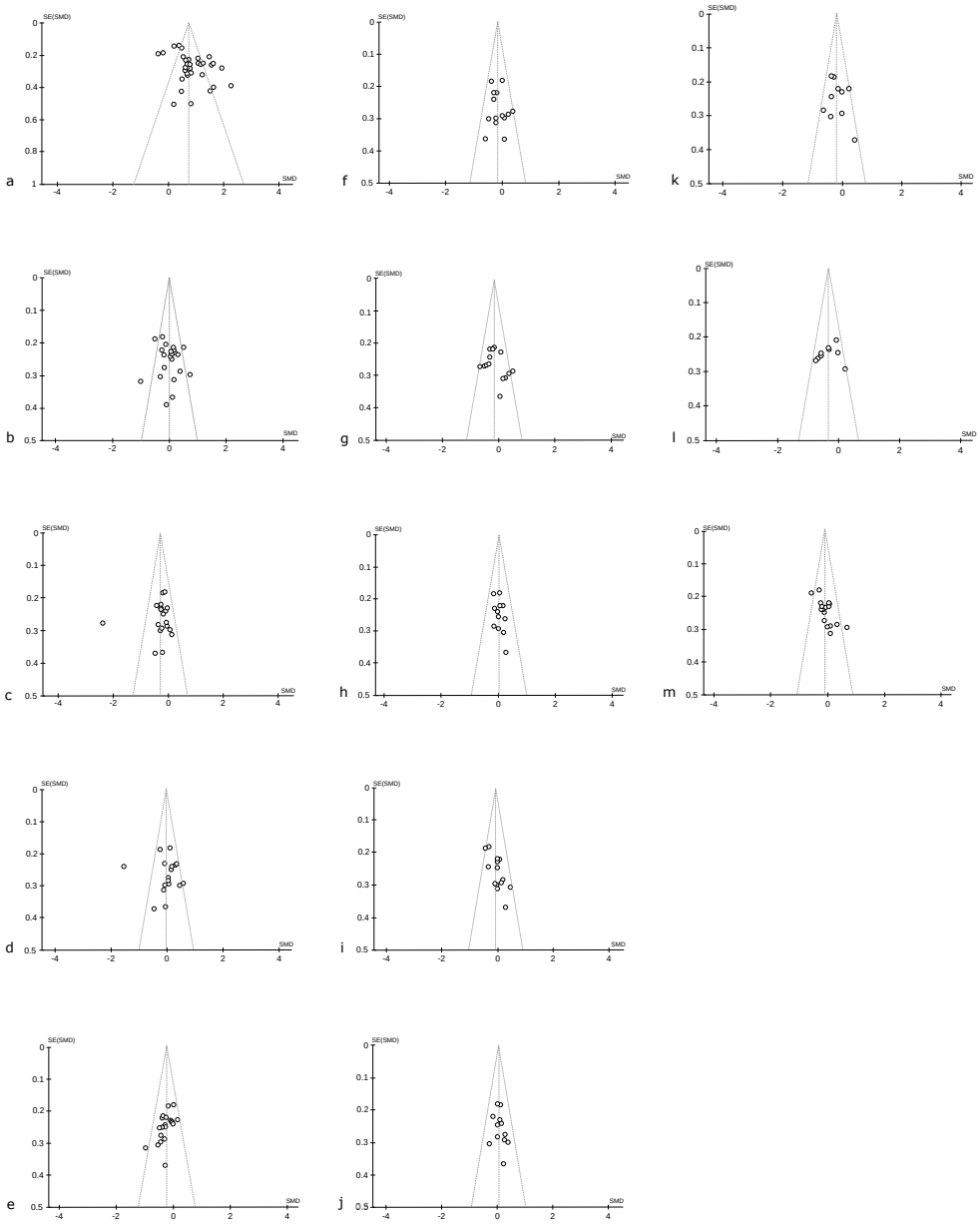

Figure S1 *Funnel plots comparing interventions with regard to (a) physical activity, (b) body mass index, (c) systolic blood pressure, (d) diastolic blood pressure, (e) waist circumference, (f) HbA1c, (g) fasting glucose concentration, (h) triglyceride concentration, (i) total cholesterol concentration, (j) high-density lipoprotein cholesterol concentration, (k) low-density cholesterol concentration, (l) resting heart rate and (m) body weight.*


LDL
HDL

Chapter 5

A 12-week consumer wearable activity tracker-based intervention reduces sedentary behaviour and improves cardiometabolic health in free-living sedentary adults: a randomised controlled trial

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Abstract

Background: Reducing sedentary behaviour significantly improves cardiometabolic health and plays an important role in the prevention and management of CMDs. However, no specific effective strategies have been proposed to combat the negative effects of sedentary lifestyles. Therefore, we is to investigate the efficacy of a single component CWAT-only intervention and the added value of a multicomponent (CWATs + motivational interviewing) behaviour change intervention to reduce sedentary behaviour and increase physical activity within sedentary adults.

Methods: In a three-armed randomised controlled trial, 59 (male/female: 21/38) sedentary adults were randomly allocated to a control group, a CWAT-only group or the CWAT+ group (CWAT + motivational interviewing) for 12 weeks. Physical activity (PA) and SB were assessed using the activPAL3™ accelerometer. In addition, anthropometrics, blood pressure, plasma lipids and insulin sensitivity using an oral glucose tolerance test were assessed at baseline and after the 12-week intervention period.

Results: As compared with the control group, the CWAT+ group significantly reduced time spent in sedentary behaviour (-81 min/day CI[95%]: [-151, -12] min/day) and significantly increased step count (+3117 [827, 5406] steps/day), standing time (+62 [14, 110] min/day), light intensity PA (+28 [5, 50] min/day) and moderate-to-vigorous PA (+22 [4, 40] min/day). Body fat mass (-1.67 [-3.21, -0.14] kg), percentage body fat (-1.5 [-2.9, -0.1] %), triglyceride concentration (-0.31 [-0.62, -0.01] mmol/l), the 2h insulin concentration (-181 [-409, -46] pmol/l), QUICKI (-0.022 [-0.043, -0.008]) and tAUC (-6464 [-26837, -2735] mmol/l*min) were significantly reduced in the CWAT+ group, compared to the control group.

Conclusion: A 12-week multicomponent CWAT-based intervention (CWAT + motivational interviewing) reduces sedentary time, increases physical activity levels and improves various cardiometabolic health variables in sedentary adults, whereas self-monitoring on itself (CWAT-only group) has no beneficial effects on sedentary time.

Introduction

The metabolic syndrome represents a cluster of cardiometabolic risk factors including insulin resistance, abdominal obesity, hypertension and dyslipidaemia, which all contribute to the development of cardiometabolic diseases (CMDs) such as type 2 diabetes mellitus and cardiovascular diseases [1]. Over the past two decades, the global prevalence of people with the metabolic syndrome has considerably increased and has caused an alarming trend of increase in CMDs. Here, physical inactivity is one of the major contributing factors that highly correlates with mortality and hospitalization [2, 3].

Engaging in regular moderate-to-vigorous physical activity (MVPA) significantly improves cardiometabolic health and plays an important role in the prevention and management of CMDs. In this respect, the World Health Organization (WHO) recommends practicing a weekly volume of 150−300 minutes at moderate intensity, 75−150 minutes at vigorous intensity or an equivalent combination of MVPA [4]. However, 28% of the adult and 80% of the adolescent population remains physically inactive [4]. In addition, although research has mainly focussed on physical activity (PA) so far, it has become evident that sedentary behaviour, independent of the volume of MVPA, is also an important contributor to CMD development. Sedentary behaviour is defined as 'any waking behaviour characterized by a low energy expenditure (≤1.5 metabolic equivalents), while being in a sitting or reclining posture' [5]. Epidemiological and meta-analytic evidence has indicated that low levels of MVPA in combination with large volumes of sedentary behaviour are jointly associated with increased cardiometabolic morbidities and mortality in a dose-dependent manner [6-8]. Despite the detrimental health effects of prolonged sitting, adults still accumulate between 7.5 and 10 hours of their day in sedentary pursuits during work, transportation and leisure time activities, such sedentary behaviour is a major problem [8]. Although the 2020 guidelines on PA and sedentary behaviour encourage reducing periods of prolonged sitting, no specific strategy has been proposed to combat the negative effects of sedentary lifestyles [4]. Therefore, there is need for behaviour change strategies to reduce sedentary behaviour and to increase physical activity levels.

A variety of effective (multicomponent) behaviour change strategies, including environmental modifications, education, motivational counselling and technologies such as consumer wearable devices and smartphone applications,

have been applied to reduce sedentary behaviour in adults [9-13]. However, the majority of the current studies has focused on workplace interventions [9, 12] or assessed intervention effects using self-report [10]. In addition, most studies were insufficiently powered to detect significant improvements in cardiometabolic health [13]. Furthermore, systematic reviews mainly included multicomponent interventions, where the multicomponent character of these interventions limits separation of the effects of the individual components [9-11]. Interestingly, Compernolle *et al*. showed that self-monitoring-based behaviour change interventions are promising to reduce sedentary behaviours [14]. However, all included interventions consisted of multiple behaviour change techniques, making it impossible to determine whether the beneficial effects on sedentary behaviour were attributable to self-monitoring on itself, or to (a combination with) other behaviour change techniques. In this respect, it has already been shown that self-monitoring with the aid of consumer wearable activity trackers (CWATs) can effectively improve physical activity volumes [15, 16]. However, interventions solely focusing on PA do not generally result in clinically meaningful reductions in sedentary time [11]. Nowadays, more sophisticated CWATs also implement information with regard to sedentary behaviour with the aid of providing alerts after prolonged sitting. In this respect, it may be possible that these CWATs are able to effectively reduce sedentary behaviour. In addition, since it is acknowledged that behaviour change benefits most from personalised coaching and from stimulating autonomy we expect that sedentary behaviour can be further reduced by adding motivational interviewing to CWAT-use.

Therefore, this study aims to investigate the efficacy of a single component CWAT-only intervention and the added value of a multicomponent (CWATs + motivational interviewing) behaviour change intervention to reduce sedentary behaviour and increase physical activity within sedentary adults. The second aim is to investigate whether a reduction in sedentary behaviour also lead to improvements in cardiometabolic health.

Research Design and Methods

Subjects

Sedentary (sitting time of ≥ 9h/day) healthy adults, or sedentary adults at risk to develop chronic diseases, aged between 40 and 75 years were recruited via online

and paper advertisements. At risk participants were reported as having at least one of the following cardiometabolic risk factors: prehypertension (systolic blood pressure: 120-140 mm Hg; diastolic blood pressure: 80-89 mm Hg), overweight/obese (BMI: 25-35 kg/m^2), hyperlipidaemia and/or prediabetes (HbA1c < 6.5%). Exclusion criteria were pregnancy, regularly (>150 min per week during the last four months) being engaged in structured moderate-to-vigorous intensity physical exercise, any known contra-indication for physical activity, more than 14 alcohol consumptions per week, plans to follow a weight reduction programme with the aid of an energy restriction diet or a physical intervention programme during the study period, or participants diagnosed with any known metabolic disease. Throughout the study trial, subjects were instructed to consume and maintain their habitual diet. All subjects were informed in detail and were asked to provide written informed consent. The study was approved by the medical ethical committee of Hasselt University and was performed at Hasselt University (Diepenbeek, Belgium) between September 2018 and February 2021 in accordance with the principles of the Declaration of Helsinki. The present study was registered at clinicaltrials.gov as NCT03853018.

Study Design

The study was carried out according to a three-armed, randomised controlled design. First, participants were invited to a screening visit involving a medical examination, including their medical history and medication use. In addition, HbA1c was measured and the cardiovascular status was screened using a resting 12-lead electrocardiogram (Mortara ELI150c, Welch Allyn, Chicago, IL, USA) and resting blood pressure measurement (Omron M2, Omron Healthcare, Lake Forest, IL, USA). Hereafter, and prior to randomisation and baseline measurements, physical activity and sedentary behaviour was assessed with the aid of an accelerometer (activPAL3™, PAL Technologies Ltd, Glasgow, Scotland) for seven consecutive days to ensure that only sedentary subjects were included. One week after the screening visit, eligible participants were included for baseline measurements. Participants were instructed to refrain from strenuous physical exercise three days before each test day and one day prior to each test day participants were requested not to consume alcohol. After a 12-h overnight fasting period prior to examination, all subjects were refrained from consuming food,

except for water *ad libitum* to prevent changes on biochemical analysis. First, anthropometry, body composition using dual energy X-ray absorptiometry and blood pressure assessed and venous blood samples were collected. Subsequently, an oral glucose tolerance test (OGTT) was performed to assess insulin sensitivity and beta cell function. Furthermore, dietary habits were assessed for seven consecutive days by means of a diary. Following baseline measurements, eligible participants were randomly assigned (Figure 1) using an established allocation ratio of 1:1:1 to either 1: a group without any intervention (control group, CON), 2: a group receiving only a consumer wearable activity tracker (CWAT) or 3: a CWAT and additional motivational messages via the ELCIES (ELCIES, Gent, Belgium) lifestyle data platform (CWAT+). The control group was instructed to continue their habitual daily physical activity patterns and sedentary behaviours. The CWAT group received the Polar M200 activity tracker (Polar Electro, Kempele, Finland) and were assisted in creating a Polar flow account, downloading the application, synchronizing the Polar M200 with their individual Polar flow account and how to use the device. Subjects received real-time feedback from the Polar device in terms of step count and inactivity alerts after 1 hour of inactivity to break up sitting time to avoid prolonged sedentary behaviours. During the interruptions they were asked to walk or stand for several minutes. Participants were instructed to increase their step count to at least 10,000 steps per day, spread throughout the day during the interruptions of sedentary behaviour. Subjects allocated to the $CWAT_+$ intervention also received the Polar M200. In addition, an initial personalized physical activity prescription was given, in accordance with the participants, based on baseline sedentary time, average number of steps per day and their occupational physical activity levels. Here, the aim was to address sedentary behaviour via three target behaviours: replacing prolonged sitting with stepping or standing, and break up prolonged bouts of sedentary behaviour. Furthermore, an information session was held to increase participants' awareness of the negative independent impact of sedentary behaviour on the risk of chronic disease development. Participants were further supported by means of motivational interviewing under guidance of a clinical psychologist, which has been found to be an effective, relatively low intensity intervention whereby the interaction was mainly based on collaboration and autonomy [17]. This technique could be defined as a person-centred directive counselling style used to address

individual ambivalence about behaviour change through placing the emphasis on individuals producing their own argument for change. Typical strategies to build motivation were goal-setting, a focus on self-efficacy, increasing beliefs about the positive health consequences of taking action (outcome expectancies), providing tips and tricks to decrease sedentary behaviour, motivate people to achieve their goal targets, probing for a rationale when participants did not reach their targets, and self-monitoring. The counselling sessions took place via chat conversations. Messages were framed positively and highlighted short-term outcomes specifically relating to social and mental health. In addition, the message content was tailored to the recipients. The frequency and content of chat conversations were tailored to the recipients, based on the needs and requests of the subject. All conversations and visualization of physical activity information was supported via the ELCIES data platform (www.elcies.com). This secured platform promotes and supports a healthy lifestyle including to address prolonged sitting and physical inactivity. Once the ultimate goal of 10,000 steps per day was reached participants were encouraged to maintain this level of physical activity. We considered intervention adherence as successful when any increase in total step count and/or postural transitions above each participant's own average baseline levels.
Blocked randomisation was performed by an independent researcher using a random block size of two, three or four with the aid of sealed envelopes. Hereafter, subjects were enrolled into a 12-week intervention period. Following 12 weeks of either CON, CWAT or CWAT+ intervention baseline measurements were repeated.

Physical Activity and Sedentary Behaviour Assessment

Physical activity and body postures were quantified using the activPAL3™ activity monitor (PAL Technologies Ltd, Glasgow, Scotland), a triaxial accelerometer and inclinometer, as previously described [18]. The device was enclosed with a nitrile sleeve and attached to the anterior mid-thigh of the participants right leg using an adhesive dressing (Tegaderm, 3M, Minnesota, USA). Participants were instructed to wear the device for a period of 7 consecutive days and 24h hours per day. The activPAL™ could accurately measure posture allocation and free-living physical activity in which discriminations were made between time spent in sleeping, sedentary behaviours (sitting or lying), standing and physical activity including step count and step cadence (low intensity physical activity and MVPA)

[19, 20]. Furthermore, step count and short (< 30 minutes) and prolonged (> 60 minutes) sedentary bouts were measured.

Anthropometry and Body Composition

Body height was measured to the nearest 0.1cm using a wall-mounted Harpenden stadiometer, with participants barefoot. Body weight (in underwear) was determined using a digital-balanced weighting scale to the nearest 0.1kg. BMI was calculated from weight and height measurements (weight/height²). Waist and hip circumferences were measured to the nearest 0.1cm using a flexible metric measuring tape with participants barefoot (in underwear) in standing position. Waist circumference was measured at the midpoint between the lower rib margin and the top of the iliac crest. Hip circumference was measured at the widest circumference of the hip at the level of the greater trochanter. Waist-to-hip ratio was calculated by dividing waist circumference (cm) by hip circumference (cm). Whole body fat, lean tissue mass and bone mineral density were evaluated using Dual Energy X-ray Absorptiometry (Hologic Series Delphi-A Fan Beam X-ray Bone Densitometer, Vilvoorde, Belgium).

Blood Glucose, Insulin and Serum Lipids

After antecubital catheter placement, fasting blood samples were obtained for the measurement of cardiometabolic risk factors. Serum separation and sodium fluoride (NaF) containing BD vacutainer™ tubes (Becton, Dickinson and Company, Franklin lakes, NY, USA) were collected. To obtain plasma, NaF tubes were immediately centrifuged at 1300 x *g* for 15 minutes. Serum tubes coagulated for at least 30 minutes prior to centrifuging at 1300 x *g* for 15 minutes. All centrifugation steps were performed at room temperature (21°C). Supernatants were immediately portioned into aliquots and frozen at −20 °C and subsequently moved to a − 80 °C freezer until analysis at the end of the trial. Glucose, insulin, total cholesterol, high-density lipoprotein cholesterol (HDL-cholesterol), low-density lipoprotein cholesterol (LDL-cholesterol) and triglycerides concentrations were automatically assessed on the Roche Cobas 8000 (Roche Diagnostics International Ltd, Rotkreuz, Switzerland). Sodium heparinized 18µl capillary tubes (Marienfeld GmbH, Lauda-Königshofen, Germany) were used to collect capillary blood from the middle finger. Blood glycated haemoglobin A1c (HbA1c)

concentration was assessed using ion exchange chromatography (Menarini HA-8180 HbA1c auto-analyser, Menarini Diagnostics, Diegem, Belgium).

Insulin Sensitivity and Beta Cell Function

A standard 5-point oral glucose tolerance test (OGTT) was performed for assessment of whole body/tissue specific insulin sensitivity and beta cell function. Subjects ingested a solution (250ml) containing 75g dextrose, and venous blood samples were obtained at t = 0, 30, 60, 90 and 120min for assessment of venous glucose and insulin concentration. From glucose and insulin concentrations, homeostatic model assessment for insulin resistance (HOMA-IR) was calculated by: fasting glucose (mmol/l) * fasting insulin (μU/ml)/22.5 [21]. In addition, whole-body insulin sensitivity was estimated using the Matsuda index and calculated as: 10,000/√[fasting glucose (mg/dl) * fasting insulin (μU/ml)) * (mean glucose during OGTT (mg/dl) * mean insulin during OGTT (μU/ml)] [22]. The quantitative insulin sensitivity check index (QUICKI) was calculated as: 1/log(fasting insulin (μU/ml) + log(fasting glucose (mg/dl) [21]. Beta cell function was estimated by calculation of the insulinogenic index (IGI) by: ratio of increment of insulin (μU/ml) and glucose (mg/dl) in the first 30 min of OGTT [21]. The total area under the curve (tAUC) for glucose and insulin for the 2 hour period is calculated using the trapezoidal rule [23]. Tissue specific insulin resistance was calculate using the hepatic insulin resistance index (HIRI) and the muscle insulin resistance index (MISI). The HIRI was calculated as the product of the tAUCs for glucose and insulin during the first 30 min of the OGTT (glucose0–30[tAUC in mg/dl h] * insulin 0–30[tAUC in μU/ml h]) and the MISI was calculated as the rate of decay of glucose concentration during the OGTT divided by the mean insulin concentration during the OGTT in mg/dl/min/ μU/ml). The rate of decay was calculated as the slope of the least square fit to the decline in glucose concentration from peak to nadir, as described by Vogelzangs *et al* [24].

Blood Pressure

After an initial resting period of 20 min with participants in a supine position in a quiet room with constant temperature (21°C), blood pressure (BP) was measured at least 3 times at 2-min intervals until blood pressure was stabilized using an electronic sphygmomanometer (Omron®, Omron Healthcare, IL, USA) from the

left arm and documented as the mean value of the 3 final measurements. Mean arterial pressure (MAP) was calculated as MAP = systolic BP + (2 x diastolic BP) / 3.

Energy and Nutrient Intake Assessment

Habitual dietary intake was assessed using a self-administered food diary. Participants recorded all food and beverages consumed over seven consecutive days and from this the total caloric intake and macronutrient content was calculated.

Statistical Analysis

Statistical analyses were performed by IBM SPSS® version 27.0 (IBM SPSS Statistics for Windows, Chicago, IL, USA). Data were expressed as mean ± SD, unless otherwise indicated. Shapiro-Wilk test was used to test normality of the data ($p < 0.05$). Baseline characteristics between the three groups were compared using a one-way ANOVA (Bonferroni post-hoc comparison test) for normally distributed data. Natural log transformation was performed if the outcome was not normally distributed. Data were analysed using an intention-to-treat approach. Comparisons between groups were tested using the Fischer's exact test for categorical variables. Differences in response between groups were analysed using general linear model analyses with the difference between baseline and 12-week intervention as dependent variable, group (control, CWAT and CWAT+) as fixed factor and baseline values of the outcome variables as covariates. Linear mixed models were used to assess whether there were differences in insulin and glucose concentration during OGTT. First, the difference between baseline and after the 12-week intervention period for each separate time point of the OGTT were calculated. Then, an interaction effect was evaluated, where group (control, CWAT and CWAT+) was a between-subjects factor, and time (five different time points of the OGTT) was a within-subjects factor. A pairwise analysis (Bonferroni post-hoc comparison test) was performed when the between-subjects factor was statistically significant. A p-value <0.05 (2-tailed) was considered statistically significant. Associations between physical activity intensities and cardiometabolic health were performed using multivariate linear regression models. Metabolic variables that were significant different between groups, including body mass,

waist circumference, fat mass, insulin concentration after 120 minutes of the OGTT, tAUC of insulin and triglyceride concentration, were included as dependent variables. Independent variables were change in standing time, LPA and MVPA over the 12-week intervention period. Model 1 was the unadjusted model, model 2 corrected for potential confounders sex, age, body height, smoking status, chronic disease, medication, food intake and baseline measurements of standing, LPA and MVPA and model 3 also corrected for all other variables (standing, LPA and/or MVPA).

The sample size calculation was performed using GPower v. 3.1 (Düsseldorf, Germany). Prince *et al*. showed in a systematic review and meta-analysis a significant reduction in sedentary behaviour (effect size d: 1.08) in adults [11]. Based on a statistical power > 0.8 and a two-sided alpha of 0.05 it was calculated that a sample size of 15 individuals per group had to be included in the present study. Taking into account a drop-out rate of 10%, the number of participants to include in this study was at least 17 subjects per group, resulting in a final sample size of 51 subjects.

Results

137 participants were initially assessed for study entry of which 79 individuals were effectively screened. From these 79 individuals, 20 subjects were excluded due to a sedentary time < 9h/day (n=11) or spending more than 150 of structured physical activity (n=9). These 59 individuals were randomly assigned to either the control (n=20), CWAT (n=20) or CWAT+ (n=19) group. Three participants from both the control (n=1) and the CWAT+ (n=2) group were dropped out mainly due to lack of time (Figure 1). The age range of the participants was between 38 and 71 years (53.3±8.7 years) and the BMI ranged between 19.7 and 34.8 kg/m^2 (26.0±4.1kg/m^2). In addition, the total population consisted of 21 (36%) males and 38 (64%) females. In total 9 participants were included with chronic diseases, of which 3 with chronic respiratory diseases (con: n=1, CWAT+: n=2) and 6 with cardiovascular diseases (CWAT: n=5, CWAT+: n=1). At baseline, participants spent 34% (8.1±0.6h) of the day sleeping, 45% (10.8±1.2h) of their waking hours sedentary, 15% (3.6±1.0h) in standing activities and only 5% (1.1±0.3h) in LPA and 2% (0.4±0.2h) in MVPA. No significant differences for all variables were found between groups at baseline.

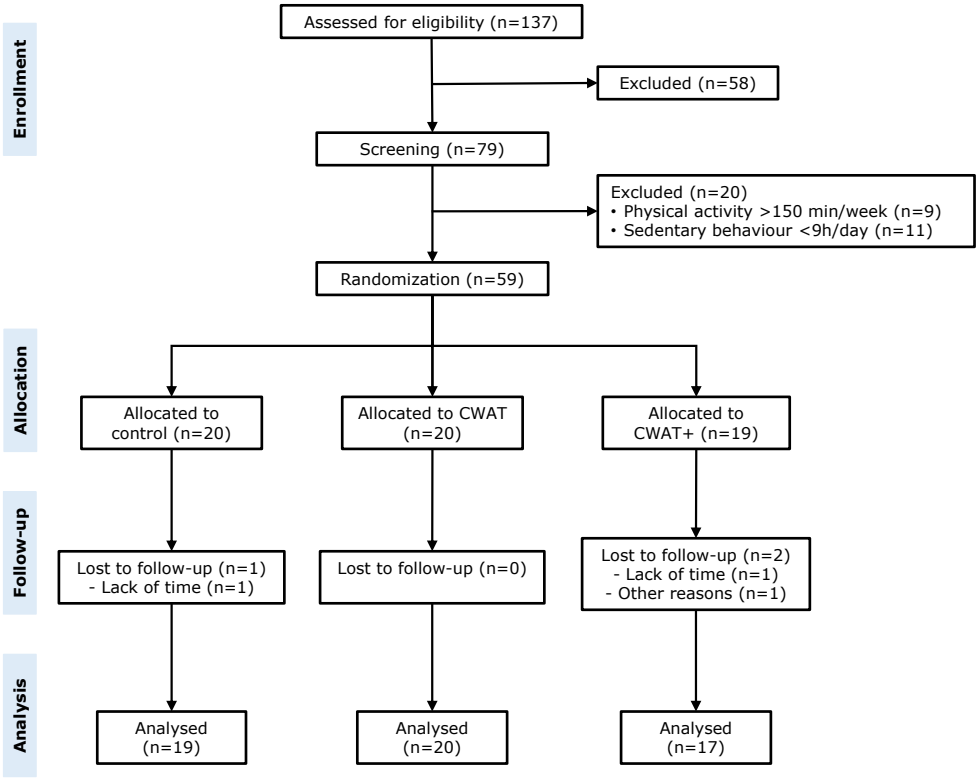

Figure 1 *Study flow chart of the eligible and ultimately included participants.*

Physical Activity and Sedentary Behaviour

After the 12-week intervention period and compared with the control group, participants from the CWAT+ group significantly increased their step count (+3301 ± 3558 vs. +184 ± 2045 steps/day; p = 0.036), LPA (+32 ± 34 vs. +3 ± 24 min/day; p = 0.040) and MVPA (+20 ± 28 vs. -2 ± 13 min/day; p = 0.005) (Figure 2). In addition, standing time was increased (+64 ± 57 vs. +2 ± 52 min/day; p = 0.015), whereas the time spent in sedentary behaviours was significantly reduced (-79 ± 89 vs. +2 ± 61 min/day), mainly due to spending less time in bouts of more than 1 hour (-85 ± 68 vs. -29 ± 97 min/day; p = 0.024) in CWAT+ when compared to the control group. In contrast, no significant improvements with respect to sitting time and PA within the CWAT group were observed, compared to the control and CWAT+ group.

Anthropometrics and Body Composition

The 12-week intervention significantly decreased body weight (CWAT+: -1.6 ± 3.1 kg, CWAT: +0.3 ± 1.0 kg; p = 0.021, Con: +0.6 ± 2.1 kg; p = 0.009) and body mass index (CWAT+: -0.5 ± 1.0 kg/m^2, CWAT: +0.1 ± 0.3 kg/m^2; p = 0.017, Con: +0.2 ± 0.7 kg/m^2; p = 0.011) within the CWAT+ population, compared to the CWAT and control group (Table 1). Waist circumference was decreased in both the CWAT (-1.1 ± 2.6 cm vs. +1.7 ± 4.1 cm; p = 0.049) and CWAT+ (-2.3 ± 4.0 cm vs. +1.7 ± 4.1 cm; p = 0.004) group compared to the controls, whereas only participants from the CWAT+ group significantly reduced their hip circumference (CWAT+: -2.0 ± 4.8 cm, CWAT: -1.1 ±3.7 cm; p = 0.952, Con: +1.4 ± 3.3 cm; p = 0.014), body fat mass (CWAT+: -1.3 ± 2.6 kg, CWAT: +0.1 ± 1.0 kg; p = 0.095, Con: +0.4 ± 1.6 kg; p = 0.021) and percentage body fat mass (CWAT+: -1.4 ± 2.4%, CWAT: +0.1 ± 1.3%; p = 0.124, Con: +0.2 ± 1.2%; p = 0.026) compared to the control group.

Lipid Profile and Insulin Sensitivity

With respect to the lipid profile only triglyceride concentrations were significantly decreased in the CWAT+ group (-0.31 ± 0.43 mmol/l; p = 0.043) compared to the control group (-0.05 ± 0.33 mmol/l) after a 12-week intervention period, while no differences were found between the CWAT group and the control group (Table 2). In addition, the insulin concentration (CWAT+: -145 ± 212 pmol/l, Con: 30 ± 301 pmol/l; p = 0.021) after 2 hours of the OGTT and the QUICKI (CWAT+: -0.02 ± 0.02, Con: 0.01 ± 0.02; p = 0.010) significantly improved in the CWAT+ group, compared to the control group. A significant between-subject difference (p = 0.039) of the tAUC of insulin concentration was found within the CWAT+ group (baseline: 51613 ± 29688 mmol/l·min vs. 12 weeks: 45233 ± 23636 mmol/l·min) compared to the control (baseline: 59012 ± 34473 mmol/l·min vs. 12 weeks: 60633 ± 39986 mmol/l·min, Figure 3) and CWAT groups (baseline: 52514 ± 38236 mmol/l·min vs. 12 weeks: 52649 ± 36907 mmol/l·min). In addition, linear mixed models revealed a significant between-subject (p = 0.029), within subject (p = 0.037) and interaction effect (p = 0.045) of insulin concentrations during the OGTT. Post-hoc comparison test showed significant between group differences at 90 (con: -9 ± 185 pmol/l; p = 0.063, CWAT: 53 ± 205 pmol/l; p = 0.017, CWAT+:

-78 ± 173 pmol/l) and 120 minutes (con: 30 ± 301 pmol/l; p = 0.039, CWAT: 27 ± 217 pmol/l; p = 0.043, CWAT+: -151 ± 218 pmol/l) of the OGTT.

Associations Between Cardiometabolic Risk, Sedentary Behaviour and Physical Activity

An increase in LPA was associated with reduced body weight (SC β = -0.341[-0.445 – -0.103]; r^2 = 0.169; p = 0.002), waist circumference (SC β = -0.314 [-0.554 – -0.107]; r^2 = 0.147; p = 0.005), fat mass (SC β = -0.216[-0.432 – -0.003]; r^2 = 0.076; p = 0.002), insulin concentration after 2 hours of OGTT (SC β = -0.360 [-0.724 – -0.086]; r^2 = 0.104; p = 0.014), tAUC insulin (SC β = -0.340 [-0.660 – -0.057]; r^2 = 0.115; p = 0.021) and triglyceride concentrations (SC β = -0.363 [-0.623 – -0.101]; r^2 = 0.132; p = 0.007). However, after adjusting for all covariates only waist circumference (SC β = -0.287 [-0.556 – -0.057]; r^2 = 0.391; p = 0.001), insulin concentration after 2 hours of OGTT (SC β = -0.369 [-0.821 – -0.010]; r^2 = 0.199; p = 0.045), tAUC insulin (SC β = -0.395 [-0.774 – -0.059]; r^2 = 0.230; p = 0.024) and triglyceride concentration (SC β = -0.367 [-0.688 – -0.043]; r^2 = 0.230; p = 0.027) remain statistically associated with increased LPA levels (Figure 4). In addition, an increased MVPA was only associated with a lower waist circumference (SC β = -0.370 [-0.574 – -0.103]; r^2 = 0.342; p = 0.006) when adjusted for all covariates.

Table 1 *Subject characteristics before and after a 12-week CWAT-based intervention period within the control, CWAT and CWAT+ groups.*

	Control		CWAT		CWAT+		Intervention effects		
General features	**Baseline (n=20)**	**12 weeks (n=19)**	**Baseline (n=20)**	**12 weeks (n=20)**	**Baseline (n=19)**	**12 weeks (n=17)**	**CWAT vs control**	**CWAT+ vs control**	**CWAT+ vs CWAT**
Age (years)	53.8 ± 8.5	54.2 ± 8.8	52.4 ± 8.7	52.8 ± 8.7	53.8 ± 9.2	54.7 ± 9.5			
Sex (m/f)	6/14	6/13	7/13	7/13	8/11	7/10			
Body weight (kg)	75.8 ± 11.5	77.2 ± 11.6	76.6 ± 14.6	76.9 ± 14.7	74.7 ± 12.7	72.6 ± 12.5	-0.28 (-2.01, 1.46)	-2.19 (-4.00, -0.37)*	-1.91 (-3.70, -0.12)*
Body height (cm)	169.7 ± 7.9	170.4 ± 7.3	171.1 ± 7.9	171.1 ± 8.0	171.3 ± 10.3	170.2 ± 10.2			
BMI (kg/m²)	26.3 ± 3.8	26.6 ± 4.1	26.2 ± 4.9	26.3 ± 4.9	25.4 ± 3.6	25.0 ± 3.6	-0.06 (-0.65, 0.52)	-0.72 (-1.33, -0.14)*	-0.66 (-1.26, -0.06)*
WC (cm)	88.5 ± 10.0	90.9 ± 10.7	89.2 ± 13.9	88.0 ± 14.3	87.2 ± 10.1	85.1 ± 9.2	-2.87 (-5.72, -0.01)*	-4.11 (-7.09, -1.13)*	-1.24 (-4.20, 1.70)
HC (cm)	98.2 ± 9.3	100.2 ± 10.4	99.7 ± 11.2	98.6 ± 11.4	97.4 ± 8.0	95.6 ± 7.2	-2.46 (-5.60, 0.67)	-3.48 (-6.75, -0.21)*	-1.02 (-4.25, 2.22)
WC/HC	0.90 ± 0.08	0.91 ± 0.08	0.89 ± 0.08	0.89 ± 0.10	0.90 ± 0.07	0.89 ± 0.07	-0.01 (-0.04, 0.02)	-0.01 (-0.04, 0.02)	-0.01 (-0.04, 0.03)
Lean mass (kg)	46.5 ± 7.1	47.3 ± 6.5	48.3 ± 6.5	48.6 ± 8.6	47.9 ± 9.1	47.3 ± 9.2	0.21 (-0.73, 1.11)	-0.36 (-1.35, 0.63)	-0.57 (-1.55, 0.41)
Fat mass (kg)	26.0 ± 9.4	26.5 ± 10.0	24.5 ± 9.9	24.6 ± 10.1	23.1 ± 6.2	21.9 ± 7.3	-0.26 (-1.70, 1.18)	-1.67 (-3.21, -0.14)*	-1.41 (-3.21, -0.14)
Fat mass (%)	34.0 ± 9.6	33.9 ± 9.9	31.9 ± 9.5	31.8 ± 9.4	31.5 ± 6.6	30.4 ± 8.0	-0.3 (-1.6, 1.1)	-1.5 (-2.9, -0.1)*	-1.3 (-2.6, 0.2)
Energy intake (kcal)	1503 ± 255	1600 ± 450	1726 ± 348	1793 ± 264	1635 ± 351	1595 ± 630	-87 (-330, 505)	-120 (-557, 317)	-33 (-437, 371
Fat (g)	53 ± 16	56 ± 23	64 ± 19	65 ± 11	58 ± 14	60 ± 26	-6 (-23, 19)	-4 (-27, 19)	2 (-19, 23)
Protein (g)	71 ± 15	76 ± 20	68 ± 18	74 ± 22	73 ± 18	68 ± 24	4 (-22, 31)	-10 (-37, 17)	-14 (-40, 11)
Carbohydrate (g)	170 ± 30	179 ± 42	196 ± 42	208 ± 40	189 ± 44	180 ± 75	-8 (-49, 34)	-10 (-54, 33)	-3 (-43, 38)
HbA1c (%)	5.3 ± 0.3		5.4 ± 0.3		5.3 ± 0.4				
Smoking status (n)									
Never	0		0		1				
Former	5		7		3				
Never	15		13		15				
Chronic disease (n)									
Respiratory	1		0		2				
Cardiovascular	0		5		1				
Medication (n)									
Beta blocker	0		3		2				
Ang II	0		2		1				
Bronchodilator	1		0		1				

Data are expressed as mean ± SD. Abbreviations: **CWAT** = consumer wearable activity tracker, **BMI** = body mass index, **WC** = waist circumference, **HC** = hip circumference, **Ang II** = Angiotensin II- antagonist. * $p < 0.05$. The intervention effects are mean changes (95% CI) obtained from general linear model analyses with baseline value as covariate.

Table 2 *Cardiometabolic risk factors and parameters before and after a 12-week CWAT-based intervention period within the control, CWAT and CWAT+ groups.*

	Control		CWAT		CWAT+		Intervention effects		
	Baseline (n=20)	12 weeks (n=19)	Baseline (n=20)	12 weeks (n=20)	Baseline (n=19)	12 weeks (n=17)	CWAT vs control	CWAT+ vs control	CWAT+ vs CWAT
Cardiovascular health									
Systolic BP (mm Hg)	120 ± 13	117 ± 12	123 ± 12	120 ± 12	124 ± 12	125 ± 15	1 (-6, 8)	4 (-3, 12)	3 (-4, 10)
Diastolic BP (mm Hg)	79 ± 8	77 ± 7	83 ± 9	80 ± 8	81 ± 8	81 ± 9	0 (-4, 4)	3 (-1, 6)	3 (-1, 6)
Mean arterial BP (mm Hg)	93 ± 10	90 ± 8	96 ± 9	93 ± 9	95 ± 9	96 ± 10	0 (-4, 5)	3 (-1, 8)	3 (-2, 7)
Resting heart rate (bpm)	62 ± 6	61 ± 7	59 ± 9	60 ± 8	57 ± 7	60 ± 8	1 (-4, 6)	3 (-2, 8)	2 (-3, 6)
Total cholesterol (mmol/l)	5.00 ± 0.93	4.80 ± 0.91	5.40 ± 1.12	4.78 ± 0.88	5.67 ± 1.27	4.64 ± 0.98	-0.17 (-0.79, 0.45)	-0.41 (-1.06, 0.24)	-0.24 (-0.87, 0.39)
HDL cholesterol (mmol/l)	1.39 ± 0.24	1.26 ± 0.33	1.62 ± 0.49	1.36 ± 0.23	1.61 ± 0.51	1.26 ± 0.29	0.07 (-0.14, 0.28)	-0.05 (-0.25, 0.18)	-0.11 (-0.31, 0.10)
LDL-cholesterol (mmol/l)	3.61 ± 0.82	3.54 ± 0.81	3.78 ± 1.10	3.42 ± 0.90	4.06 ± 0.98	3.38 ± 0.82	-0.20 (-0.67, 0.27)	-0.38 (-0.87,0.11)	-0.18 (-0.67, 0.31)
Triglycerides (mmol/l)	0.98 ± 0.41	1.05 ± 0.55	1.25 ± 0.71	1.02 ± 0.57	1.22 ± 0.38	0.94 ± 0.37	-0.25 (-0.55, 0.05)	-0.36 (-0.70, -0.03)*	-0.07 (-0.63, 0.23)
Glucose tolerance									
Fasting glucose (mmol/l)	5.3 ± 0.5	5.2 ± 0.5	5.1 ± 0.7	5.2 ± 0.5	5.3 ± 0.4	5.5 ± 1.0	0.3 (-0.5, 0.5)	0.2 (-0.3, 0.7)	0.2 (-0.3, 0.7)
Fasting insulin (pmol/l)	60 ± 31	55 ± 24	54 ± 35	46 ± 29	44 ± 28	52 ± 17	-5 (-20, 10)	5 (-11, 21)	10 (-5, 25)
Glucose 120 min (mmol/l)	6.5 ± 1.8	7.3 ± 2.3	6.2 ± 1.7	6.4 ± 1.9	6.9 ± 1.7	6.6 ± 1.5	-0.3 (-1.6, 0.9)	-0.6 (-1.9, 0.7)	-0.3 (-1.6, 1.0)
Insulin 120 min (pmol/l)	547 ± 389	571 ± 425	490 ± 429	421 ± 396	551 ± 433	371 ± 241	-68 (-266, 129)	-173 (-375, -29)*	-104 (-304, 95)
Glucose tAUC (mmol/l · min)	862 ± 159	903 ± 209	832 ± 155	845 ± 196	890 ± 139	862 ± 180	-2 (-132, 127)	-60 (-192, 72)	-57 (-194, 79)
Matsuda index	5.04 ± 3.42	5.45 ± 3.51	6.07 ± 3.71	7.13 ± 4.59	5.75 ± 2.37	5.18 ± 1.72	0.27 (-1.70, 2.24)	-0.65 (-2.70, 1.40)	-0.91 (-2.94, 1.11)
IGI	209 ± 151	178 ± 109	173 ± 155	183 ± 165	113 ± 201	156 ± 81	-9 (-53, 71)	6 (-59, 72)	-3 (-67, 62)
QUICKI	0.35 ± 0.03	0.36 ± 0.04	0.36 ± 0.04	0.37 ± 0.04	0.37 ± 0.03	0.35 ± 0.02	0.01 (-0.01, 0.03)	-0.02 (-0.04, 0.00)*	-0.03 (-0.05, 0.01)*
HOMA-IR	2.07 ± 1.16	1.88 ± 0.93	1.86 ± 1.40	1.55 ± 1.07	1.54 ± 1.11	1.90 ± 0.91	-0.19 (-0.79, 0.42)	0.30 (-0.34, 0.93)	0.49 (-0.14, 1.11)
mISI	0.11 ± 0.08	0.13 ± 0.1	0.14 ± 0.10	0.18 ± 0.19	0.14 ± 0.08	0.16 ± 0.08	0.03 (-0.09, 0.14)	0.03 (-0.09, 0.15)	0.00 (-0.12, 0.12)
HIRI	32.8 ± 11.0	34.0 ± 13.0	32.2 ± 13.0	31.7 ± 13.5	27.7 ± 10.7	30.1 ± 6.7	-1.0 (-7.2, 5.2)	-0.8 (-7.3, 5.7)	0.2 (-6.2, 6.6)

Data are expressed as mean ± SD. Abbreviations: **CWAT** = consumer wearable activity tracker, **BP** = blood pressure, **bpm** = beats per minute, **HDL** = high-density lipoprotein, **LDL** = low-density lipoprotein, **AUC** = area under curve, **IGI** = insulinogenic index, **QUICKI** = quantitative insulin sensitivity check index, **HOMA-IR** = homeostatic model assessment of insulin resistance, **mISI** = muscle insulin sensitivity index, **HIRI** = hepatic insulin resistance index. * $p < 0.05$. The intervention effects are mean changes (95% CI) obtained from general linear model analyses with baseline value as covariate.

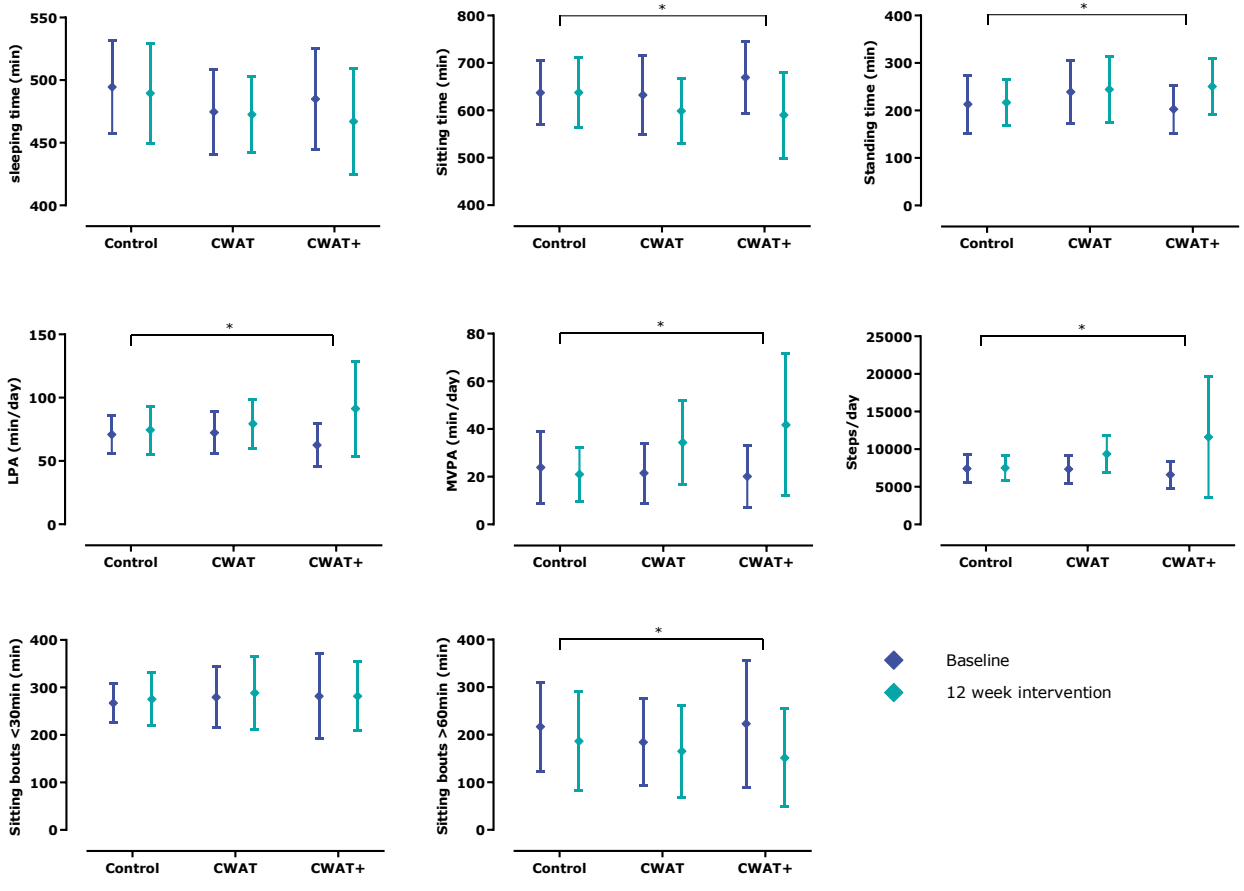

Figure 2 *Average time spent in sleeping, different physical activity intensities and sedentary behaviours before and after a 12-week CWAT-based intervention period within the control, CWAT and CWAT+ groups. Data are presented as means ± standard deviations. * p < 0.05 of mean difference (12 weeks - baseline) between groups. Abbreviations:* ***CWAT*** *= consumer wearable activity tracker,* ***LPA*** *= light intensity physical activity,* ***MVPA*** *= moderate-to-vigorous intensity physical activity.*

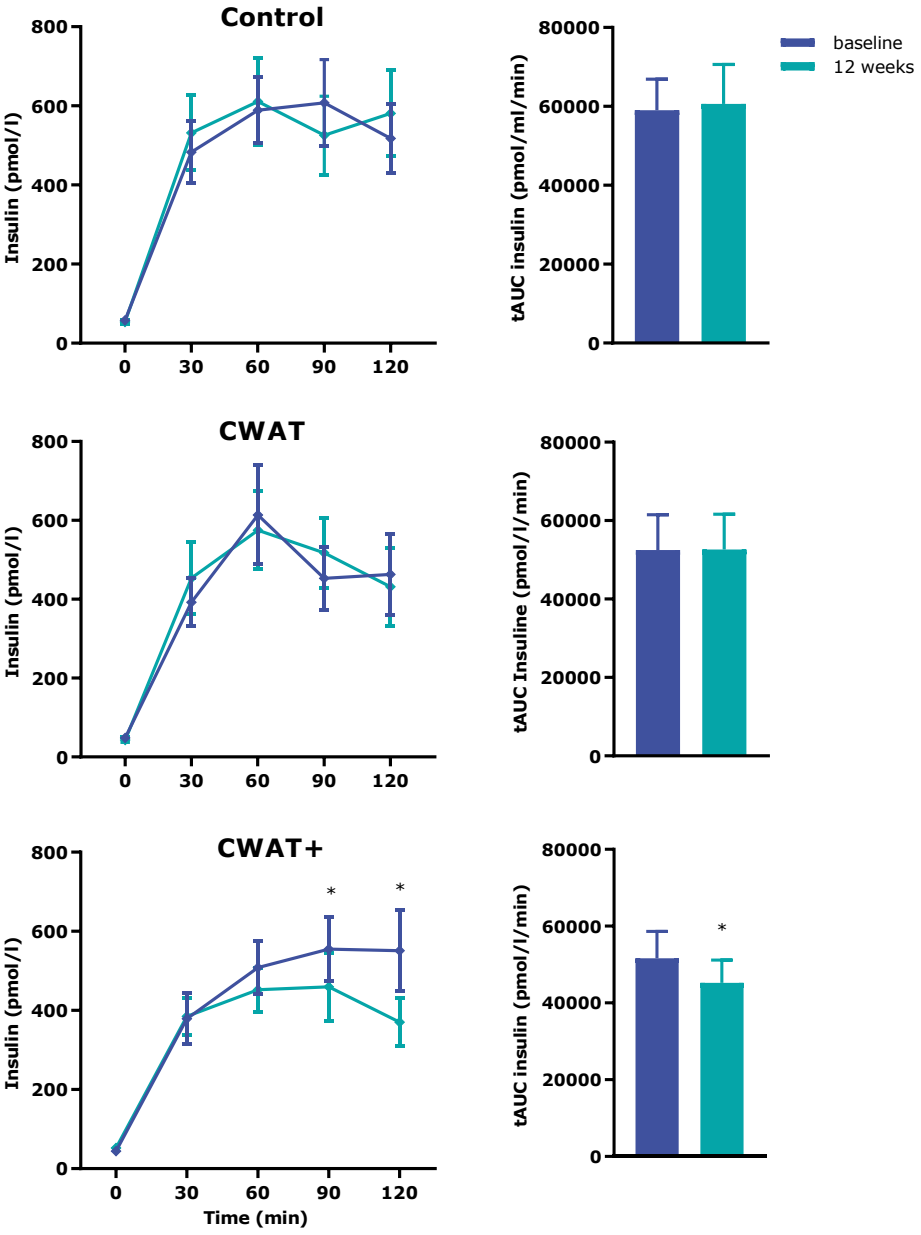

Figure 3 *Insulin concentrations during a 2-hour oral glucose tolerance test (left hand panel) and the average area under the curve (right hand panel) for each individual group (control, CWAT and CWAT+) at baseline and after a 12-week intervention period. Data are presented as means ± standard errors of the mean. * p < 0.05 of mean difference (12 weeks - baseline) between groups. Abbreviations:* ***tAUC*** *= total area under the curve,* ***CWAT*** *= consumer wearable activity tracker.*

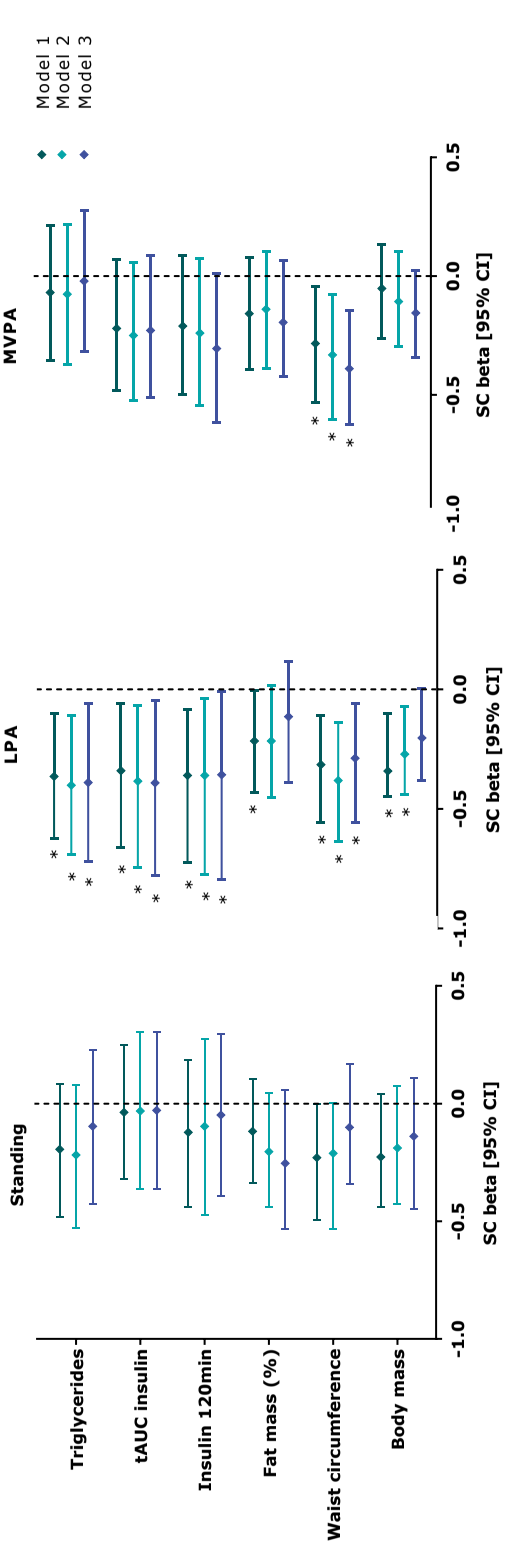

Figure 4 *Multivariate regression analyses for the associations between standing, LPA, MVPA and different cardiometabolic health outcomes. Model 1: unadjusted; model 2: adjusted for covariates sex, body height, smoking status, chronic disease, medication, food intake and baseline measurements of standing, LPA and MVPA; model 3: adjusted for all covariates from model 2 and standing, LPA and/or MVPA. Data are presented as standardized coefficient of beta [95% confidence interval]. * p < 0.05. Abbreviations:* ***LPA****: light intensity physical activity,* ***MVPA****: moderate-to-vigorous intensity physical activity,* ***HDL*** *= high-density lipoprotein,* ***tAUC****: total area under the curve.*

Discussion and Conclusions

The aim of the current study was to investigate the efficacy of a single component CWAT-only intervention and the added value of a multicomponent (CWATs + motivational interviewing) behaviour change intervention to reduce sedentary behaviour and increase physical activity within sedentary adults. Here, we found that the multicomponent intervention (CWAT+: CWAT-use + motivational interviewing) significantly reduced sedentary behaviour and increased physical activity, whereas the single component (CWAT-only) intervention did not. Moreover, the reduction of sedentary behaviour within the CWAT+ group was accompanied by an improvement in cardiometabolic health variables such as reduced body weight, waist circumference, fat mass, triglyceride concentration and enhanced insulin sensitivity. In addition, most favourable effects were found when LPA was increased instead of standing or MVPA.

Participants from the CWAT-group were not provided with behavioural change strategies, tips and tricks to decrease sedentary behaviour and information regarding the health consequences of prolonged sedentary behaviour. Therefore, these additional motivational techniques seem to be essential for improving both sedentary time and physical activity. This was also confirmed by Gardner *et al.* who showed that self-monitoring, goal setting, information on health consequences and motivational counselling were important components to reduce sedentary behaviours [25]. This is the reason why participants from the CWAT-group were not able to reduce their sedentary behaviours. Although it is known that CWATs could be effective tools to improve physical activity levels [16], Martin *et al.* showed that beneficial effects were observed for interventions specifically targeting the reduction in sedentary time instead of interventions in which combined approaches (reducing sedentary behaviour and increasing physical activity levels) were used [10]. Indeed, in the current study, participants from the CWAT-only group only focused on their step count (physical activity intervention), whereas CWAT+ subjects were mainly focused on reducing their sedentary time due to behavioural changes. Participants from the CWAT+ group significantly reduced their daily sitting time by almost 80 minutes, which are in line with a systematic review from Prince *et al* [11]*.* They focused on both sedentary behaviour and physical activity interventions and found that interventions with a focus on physical activity produced less consistent findings and generally resulted in

modest reductions in sedentary time compared to interventions solely targeting sedentary behaviour. Therefore, although CWATs include behaviour change strategies, including social support and providing feedback to increase physical activity, more attention needs to be paid on reducing sedentary behaviour to bring this into conscious awareness.

Furthermore, the specific goal setting approach also affects the decrease of sedentary behaviour. Here, participants from the CWAT-group were instructed to reach a daily step count of 10,000 steps per day, which probably led to a lower self-efficacy to achieve this goal. In contrast, CWAT+ subjects made their own goals to reduce sedentary behaviour and increase physical activity levels, possibly leading to a higher self-efficacy and motivation. Due to these self-defined goals, the step count varied substantially from each other and may explain the high dispersion of the physical activity variables such as MVPA and LPA within the CWAT+ group.

These results are confirmed by Qiu *et al.* who showed that setting an alternative personalized step goal (used in the CWAT+ group) yields significantly reduced sedentary behaviours among participants with a CWAT-device instead of a goal of 10,000 steps/day, which were not able to significantly reduce sedentary time [26]. This means that setting small specific own goals are an important part of motivating individuals to reduce their sedentary behaviour.

The reduction in sedentary time and increment in standing and physical activity (LPA and MVPA) resulted in significant improvements in cardiometabolic health outcomes. These findings were consistent with a recent meta-analysis of Hadgraft *et al.* who showed beneficial effects on body weight, percentage body fat, waist circumference, insulin sensitivity and lipid metabolism after sedentary behaviour interventions in free-living conditions [9]. In addition, isotemporal substitution analyses indicated beneficial cardiometabolic health effects with the reallocation of 30 minutes per day of sedentary time with equal time of either LPA or MVPA, suggesting clinically meaningful [27]. These improvements were consistent with our results, especially in terms of triglycerides and insulin sensitivity. We found a significantly decrease in anthropometrics, of which waist circumference (CWAT+ vs. control: -2 cm; -2.4%) is most important in clinical practice, and triglyceride concentration (CWAT+ vs. control: -0.31 mmol/l). It has been shown that these reductions have clinical significance as it reduces the relative risk of a CVD event

by 2-4% [28, 29]. In addition, an improvement in insulin sensitivity was reflected by a reduced tAUC, 2-hour insulin concentration and the QUICKI. These reductions are clinically meaningful since insulin resistance is a strong predictor of developing T2DM and CVD [30]. Because lipid metabolism and glucose tolerance are important risk factors for the development of CMDs, these multicomponent CWAT-based interventions could be promising for the management and prevention of these chronic diseases.

Multivariate linear regression models from the current study showed a significant association between reduced cardiometabolic risk outcomes and an increase in LPA, independent of the amount of standing time and MVPA. It seems that prolonged sitting was mostly substituted by lower intensity physical activities instead of MVPA, as evidenced by the significant correlation between changes in prolonged sedentary time (bouts > 60 minutes) and LPA ($r = -0.488$, $p < 0.001$), whereas no correlation between prolonged sedentary time and MVPA was found (Appendix Figure S1). This builds on previous experimental studies on the beneficial effects of frequently interrupt sitting time with LPA on cardiometabolic health [18, 31, 32]. This means that it is indicated that individuals who accumulate sedentary bouts of longer duration have a worse cardiometabolic risk profile compared to those with an equal total sedentary time, but regularly interrupt prolonged sitting with LPA. Therefore, it appears that frequently interrupting sedentary behaviour may attenuate the negative effects of sedentary behaviour more than a continuous bout of MVPA. Interestingly, although most experimental studies showed that PA interruptions every 20-30 minutes positively affected cardiometabolic health, our study showed that the same beneficial effects could be achieved with less frequent PA interruptions (reduced total time in sedentary bouts of more than 60 minutes with equal time spent in sedentary bouts <30min). Therefore, because LPA is more accessible than MVPA, frequently interrupting sedentary behaviour with LPA could be a promising way for people who fail to reach the recommended levels of MVPA to improve cardiometabolic health and a delayed onset of chronic diseases.

A strength of the study was the use of the ActivPAL™ activity monitor, often referred to as the gold standard for free-living monitoring of sedentary behaviours [33-36], which has the capability to discriminate between postures. In addition, this is one of the few studies that was able to discriminate between the effectiveness

of mono- and multicomponent intervention strategies. This study also included participants based on objectively measured time spend in sedentary behaviour instead of physical activity levels, which is often the inclusion criterion in papers within the research field of sedentary behaviour.

However, with respect to the long-term clinical implications, the duration of the interventions period and the extent to which the outcomes are maintained after cessation of the 12-week intervention period should be further investigated. For example, results from meta-analyses have suggested that short-term (<3 months) sedentary behaviour interventions, as in the current study, have the highest impact, whereas the intervention effects may attenuate after 6 months [10, 37]. Furthermore, although participants were randomly allocated to the control group or one of the intervention groups, we were not able to blind the assessors and participants itself. However, all assessments were performed in an objective way, resulting in less performance bias.

In conclusion, a 12-week multicomponent CWAT-based intervention (CWAT + motivational interviewing) reduces sedentary time, increases physical activity levels and improves various cardiometabolic health variables in sedentary adults. However, self-monitoring on itself (CWAT-only group) has no beneficial effects on sedentary time and additional behaviour change techniques are necessary to effectively reduce sedentary behaviour. From a public health perspective, consumer wearable technology in combination with motivational interviewing may hold the promise for largescale, cost-effective interventions within both healthy individuals and people with cardiometabolic diseases.

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Appendix

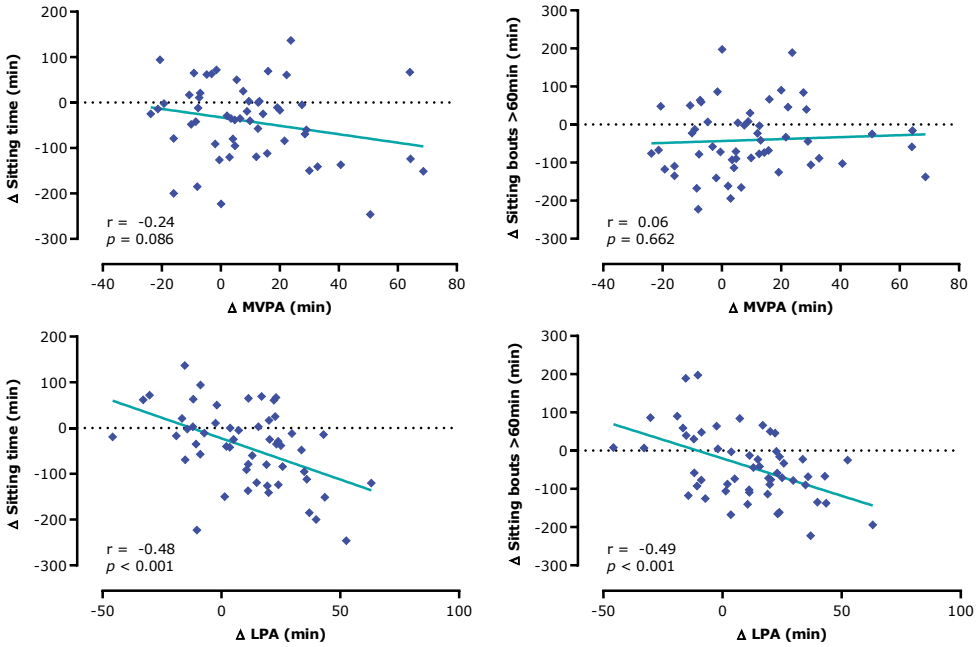

Figure S1 *Correlations between the difference in sitting time, sitting time of bouts > 60 minutes and physical activity reflected by moderate-to-vigorous physical activity and light intensity physical activity. Abbreviations:* ***LPA*** *= light intensity physical activity,* ***MVPA*** *= moderate-to-vigorous intensity physical activity.*


LDL
HDL

Chapter 6

The efficacy of a consumer wearable activity tracker-based behaviour change intervention to reduce sedentary behaviour and improve cardiovascular health in sedentary adults: a randomised controlled trial

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Submitted

Abstract

Background: Insufficient physical activity and sedentary behaviour (SB) are major contributors to the development of cardiovascular diseases and, therefore, effective intervention strategies to reduce SB within adults are necessary. The aim is to investigate the effectiveness of consumer wearable activity trackers (CWATs) as self-monitoring tool (CWAT-only) and as part of a multiple behaviour cha technique (self-monitoring + motivational counselling) to reduce sedentary behaviour and improve cardiovascular health in sedentary adults.

Methods: In a three-armed randomised controlled trial, 59 (male/female: 21/38) sedentary adults (sitting time of ≥ 9h/day; age: 53.3 ± 8.7 years; BMI: 26.0 ± 4.1 kg/m^2) were randomly allocated to a control group, a CWAT-only group or the CWAT+ group (CWAT + motivational interviewing) for 12 weeks. Physical activity (PA) and SB were assessed using the activPAL3™ accelerometer. In addition, anthropometrics, plasma lipids, systemic inflammation and markers of microvascular endothelial function, blood pressure, heart rate variability (square root of the mean of the sum of squares of differences between adjacent R-R intervals [RMSSD], power of the low-frequency [LF] and power of the high-frequency [HF]) and vascular endothelial function were assessed at baseline and after the 12-week intervention period.

Results: As compared with the control group, the CWAT+ group significantly reduced time spent in sedentary behaviour (-81 min/day CI[95%]: [-151, -12] min/day; p = 0.021) and significantly increased step count (+3117 [827, 5406] steps/day; p = 0.036), standing time (+62 [14, 110] min/day; p = 0.015), light intensity PA (+28 [5, 50] min/day; p = 0.040) and moderate-to-vigorous PA (+22 [4, 40] min/day; p = 0.005). Body weight (-2.19 kg [-4.00, -0.37] kg; p = 0.021), BMI (-0.72 [-1.33, -0.14] kg/m^2; p = 0.017), body fat mass (-1.67 [-3.21, -0.14] kg; p = 0.021), percentage body fat (-1.5 [-2.9, -0.1] %; p = 0.026) and triglyceride concentration (-0.31 [-0.62, -0.01] mmol/l; p = 0.028) were significantly decreased within the CWAT+ population, while RMSSD (11 [2, 23] ms; p = 0.014), LF (1178 [11, 2344] ms^2; p = 0.039) and HF (471 [18, 960] ms^2; p = 0.035) were all significantly increased, compared to the control group.

Conclusion: a 12-week multiple behaviour change intervention (self-monitoring + motivational interviewing) is effective to significantly reduce sedentary time and increases physical activity in terms of standing time, LPA and MVPA. These changes in sedentary behaviour and physical activity improve triglyceride concentrations and heart rate variability in sedentary adults.

Introduction

Cardiovascular diseases (CVDs) are the major cause of death worldwide, leading to an estimated 32% of all deaths each year [1]. The risk of developing CVD could considerably be reduced by addressing behavioural risk factors such as tobacco use, unhealthy diet, physical inactivity and sedentary behaviour. Here, the health benefits of daily moderate-to-vigorous physical activity (MVPA) are well established due to the positive effects on blood pressure, serum lipids, endothelial function and cardiac autonomic function [2-4]. Next to the positive cardiovascular health effects associated with increases in MVPA, there is emerging evidence that prolonged sedentary behaviour (SB), defined as 'any waking behaviour characterized by ≤1.5 metabolic equivalents of task, while being in a sitting or reclining posture' [5], is associated with several negative consequences on cardiovascular health [6] and an increased risk for developing CVD [7], independent of the volume of MVPA. Here, an important early marker of CVD is endothelial dysfunction, which is also affected during prolonged periods of SB [8, 9]. Despite the negative association between SB and a plethora of cardiovascular health outcomes, it is clear that adults in westernized societies still spend on average nine hours of their day in SB [10]. Interestingly, well-controlled laboratory-based studies showed that breaking up prolonged periods of SB with physical activity interruptions significantly improved cardiovascular health, including endothelial function [9]. In addition, it has been shown that every 30-minute increment per day in light-intensity (LPA) or MVPA was associated with 11% and 36% decreases in the risk of CVD mortality in older adults, respectively [11]. Therefore, reducing SB should be a public health priority.

Unfortunately, effective intervention strategies to reduce SB within adults are still limited [12]. Existing evidence showed that interventions are mainly based on workplace interventions instead of leisure time SB, which is proportionally the largest SB domain [13]. Furthermore, there is a need for specific behaviour change techniques (BCT) to better control and reduce sedentary behaviour. Interestingly, it has been shown that self-monitoring might be a promising BCT to reduce SB by means of disrupting undesired habits. This can be achieved by bringing habitual behaviour and its context into conscious awareness [14]. Indeed, Compernolle *et al*. showed that self-monitoring interventions were effective to reduce short-term SB in adults [15]. However, all included studies used multicomponent interventions,

which made it impossible to determine whether the decrease in SB was attributable to self-monitoring by itself or in combination with multiple BCT. In addition, they included four studies in which the self-monitoring component was based on a traditional/electronic logbook or a questionnaire, which often leads to a discrepancy between self-reported and actual performance [14]. Instead of these subjective measures, bodily worn electronic devices, also called consumer wearable activity trackers (CWATs), have a large potential to self-monitor physical activity and SB. However, it remains unclear whether CWATs are effective to induce a behaviour change and reduce sedentary behaviour in adults. CWATs are known to mainly target the motivation of conscious effort to increase physical activity by reaching a daily goal of total physical activity or step count with the aid of self-monitoring, goal setting and feedback. This means that these devices are focused on increasing physical activity rather than reducing sedentary behaviour, which is also an important component for improvements in cardiovascular health. Therefore, it could be questioned whether additional behaviour change techniques, such as motivational counselling, are necessary to effectively reduce sedentary behaviour, or CWAT-only interventions are enough to induce behaviour changes to lower daily sedentary time.

Therefore, the aim of this study is to investigate the efficacy of self-monitoring (CWAT-only) and multiple BCT (self-monitoring + motivational counselling) to reduce sedentary behaviour. This will give more insights into the working mechanism of CWATs as well as the interaction of a multicomponent intervention with multiple BCT. In addition, the second aim is to investigate the effectiveness of these BCT to improve cardiometabolic health and vascular function in sedentary adults and to what extent standing, LPA and MVPA affect these parameters.

Material & Methods

Subjects

Sixty sedentary (sitting time of ≥ 9h/day, 40-75 years of age) adults were recruited via online and paper advertisements, as described previously in Chapter 5. Participants were excluded when systolic blood pressure was > 140 mm Hg, diastolic blood pressure > 90 mm Hg, BMI: > 35 kg/m^2, HbA1c >6.5%, when they were pregnant or physically active (>150 min per week during the last four months), any cardiometabolic disease or diseases which interfered with physical

activity, frequent alcohol use (> 14 alcohol consumptions per week), or planning a weight reduction programme (energy restriction or increase in physical activity). Subjects maintained their habitual diet during the study trial. All subjects provided written informed consent. The study was conducted at Hasselt University between September 2018 and February 2021 in accordance with the principles of the Declaration of Helsinki and approved by the medical ethical committee of Hasselt University (clinicaltrials.gov registration number: NCT03853018).

Study Design

The study was performed under free-living conditions using a randomised controlled design. As described in a previous study (Chapter 5), a medical examination was performed for all participants during a screening visit. To assess whether participants were sedentary physical activity and sedentary behaviour was assessed using the activPAL3™ (PAL Technologies Ltd, Glasgow, Scotland) for seven consecutive days. Eligible participants were included for baseline measurements and instructed to refrain from strenuous physical exercise (3 days prior to the test day), consuming alcohol (1 day prior to the test day) and consuming food (1 day prior to the test day; from 8 p.m.).During the testing day, the following measurements were performed in sequential order: 1) anthropometry and body composition, 2) blood pressure measurement, 3) heart rate variability, 4) vascular endothelial function and 5) venous blood samples were collected for measurements of serum lipids, systemic low-grade inflammation and markers of microvascular endothelial function. After 12-weeks all baseline measurements were repeated. In addition, at the beginning and at the end of the intervention period, dietary intake was assessed for seven consecutive days.

Control and Intervention Regimens

Study participants were randomly allocated to 1) the control group (CON) without any intervention, 2) the CWAT-only (CWAT) group receiving only a consumer wearable activity tracker or 3) the CWAT+ group where participants got a CWAT in combination with additional motivational techniques via the ELCIES (ELCIES, Gent, Belgium) lifestyle data platform. As described in Chapter 5, the control group continued their habitual daily physical activity behaviours. The CWAT-group received real-time feedback from a CWAT-device (Polar M200, Polar Electro,

Kempele, Finland) by means of step count and inactivity cues and were instructed to reach 10,000 steps per day and reduce their sedentary behaviour as much as possible. Participants from the CWAT+ group were motivated by both the Polar M200 device and motivational techniques such as an information session to increase participants' awareness of the negative independent impact of sedentary behaviour on the risk of chronic disease development and, motivational interviewing via weekly chat conversations under guidance of a psychologist [16]. All communication and visualization of physical activity information was supported via a healthy lifestyle data platform (www.elcies.com). During the chat conversations, participants set their own goals of daily sedentary time and physical activity levels, the reasons for interrupting sitting time were identified and enforced, participant's concerns with respect to sitting less were identified and solutions were provided and possibilities to reduce and interrupt sedentary time as much as possible were provided. A more detailed description of the interventions groups has been described previously (Chapter 5).

Physical Activity and Sedentary Behaviour Assessment

Physical activity was measured 24 hours per day for 7 consecutive days using the activPAL3™ activity monitor (PAL Technologies Ltd, Glasgow, Scotland), The device was fully waterproofed using nitrile sleeves and attached to the anterior mid-thigh of the participants right leg using an adhesive dressing (Tegaderm, 3M, Minnesota, USA). The activPAL™ could accurately discriminate between sedentary behaviour (sitting and lying), standing and walking in free-living conditions [17, 18]. The following variables were determined: sleeping time, sedentary time (including bouts < 30 minutes and > 60 minutes), standing time, step count and time spent in LPA and MVPA.

Anthropometry, Body Composition and Blood Pressure Assessment

Body height and weight were with participants barefoot. Waist and hip circumferences were measured in triplicate to the nearest 0.1cm and the mean value of the triplicate measurements was used in the analysis. Whole body composition (fat mass and lean tissue mass) was measured with the aid of Dual Energy X-ray Absorptiometry (Hologic Series Delphi-A Fan Beam X-ray Bone Densitometer, Vilvoorde, Belgium).

The mean arterial pressure (MAP) was calculated from the systolic and diastolic blood pressure (BP) using an electronic sphygmomanometer (Omron®, Omron Healthcare, IL, USA).

Energy and Nutrient Intake Assessment

Habitual dietary intake was assessed using a self-administered food diary. Participants recorded all food and beverages consumed over seven consecutive days and from this the total caloric intake and macronutrient content was calculated.

Heart Rate Variability

The heart rate variability (HRV) is a non-invasive and easily measured parameter in a time-dominant or frequency-dominant form and reflects cardiac autonomic function [19, 20]. After a 20-min resting period in supine position, continuous beat-to-beat heart rate signal measurements were obtained at a sampling frequency of 1000Hz for the duration of ten minutes using the Polar V800 heart rate monitor (Polar Electro, Kempele, Finland) in combination with a Polar H10 chest strap heart rate sensor. During the measurement participants were instructed to breath 10 times per minute, had to remain lying down and stayed as relaxed as possible. Prior to analysis, the R-R intervals were corrected by cubic spline interpolation for ectopic beats and artefacts according to the recommendations of the Task Force of the Society of Cardiology and the North American Society of Pacing and Electrophysiology [21]. Then, time domain analysis of the R-R intervals was performed, including the root mean square of successive differences between normal adjacent R-R intervals (RMSSD). Power spectral density (PSD) of HRV signals was applied using a fast Fourier transformation and were classified as: power of the very low-frequency (VLF; 0.00 – 0.04Hz) band, power of the low-frequency (LF; 0.04 – 0.15 Hz) band, power of the high-frequency (HF; 0.15 – 0.40Hz) band and the LF/HF ratio. These variables reflect the autonomic system dynamics (autonomic balance) where the HF band is designated as parasympathetic nervous system activity, the LF band reflects both parasympathetic and sympathetic activity and the LF/HF ratio reflects the autonomic balance [22].

Vascular Endothelial Function

Endothelial function was assessed by non-invasive peripheral arterial tonometry (PAT) using the EndoPAT® 2000 device (Itamar Medical Ltd, Caesarea, Israel), according to manufacturer's instructions. Subjects were tested in supine position in a quiet room with constant temperature (19-21°C). Two flexible pneumatic probes were placed on the right (ischaemic) and left (control) index fingers to measure the peripheral arterial tone (PAT), a noninvasive measure to detect pulsatile volume changes in peripheral arterial beds. In addition, a constant inflation pressure (pre-determined resting diastolic blood pressure) was applied through these flexible probes to avoid distal venous distention, thereby preventing venous pooling and a subsequent venoarteriolar reflex vasoconstrictor response [23]. The test protocol consisted of a 5-min reference phase, a 5-min occlusion (ischaemic) period and a 5-min reactive hyperaemia (hyperaemic) phase. After the 5-min baseline period, a blood pressure cuff on the right upper arm was inflated to 250 mmHg for 5 minutes. Temporary occlusion of the pulsatile arterial flow, causing transitory arm ischemia, was confirmed by the reduction of the PAT signal to zero. Upon cuff deflation changes in PAT signal (increase in PAT signal) were recorded in response to reactive hyperaemia. The reactive hyperaemia response was reflected by the reactive hyperaemia index (RHI) and calculated as the ratio of the average PAT signal in the hyperemic phase to the baseline PAT signal (post-to-pre occlusion PAT signal ratio) in the occluded arm, with normalization to the ratio of the PAT signal in the control arm to account for any systemic hemodynamic changes. A high value (> 1.67) of the RHI was indicated a normal endothelial function, whereas a RHI of < 1.67 was indicated as endothelial dysfunction.

Serum Lipids, Systemic Low-grade Inflammation and Markers of Microvascular Endothelial Function

After antecubital catheter placement, fasting blood samples were obtained for the measurement of cardiovascular risk markers. Serum separation and ethylenediaminetetraacetic acid (EDTA) containing BD vacutainer™ tubes (Becton, Dickinson and Company, Franklin lakes, NY, USA) were collected. To obtain plasma, EDTA tubes were immediately centrifuged at 1300 x *g* for 15 minutes. Serum tubes coagulated for at least 30 minutes prior to centrifuging at

1300 x *g* for 15 minutes. All centrifugation steps were performed at room temperature (21°C). Supernatants were immediately portioned into aliquots and frozen at −20 °C and subsequently moved to a − 80 °C freezer until analysis at the end of the trial. Sodium heparinized 18µl capillary tubes (Marienfeld GmbH, Lauda-Königshofen, Germany) were used to collect capillary blood from the middle finger. Blood glycated haemoglobin A1c (HbA1c) concentration was assessed using ion exchange chromatography (Menarini HA-8180 HbA1c auto-analyser, Menarini Diagnostics, Diegem, Belgium). Total cholesterol, high-density lipoprotein cholesterol (HDL-cholesterol), low-density lipoprotein cholesterol (LDL-cholesterol) and triglycerides concentrations were automatically assessed on the Roche Cobas 8000 (Roche Diagnostics International Ltd, Rotkreuz, Switzerland) in serum samples. Furthermore, plasma from EDTA tubes was used for measurements of markers of low-grade systemic inflammation (C-reactive protein [CRP] and serum amyloid A [SAA]) and markers of microvascular endothelial function (soluble vascular cell adhesion molecule [sVCAM]-1, soluble intercellular adhesion molecule [sICAM]-1 and soluble endothelial selectin [sE-selectin]) using a Meso Scale Discovery single or multiplex sandwich immunoassay detection system based on electro-chemiluminescence technology (SECTOR Imager 2400; Meso Scale Discovery, Rockville, MD, USA), according to the manufacturer's instructions. All measurements were performed in duplicate. The intra- and inter-assay coefficients of variation were 4.7% and 4.1% for CRP, 5.2% and 4.9% for SAA, 4.3% and 4.7% for sVCAM-1, 5.5% and 4.5% for sICAM-1 and 6.1% and 6.6% for sE-selectin, respectively.

Statistical Analysis

Statistical analyses were performed by IBM SPSS® version 27.0 (IBM SPSS Statistics for Windows, Chicago, IL, USA). Data were expressed as mean ± SD, unless otherwise indicated.

Shapiro-Wilk test was used to test normality of the data ($p < 0.05$). If the data was not normally distributed, natural log transformation was performed. Because the markers of endothelial function and low-grade inflammation show a marked intra-individual variation, the biological variability of each measure was reduced by calculating a standardized averaged sum score (*z*-score). *Z*-scores were determined according to a predefined cluster of conceptually related biomarkers,

as described elsewhere [24], and calculated as follows: first, for each individual biomarker a *z*-score was calculated as: (individual value – population mean) / population standard deviation. The endothelial function overall *z*-score (zEF) was calculated by averaging the individual *z*-scores of the biomarkers sICAM-1, sVCAM-1 and sE-selectin. The low-grade inflammation overall z-score (zLGF) was calculated by averaging the individual *z*-scores of the biomarkers CRP, SAA, and sICAM-1. The sICAM-1 levels were included in both of the overall *z*-scores as it is expressed by both monocytes and the endothelium and is strongly affected by inflammatory stimuli [25].

Baseline characteristics between the three groups were compared using a one-way ANOVA (Bonferroni post-hoc comparison test) for normally distributed data. Data were analysed using an intention-to-treat approach. Comparisons between groups were tested using the Fischer's exact test for categorical variables. Differences in response between groups were analysed using general linear model analyses with the difference between baseline and 12-week intervention as dependent variable, group (control, CWAT and CWAT+) as fixed factor and baseline values of the outcome variables as covariates. The treatment effects were presented as mean changes (95% confidence interval [CI]). A pairwise analysis (Bonferroni post-hoc comparison test) was performed when the between-subjects factor was statistically significant. A *p*-value <0.05 (2-tailed) was considered statistically significant. Multivariate regression analyses were performed to examine associations between sedentary behaviour, physical activity and cardiovascular health outcomes that significantly improved after the 12-week intervention period. Cardiac autonomic function (RMSSD, LF and HF), percentage fat mass, waist circumference and BMI were used as dependent variables and standing time, LPA and MVPA as independent variables. Model 1 was the unadjusted model, model 2 corrected for potential confounders sex, age, body height, smoking status, chronic disease, medication, food intake and baseline measurements of standing, LPA and MVPA and model 3 also corrected for all other variables (standing, LPA and/or MVPA).

Results

Subject Characteristics

A total of 137 persons showed interest to participate in the study, of which 79 were invited to be screened for study eligibility. Twenty subjects were excluded due to a sedentary time < 9h/day (n=11) or spending more than 150 of structured physical activity per week (n=9). A total of 59 individuals were randomly assigned to either the control (n=20), CWAT (n=20) or CWAT+ (n=19) group. Three participants from both the control (n=1) and the CWAT+ (n=2) group dropped out mainly due to lack of time (Appendix Figure S1). In addition, no significant differences for all variables were found between groups at baseline (Appendix Table S1).

Physical Activity and Sedentary Behaviour, Anthropometrics, Body Composition and Blood Pressure

Results of these variables can be found in Table 1 and are already described earlier in Chapter 5. Briefly, As compared with the control group, a 12-week intervention period with both CWATs and motivational interviewing (CWAT+) significantly reduced time spent in sedentary behaviour, mainly due to spending less time in bouts of more than 1 hour. Here, sedentary time was replaced by significant increases in step count, standing time, LPA and MVPA. However, no significant improvements with respect to sedentary time and PA within the CWAT group were observed, compared to the control and CWAT+ group.

Anthropometrics, Body Composition and Blood Pressure

Body weight and body mass were significantly decreased within the CWAT+ population, compared to the CWAT and control group (Appendix Table S1). Compared to the control group, hip circumference, body fat mass and percentage body fat mass were only reduced in participants from the CWAT+ group. In addition, waist circumference was decreased in both the CWAT and CWAT+ group, compared to the control group. No differences between groups were found in blood pressure after the 12-week intervention period.

Table 1 *Physical activity and sedentary behaviour parameters.*

	Control		CWAT		CWAT+		Intervention effects		
	Baseline (n=20)	**12 weeks (n=19)**	**Baseline (n=20)**	**12 weeks (n=20)**	**Baseline (n=19)**	**12 weeks (n=17)**	**CWAT vs control**	**CWAT+ vs control**	**CWAT+ vs CWAT**
Physical activity									
Standing time (min/day)	213 ± 61	217 ± 49	239 ± 67	244 ± 70	203 ± 51	251 ± 59	1 (-45, 47)	62 (14, 110)*	61 (14, 109)*
LPA (min/day)	71 ± 15	75 ± 19	72 ± 17	79 ± 20	63 ± 17	91 ± 38	4 (-17, 25)	28 (7, 50)*	24 (3, 46)
MVPA (min/day)	24 ± 15	21 ± 11	22 ± 13	34 ± 18	20 ± 13	51 ± 47	15 (-1, 30)	23 (4, 40)*	4 (-14, 22)
Steps per day	7424 ± 1828	7505 ± 1721	7336 ± 1884	9391 ± 2447	6597 ± 1765	11615 ± 8014	1750 (-440, 3939)	3117 (827, 5406)*	1367 (-923, 3656)
Sleeping behaviour									
Sleeping time (min/day)	495 ± 37	490 ± 40	472 ± 32	476 ± 33	485 ± 41	467 ± 43	2 (-28, 32)	-16 (-47, 15)	-18 (-49, 13)
Sedentary behaviour									
Total ST (min/day)	637 ± 68	638 ± 73	633 ± 83	599 ± 69	669 ± 75	590 ± 91	-31 (-97, 36)	-81 (-151, -12)*	-51 (-120, 19)
SB <30 min (min/day)	267 ± 41	275 ± 55	280 ± 64	288 ± 77	282 ± 90	266 ± 97	1 (-48, 49)	7 (-44, 57)	6 (-45, 57)
SB >60 min (min/day)	217 ± 94	187 ± 104	184 ± 91	166 ± 96	223 ± 133	151 ± 103	-8 (-75, 59)	-56 (-126, -14)*	-48 (-117, 22)

Data represented physical activity and sedentary behaviour parameters before and after a 12-week CWAT-based intervention period within the control, CWAT and CWAT+ groups (see Methods) and are expressed as mean ± SD. * $p < 0.05$. The intervention effects are mean changes (95% confidence interval) obtained from general linear model analyses with baseline value as covariate. Abbreviations: **ST** = sedentary time, **SB** = sedentary bouts.

Table 2 *Cardiovascular health, metabolic risk markers and endothelial function parameters.*

	Control		CWAT		CWAT+		Treatment effects		
	Baseline (n=20)	**12 weeks (n=19)**	**Baseline (n=20)**	**12 weeks (n=20)**	**Baseline (n=19)**	**12 weeks (n=17)**	**CWAT vs control**	**CWAT+ vs control**	**CWAT+ vs CWAT**
Blood pressure									
Systolic BP (mm Hg)	120 ± 13	117 ± 12	123 ± 12	120 ± 12	124 ± 12	125 ± 15	1 (-7, 7)	3 (-4, 11)	3 (-4, 11)
Diastolic BP (mm Hg)	79 ± 8	77 ± 7	83 ± 9	80 ± 8	81 ± 8	81 ± 9	-1 (-5, 3)	2 (-2, 6)	3 (-1, 7)
MAP (mm Hg)	93 ± 10	90 ± 8	96 ± 9	93 ± 9	95 ± 9	96 ± 10	-1 (-5, 4)	2 (-2, 7)	3 (-2, 8)
Resting heart rate (bpm)	62 ± 6	61 ± 7	59 ± 9	60 ± 8	57 ± 7	60 ± 8	2 (-3, 7)	4 (-1, 9)	2 (-3, 7)
Metabolic risk markers									
Total cholesterol (mmol/l)	5.00 ± 0.93	4.80 ± 0.91	5.40 ± 1.12	4.78 ± 0.88	5.67 ± 1.27	4.64 ± 0.98	-0.17 (-0.79, 0.45)	-0.41 (-1.06, 0.24)	-0.24 (-0.87, 0.39)
HDL cholesterol (mmol/l)	1.39 ± 0.24	1.26 ± 0.33	1.62 ± 0.49	1.36 ± 0.23	1.61 ± 0.51	1.26 ± 0.29	0.07 (-0.14, 0.28)	-0.05 (-0.25, 0.18)	-0.11 (-0.31, 0.10)
LDL-cholesterol (mmol/l)	3.61 ± 0.82	3.54 ± 0.81	3.78 ± 1.10	3.42 ± 0.90	4.06 ± 0.98	3.38 ± 0.82	-0.20 (-0.67, 0.27)	-0.38 (-0.87, 0.11)	-0.18 (-0.67, 0.31)
Triglycerides (mmol/l)	0.98 ± 0.41	1.05 ± 0.55	1.25 ± 0.71	1.02 ± 0.57	1.22 ± 0.38	0.94 ± 0.37	-0.25 (-0.55, 0.05)	-0.36 (-0.70, -0.03)*	-0.07 (-0.63, 0.23)
C-reactive protein (mg/l)	2.69 ± 3.53	2.33 ± 3.10	2.51 ± 3.79	2.38 ± 3.36	2.07 ± 2.44	1.91 ± 1.62	0.18 (-1.06, 1.41)	-0.27 (-1.56, 1.02)	-0.44 (-1.73, 0.84)
Serum amyloid A (mg/l)	3.77 ± 2.51	3.07 ± 1.95	4.63 ± 5.58	3.46 ± 2.70	3.30 ± 2.42	3.96 ± 2.84	0.19 (-2.45, 2.83)	1.11 (-1.65, 3.87)	0.92 (-1.84, 3.68)
zLGI	0.05 ± 1.03	0.16 ± 0.46	-0.20 ± 0.53	0.16 ± 0.43	-0.28 ± 0.46	0.68 ± 2.41	0.07 (-1.04, 1.17)	0.59 (-0.54, 1.73)	0.52 (-0.61, 1.66
Endothelial function									
sICAM (µg/l)	437 ± 143	410 ± 97	399 ± 52	393 ± 59	402 ± 65	397 ± 91	13.8 (-27.4, 55.0)	12.3 (-29.8, 54.4)	-1.5 (-43.2, 40.1)
sVCAM (µg/l)	470 ± 121	443 ± 103	440 ± 62	435 ± 70	440 ± 73	422 ± 65	13.4 (-21.4, 48.3)	-1.4 (-37.2, 34.4)	-14.8 (-50.4, 20.7)
sE-selectin (µg/l)	10.6 ± 7.1	10.0 ± 4.4	11.2 ± 4.88	9.9 ± 4.2	9.3 ± 3.6	10.2 ± 4.6	-0.24 (-4.02, 3.55)	1.40 (-2.49, 5.30)	1.64 (-2.26, 5.53)
zEF	0.04 ± 1.03	-0.23 ± 0.44	-0.18 ± 0.49	-0.26 ± 0.41	-0.28 ± 0.58	-0.29 ± 0.41	0.08 (-0.15, 0.31)	0.06 (-0.17, 0.30)	-0.01 (-0.25, 0.22)
RHI	2.09 ± 0.43	2.07 ± 0.59	2.11 ± 0.51	2.17 ± 0.58	2.21 ± 0.47	2.46 ± 0.50	0.03 (-0.40, 0.45)	0.31 (-0.12, 0.75)	0.29 (-0.15, 0.72)

Data represented cardiovascular risk factors before and after a 12-week CWAT-based intervention period within the control, CWAT and CWAT+ groups (see Methods) and are expressed as mean ± SD. Abbreviations: **BP** = blood pressure, **bpm** = beats per minute, **CWAT** = consumer wearable activity tracker, **HDL** = high-density lipoprotein, **LDL** = low-density lipoprotein, **MAP** = mean arterial pressure, **RHI** = reactive hyperaemia index, **sICAM** = soluble intercellular adhesion molecule, **sVCAM** = soluble vascular cell adhesion molecule, **zEF** = endothelial function overall *z*-score, **zLGI** = low-grade inflammation overall z-score. * $p < 0.05$. The intervention effects are mean changes (95% CI) obtained from general linear model analyses with baseline value as covariate.

Serum Lipids, Systemic Low-grade Inflammation and Markers of Microvascular Endothelial Function

The triglyceride concentration was significantly decreased in the CWAT+ group, compared to the control group (-0.36 [-0.70, -0.03] mmol/l; $p = 0.028$), whereas no differences were found between the CWAT group and the control group (Table 2). No significant differences were found between groups for markers of vascular endothelial function and low-grade systemic inflammation.

Cardiac Autonomic Function

Measurements of HRV reflected by RMSSD (CWAT+ vs. control: 11 [2, 23] ms; $p = 0.014$), LF (CWAT+ vs. control: 1178 [11, 2344] ms^2; $p = 0.039$) and HF (CWAT+ vs. control: 471 [18, 960] ms^2; $p = 0.035$) were all significantly increased in subjects allocated to the CWAT+ group, compared to the control group (Figure 1). However, VLF and the LF/HF ratio were not statistically different between groups. No significant differences were found between subjects from the CWAT group compared to the control and CWAT+ group.

Associations Between Cardiovascular Risk, Sedentary Behaviour and Physical Activity

Reallocating sedentary time with standing was not associated with improvements in cardiovascular health outcomes (Figure 2). In addition, LPA beneficially affected BMI (SC β = -0.574 [-0.806 – -0.351]; $r^2 = 0.329$; $p < 0.001$), waist circumference (SC β = -0.314 [-0.554 – -0.107]; $r^2 = 0.147$; $p = 0.005$), percentage fat mass (SC β = -0.332 [-0.593 – -0.069]; $r^2 = 0.110$; $p = 0.014$) and LF (SC β = 0.313 [0.033 – 0.517]; $r^2 = 0.098$; $p = 0.029$). However, after adjusting for all covariates only BMI (SC β = -0.409 [-0.771 – -0.180]; $r^2 = 0.329$; $p = 0.002$) and waist circumference (SC β = -0.287 [-0.556 – -0.057]; $r^2 = 0.241$; $p < 0.001$) remain statistically associated with increased LPA levels. In addition, reallocating sedentary time with MVPA was associated with a lower waist circumference (SC β = -0.302 [-0.483 – 0.074]; $r^2 = 0.353$; $p = 0.009$), percentage fat mass (SC β = -0.287 [-0.545 – 0.017]; $r^2 = 0.082$; $p = 0.037$), RMSSD (SC β = 0.496 [0.229 – 0.724]; $r^2 = 0.246$; $p < 0.001$), LF (SC β = 0.572 [0.311 – 0.772]; $r^2 = 0.327$; $p < 0.001$) and HF (SC β = 0.570 [0.323 – 0.807]; $r^2 = 0.325$; $p < 0.001$), when adjusted for all covariates.

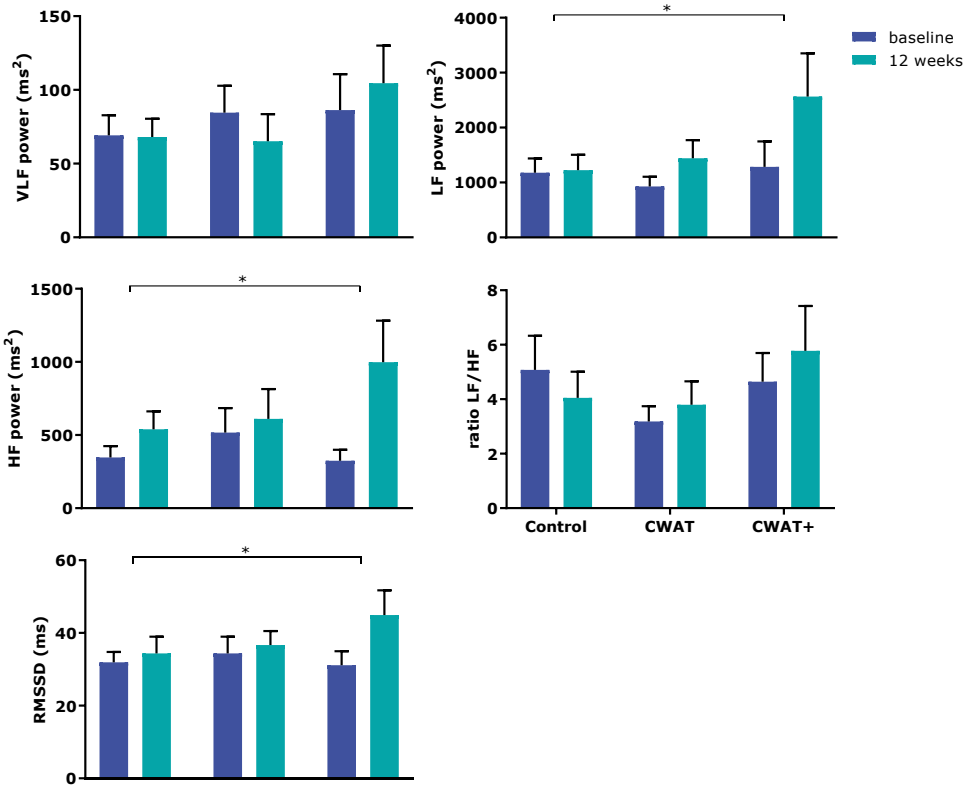

Figure 1 *Cardiac autonomic function, reflected by RMSSD, VLF, LF, HF and the ratio of LF/HF, before and after a 12-week CWAT-based intervention period within the control, CWAT and CWAT+ groups. Data are presented as means ± standard errors. * p < 0.05 of mean difference (12 weeks - baseline) between groups. Abbreviations:* ***CWAT*** *= consumer wearable activity tracker,* ***HF*** *= high frequency,* ***LF*** *= low frequency,* ***RMSSD*** *= Root Mean Square of the Successive Differences,* ***VLF*** *= very low frequency.*

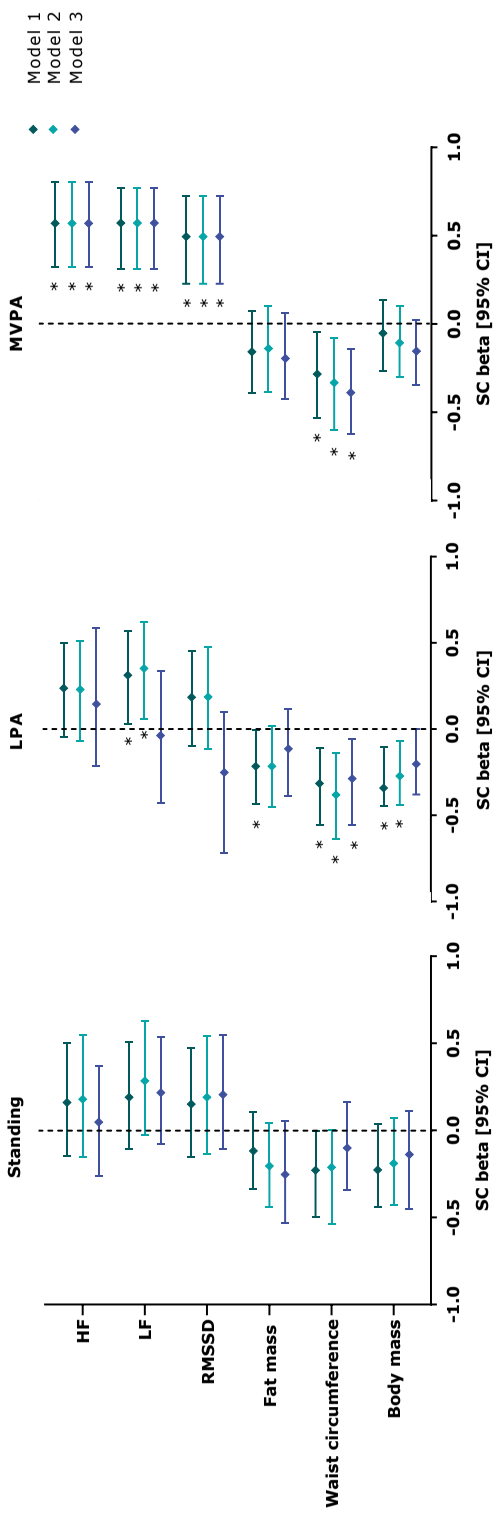

Figure 2 *Multivariate regression analyses for the associations between standing, LPA, MVPA and different cardiovascular health outcomes. Model 1: unadjusted; model 2: adjusted for covariates sex, body height, smoking status, chronic disease, medication, food intake and baseline measurements of standing, LPA or MVPA; model 3: adjusted for all covariates from model 2 and standing, LPA and/or MVPA. Data are presented as standardized coefficient of beta [95% confidence interval]. * p < 0.05. Abbreviations:* ***RMSSD*** *= Root Mean Square of the Successive Differences,* ***LF*** *= low frequency,* ***HF*** *= high frequency.*

Discussion & Conclusion

In this randomised controlled trial we observed that the behaviour change intervention consisting of both a CWAT and motivational interviewing (CWAT+ group) significantly improved sedentary time and physical activity, compared to subjects who only wore a CWAT (CWAT-group) or continued their sedentary behaviour and physical activity habits (control group). In addition, the multicomponent BCT intervention resulted in significant improvements in triglyceride concentration and cardiac autonomic function reflected by RMSSD, LF and HF. Here, regression analyses showed that these improvements were mainly due to an increased MVPA. In contrast, no differences were found on vascular endothelial function and low-grade inflammatory markers.

The results of the current study suggest that using CWATs in combination with motivational interviewing significantly reduces daily sitting time by almost 80 minutes. These results were in line with a meta-analysis that already identified an overall effect of interventions solely targeting sedentary behaviour which attributed to a significant reduction in sedentary time by approximately 91 minutes per day [26]. In contrast, interventions with either a focus on physical activity or those including a physical activity and sedentary behaviour component generally resulted in smaller and more modest reductions in sedentary time of 20 and 35 minutes per day, respectively [26, 27]. These results are similar to our results from participants in the CWAT-only group, who also showed a reduction in sedentary time of 31 minutes per day, compared to the control group. In this group, the reduction in sedentary behaviour was largely due to an increase in MVPA, which is supported by a study from Kozey Keadle *et al.* who showed that interventions focused on exercise and reducing sedentary time experienced increases in physical activity similar to their reductions in sedentary time. Only the group who solely focused on sedentary behaviour resulted in reduction in sedentary time, which was much higher than the increments in physical activity [28]. This was also found within the CWAT+-group in which sedentary time had a higher reduction in comparison with the increase in physical activity, due to a significantly increased standing time and LPA. This might be explained by the fact that subjects allocated to interventions targeting physical activity (or in combination with sedentary behaviour) are more likely to focus on increasing physical activity instead of reducing their sedentary time. This supports the need

for interventions to place a significant focus on changing sedentary behaviour in order to elicit a clinically meaningful reduction in sedentary time.

In addition, it has also been shown that the largest reductions in sedentary behaviour could be accomplished with multicomponent behavioural change techniques (i.e. persuasion, problem solving and/or education) instead of self-monitoring on its own [29]. Here, Prince *et al*. highlighted self-monitoring and motivational counselling as important components [30]. The current findings further support that the combination of these intervention components is highly valuable to decrease sedentary time and improve cardiovascular health.

The reduction in sedentary time and increased physical activity within the CWAT+ group resulted in significant improvements in cardiovascular risk factors, as compared to the control group. We observed an increased heart rate variability (RDSSM, LF and HF), a significant lower triglyceride concentration and improvements in anthropometrics and body composition, whereas no significant differences were found in markers of endothelial function and low-grade inflammation. A robust level of HRV is a positive indicator of cardiovascular health status [31] and recent studies showed that objective accelerometer-derived PA had a positive association with HRV [32-34]. Here, we showed as one of the first that the HRV, reflected by RDSSM, LF and HF, was significantly improved when sedentary time was replaced by MVPA since an increase in MVPA was significantly associated with a higher HRV. However, because no inverse association was found between prolonged sedentary time and MVPA, it is more plausible that the increased HRV comes from enhanced MVPA volumes instead of reducing prolonged sedentary behaviours. Indeed, de Sousa *et al.* found a dose-response association between intensity of physical activity and HRV [4]. Therefore, it is important to encourage individuals to incorporate MVPA into their daily physical activity pattern. Interestingly, our results might have important implications for a potential clinical tool for cardiovascular health given the widespread availability of sophisticated CWATs, which are often able to monitoring heart rate and provide information on HRV, and thus cardiovascular health status.

Although prolonged sedentary time (sedentary bouts > 60 minutes) was significantly reduced within the CWAT+ group, mainly due to an increase in standing time and LPA, we only found a significant association between triglyceride concentration and LPA. These results are not consistent with Thosar

et al., who found, next to metabolic adaptations, also effects on endothelial function [35]. They found an improvement in superficial femoral artery endothelial function after interrupting prolonged sedentary time with 5-min bouts of LPA [35]. In addition, Carter *et al*. showed that 8-min physical activity breaks may be needed every 1-2 hours to prevent sedentary induced impairments in endothelial function [36]. This suggests that longer duration of LPA bouts may be more effective than shorter, more frequent breaks in preventing lower limb endothelial dysfunction. This could be the reason why no significant differences in vascular endothelial function was observed in the current study. However, little is known with regard to the optimal strategy or dose of physical activity necessary to achieve protective effects on the vasculature and further studies are highly warranted.

Furthermore, findings of epidemiological and early experimental studies demonstrated that MVPA outperformed LPA [37] and that reducing sitting time by a continuous bout of approximately 60 minutes of MVPA a day is likely to gain benefits in cardiometabolic biomarkers [38]. In our study, the CWAT+ group spent on total 51 minutes in MVPA per day and, therefore, we would expect the same clinical benefits on endothelial function. An important reason why we did not find an improvement in endothelial function could be due to the physical activity intensity. It has been shown that physical activity intensity is an important determinant of endothelial function in lean adults, which may be associated with elevations in blood pressure and related increases in shear stress [39, 40]. Here, the optimal improvements of endothelial function were found after higher-intensity physical activity (75-85% of maximal oxygen uptake). Although we measured MVPA, this already starts from 3 metabolic equivalents of task (□50-60% of maximal oxygen uptake) and, therefore, it could be the case that the intensity was not high enough to exert improvements in endothelial function.

Another reason why no significant improvements were found could be due to the measurement site. Taylor *et al.* showed in a systematic review that mainly the lower-limb vascular function (i.e. femoral or popliteal artery) will be improved after breaking up sedentary time due to a higher shear-stress [41, 42], instead of measuring endothelial function in the fingertips. However, these results were only based on acute effects rather than effects on the longer-term as in our study.

Next to endothelial function, no differences were found on low-grade inflammatory markers. Because it has been shown that prolonged sitting leads to impaired low-grade systemic inflammatory markers [43], we would expect that this impairment was reversible when sedentary time was reduced. A possible reason why no differences in low-grade inflammation were found is that we evaluated inflammation using adhesion molecules rather than interleukins (IL), which may be more sensitive. This is in line with a study from Karch *et al.* who found lower resting IL-6 levels in athletes as compared to nonathletes and IL-6 levels were increased after exercise, whereas no differences were found in sICAM [44]. In addition, Henson *et al.* showed that substituting sedentary time with MVPA was associated with lower IL-6 levels [38]. Taken together, it seems that longer periods of interrupting sedentary time (>5 minutes) and/or physical activity of higher intensities will improve vascular endothelial function and low-grade inflammation. This study has multiple strengths which includes the use of an accelerometer, which can distinguish postures and is the most accurate to assess time spent in sedentary behaviours [45]. Due to the randomised controlled study design, we were able to discriminate between the effectiveness of mono- and multicomponent intervention strategies. Furthermore, we only included sedentary adults (10.8 ± 1.2 hours per day) based on objective measurements. Here, only a few clinical trials in the current literature included individuals based on sedentary time. So far, most of the studies included participants based on physical (in)activity levels, which not guarantees a sedentary population. Hence, based on physical activity measurements, people could both be physically inactive and not sedentary at the same time.

Our study had also some limitations. First, although participants were randomly allocated to the control group or one of the intervention groups, we were not able to blind the assessors and participants itself. However, all assessments were performed in an objective way, resulting in less performance bias. In addition, although we measured two different aspects of endothelial function (small vascular reactivity with endoPAT® and microvascular function with soluble endothelial markers), it is warranted to also investigate other sensitive endothelial function markers. For example, flow-mediated dilation responses as the current non-invasive gold standard approach, especially for measurements of the lower-limb vasculature [46].

In conclusion, a 12-week multiple behaviour change intervention (self-monitoring + motivational interviewing) is effective to significantly reduce sedentary time and increases physical activity in terms of standing time, LPA and MVPA. As a result, these changes in sedentary behaviour and physical activity improve triglyceride concentrations and cardiac autonomic function (HRV) in sedentary adults, whereas self-monitoring only does not.

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Appendix

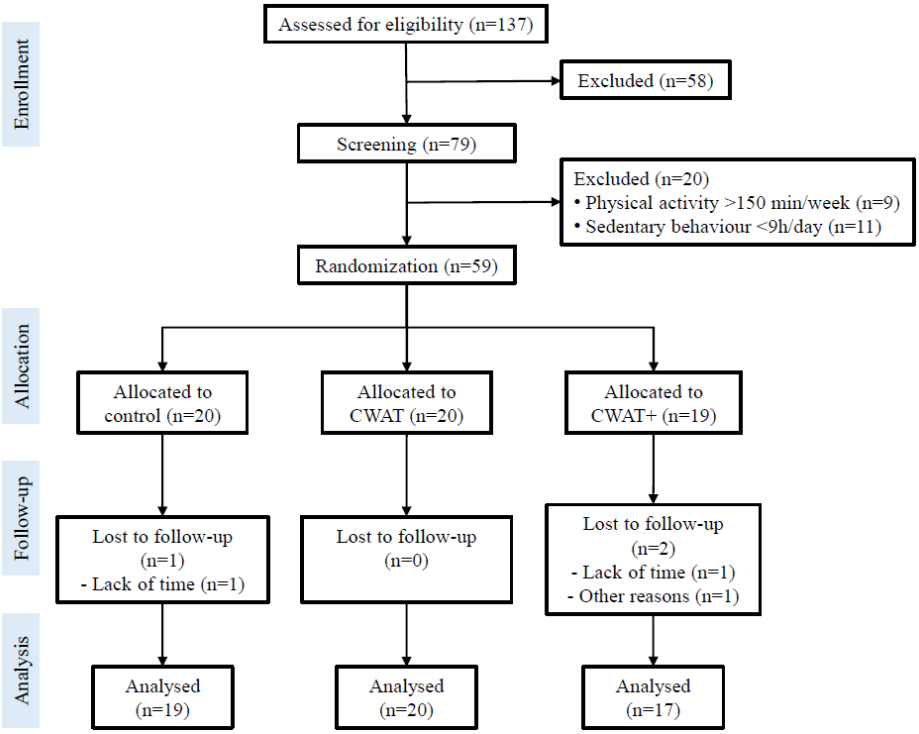

Figure S1 *Study flow chart of the eligible and ultimately included participants.*

Table S1 *Subject characteristics before and after a 12-week CWAT-based intervention period within the control, CWAT and CWAT+ groups.*

	Control		CWAT		CWAT+		Intervention effects		
General features	**Baseline (n=20)**	**12 weeks (n=19)**	**Baseline (n=20)**	**12 weeks (n=20)**	**Baseline (n=19)**	**12 weeks (n=17)**	**CWAT vs control**	**CWAT+ vs control**	**CWAT+ vs CWAT**
Age (years)	53.8 ± 8.5	54.2 ± 8.8	52.4 ± 8.7	52.8 ± 8.7	53.8 ± 9.2	54.7 ± 9.5			
Sex (m/f)	6/14	6/13	7/13	7/13	8/11	7/10			
Body weight (kg)	75.8 ± 11.5	77.2 ± 11.6	76.6 ± 14.6	76.9 ± 14.7	74.7 ± 12.7	72.6 ± 12.5	-0.28 (-2.01, 1.46)	-2.19 (-4.00, -0.37)*	-1.91 (-3.70, -0.12)*
Body height (cm)	169.7 ± 7.9	170.4 ± 7.3	171.1 ± 7.9	171.1 ± 8.0	171.3 ± 10.3	170.2 ± 10.2			
BMI (kg/m²)	26.3 ± 3.8	26.6 ± 4.1	26.2 ± 4.9	26.3 ± 4.9	25.4 ± 3.6	25.0 ± 3.6	-0.06 (-0.65, 0.52)	-0.72 (-1.33, -0.14)*	-0.66 (-1.26, -0.06)*
WC (cm)	88.5 ± 10.0	90.9 ± 10.7	89.2 ± 13.9	88.0 ± 14.3	87.2 ± 10.1	85.1 ± 9.2	-2.87 (-5.72, -0.01)*	-4.11 (-7.09, -1.13)*	-1.24 (-4.20, 1.70)
HC (cm)	98.2 ± 9.3	100.2 ± 10.4	99.7 ± 11.2	98.6 ± 11.4	97.4 ± 8.0	95.6 ± 7.2	-2.46 (-5.60, 0.67)	-3.48 (-6.75, -0.21)*	-1.02 (-4.25, 2.22)
WC/HC	0.90 ± 0.08	0.91 ± 0.08	0.89 ± 0.08	0.89 ± 0.10	0.90 ± 0.07	0.89 ± 0.07	-0.01 (-0.04, 0.02)	-0.01 (-0.04, 0.02)	-0.01 (-0.04, 0.03)
Lean mass (kg)	46.5 ± 7.1	47.3 ± 6.5	48.3 ± 6.5	48.6 ± 8.6	47.9 ± 9.1	47.3 ± 9.2	0.21 (-0.73, 1.11)	-0.36 (-1.35, 0.63)	-0.57 (-1.55, 0.41)
Fat mass (kg)	26.0 ± 9.4	26.5 ± 10.0	24.5 ± 9.9	24.6 ± 10.1	23.1 ± 6.2	21.9 ± 7.3	-0.26 (-1.70, 1.18)	-1.67 (-3.21, -0.14)*	-1.41 (-3.21, -0.14)
Fat mass (%)	34.0 ± 9.6	33.9 ± 9.9	31.9 ± 9.5	31.8 ± 9.4	31.5 ± 6.6	30.4 ± 8.0	-0.3 (-1.6, 1.1)	-1.5 (-2.9, -0.1)*	-1.3 (-2.6, 0.2)
Energy intake (kcal)	1503 ± 255	1600 ± 450	1726 ± 348	1793 ± 264	1635 ± 351	1595 ± 630	-87 (-330, 505)	-120 (-557, 317)	-33 (-437, 371
Fat (g)	53 ± 16	56 ± 23	64 ± 19	65 ± 11	58 ± 14	60 ± 26	-6 (-23, 19)	-4 (-27, 19)	2 (-19, 23)
Protein (g)	71 ± 15	76 ± 20	68 ± 18	74 ± 22	73 ± 18	68 ± 24	4 (-22, 31)	-10 (-37, 17)	-14 (-40, 11)
Carbohydrate (g)	170 ± 30	179 ± 42	196 ± 42	208 ± 40	189 ± 44	180 ± 75	-8 (-49, 34)	-10 (-54, 33)	-3 (-43, 38)
HbA1c (%)	5.3 ± 0.3		5.4 ± 0.3		5.3 ± 0.4				
Smoking status (n)									
Never	0		0		1				
Former	5		7		3				
Never	15		13		15				
Chronic disease (n)									
Respiratory	1		0		2				
Cardiovascular	0		5		1				
Medication (n)									
Beta blocker	0		3		2				
Ang II	0		2		1				
Bronchodilator	1		0		1				

Data are expressed as mean ± SD. Abbreviations: **CWAT** = consumer wearable activity tracker, **BMI** = body mass index, **WC** = waist circumference, **HC** = hip circumference, **Ang II** = Angiotensin II- antagonist. * $p < 0.05$. The intervention effects are mean changes (95% CI) obtained from general linear model analyses with baseline value as covariate.


LDL
HDL

Chapter 7

General Discussion and Conclusion

Summary of the Main Findings

Sedentary behaviour has increasingly been shown to be a strong modifiable risk factor for cardiometabolic health and the development of chronic non-communicable diseases (NCDs), such as cardiovascular diseases (CVD) and type 2 diabetes mellitus (T2DM), which appears to be independent of the volume of MVPA. Importantly, sedentary behaviour is different from physical inactivity (not reaching the recommended volume of MVPA) and, therefore, both sedentary behaviour and physical inactivity should be targeted to improve health. Physical activity research has typically focused on MVPA so far, and has recognized MVPA as an important factor to improve cardiometabolic health. However, whether high volumes of MVPA can also improve cardiometabolic health despite spending in high volumes of sedentary time has not been investigated yet. Therefore, it could be questioned if the inverse association between sedentary time and cardiometabolic health could be attenuated or even eliminated in individuals engaging in high volumes of MVPA. In **Chapter 3** we found that high volumes of MVPA could fully eliminate the association between sedentary behaviour and cardiometabolic health in highly active individuals. However, for the majority of the population these high volumes of MVPA are not attainable and, if so, only comprises a relatively small part of all daily activities. In fact, most people spend the largest part of the day in sedentary behaviour. Therefore, interventions to reduce sedentary behaviour and increase physical activity levels are necessary to combat the increase in NCD development in the general population.

It is known, that consumer wearable activity tracker (CWAT)-based multicomponent interventions can increase physical activity in healthy populations [1, 2]. This fact is promising for global public health and potentially reduces the risk of NCD development [2]. Indeed, it has been shown that even small increases in physical activity at a population level could have positive impacts on the risk of NCD development as CVD, T2DM and several cancers [3-5]. Next to decreasing the risk of NCDs, physical activity could also play an important role in the progression and management of people who already developed NCDs. However, in the current literature it is not yet known if CWAT-based interventions are also able to effectively increase physical activity and improve cardiometabolic health in populations with NCDs. Therefore, in **Chapter 4** we systematically reviewed the

effect of CWAT-based interventions on physical activity in populations with NCDs, including chronic respiratory disease, overweight/obesity, T2DM and CVD. We found that these diseased populations were also able to significantly increase their physical activity by approximately 2100 steps per day, by using CWAT-based interventions, consisting of CWAT-only or as part of a multicomponent intervention. In addition, the increase in physical activity resulted in an improvement of cardiometabolic health reflected by a reduced waist circumference, systolic blood pressure and low-density lipoprotein cholesterol concentration. Given the fact that both physical activity and sedentary behaviour should be targeted, we subsequently investigated whether these CWAT-based interventions were also capable to reduce sedentary behaviour in healthy sedentary adults. In addition, because CWATs are mostly included as part of a multicomponent intervention, we also wanted to know the efficacy of a monocomponent (CWAT-only) intervention to reduce sedentary time and increase physical activity. In **Chapter 5** and **Chapter 6,** we showed that a multicomponent CWAT-based intervention, consisting of CWATs in combination with motivational interviewing, significantly reduced sedentary behaviour and increased physical activity of any intensity, whereas a monocomponent CWAT-only intervention did not. In addition, we also showed that the reduction in sedentary time and increment in physical activity resulted in improved metabolic (**Chapter 5**) and cardiovascular health (**Chapter 6**).

Explanation of the Findings

Less Sedentary Behaviour, More Physical Activity or Higher Cardiorespiratory Fitness?

Although many studies have examined the association between sedentary behaviour, cardiometabolic health and NCD development, only a few have considered the protective impact of cardiorespiratory fitness, which is known to be a strong predictor of cardiovascular disease incidence and mortality [6, 7]. Recent studies have indicated that sedentary behaviour, MVPA and cardiorespiratory fitness (CRF) are important contributors to cardiometabolic health [8, 9]. Moreover, Shuval *et al*. showed that the association between sedentary behaviour and

impaired cardiometabolic health was considerably less pronounced when CRF was taken into account [7]. However, these studies were based on 1) self-reported physical activity behaviours; 2) population-based studies with low or normal levels of MVPA and/or CRF, and 3) did not consider other physical activity behaviours such as sleep, standing and light-intensity physical activity (LPA). In this respect, results from **Chapter 3** showed that, within highly trained athletes, no inverse association was found between time spent in sedentary behaviour and cardiometabolic health when all other remaining behaviours were taken into account, possibly due to engaging in high levels of MVPA (at least 60 minutes per day). In addition, we also demonstrated that CRF was significantly associated with both sedentary behaviour and MVPA. From this, we can assume that the CRF could modify the associations between sedentary behaviour, MVPA and cardiometabolic health. These results could further be confirmed by a study from Franks *et al*. who showed that CRF modified the inverse association between MVPA and clustered cardiometabolic risk to such an extent that within individuals with a high CRF the association did not existed anymore [10]. In addition, Nauman *et al*. substantially extended these findings by showing that high levels of CRF ($\dot{V}O_{2max}$>43.3 mL·kg^{-1}·min^{-1} in men and >35.2 mL·kg^{-1}·min^{-1} in women) compensated for the deleterious health consequences related to prolonged sitting [11]. Although these values of CRF were much lower compared to our results, sedentary behaviour and CRF were estimated using self-report and a non-exercise prediction model, respectively [11]. Based on these results, it seems that an extreme high CRF protects the potential harmful effects of prolonged sitting and that CRF partly mediates associations between sedentary behaviour, MVPA and cardiometabolic health [12]. A cross-sectional study from Sassen *et al*. showed that 78% of the relation between average physical activity and cardiovascular disease risk score was mediated by CRF [13]. In addition, Knaeps *et al.* found the association between CRF and cardiometabolic risk was always more pronounced than those with sedentary behaviour and MVPA [14].

Furthermore, multiple studies have shown an inter-relationship between physical activity, sedentary behaviour and CRF, which means that physical activity behaviours, including sedentary behaviour and physical activity, are important contributors that affect CRF [15]. The results from our study further extent the existing evidence that CRF is significantly associated with sedentary behaviour

and MVPA, when adjusted for the other remaining behaviours. Thus, sedentary behaviour, MVPA and CRF are all independently associated with cardiometabolic health, although it seems that high levels of CRF are able to fully protect against the harmful effects of prolonged sitting.

Interventions Targeting Physical Activity

We showed in a systematic review and meta-analysis (**Chapter 4)** that CWAT-based interventions increased physical activity levels (+2123 steps per day) in populations with NCDs and, are thus able to contribute to the management of these NCDs. These results were comparable with the current literature showing increased physical activity levels (+1000 – 2500 steps per day) among outpatient adults and adults with T2DM, obesity and COPD [16-18]. These studies all confirm that CWATs, as a single component or included into a multicomponent physical activity intervention, have a positive effect in favour of the intervention groups. It seems that CWAT-based interventions may serve as a tool to enhance self-awareness of daily physical activity and to support individual behavioural physical activity interventions. This demonstrates that offering adults with NCDs a CWAT-based intervention has clinical relevance when increasing physical activity is targeted. However, due to a limited number of studies that included both a multi- and monocomponent (i.e. CWAT-only) intervention, it is difficult to draw conclusions on the added value of the individual intervention components. Therefore, further research is necessary to increase the evidence base of the efficacy with respect to all different components.

Furthermore, all included interventions had as main goal to target physical activity rather than sedentary behaviour. These interventions only targeting physical activity might not be able to modify habitual activities or non-conscious regulatory processes, such as sedentary behaviour [19]. In addition, previous research already showed that targeting physical activity predominantly leads to an increase in MVPA instead of reducing sedentary behaviour. In this case, LPA and standing time are most of the time replaced by MVPA, rather than replacing sedentary behaviour with LPA and/or MVPA. [20]. On the other hand, it has also been shown that an increase in MVPA resulted in behavioural compensatory responses reflected by an increase in sedentary time [21, 22]. However, these results are in contrast with our findings from **Chapter 5** and **Chapter 6,** since we found no

significant differences in physical activity behaviours within the CWAT-only group. Here, we performed a randomised controlled trial with both a CWAT-only group and a CWAT as part of a multicomponent intervention. For the CWAT-only group we did not find a change in MVPA, possibly because the study was powered to reduce sedentary behaviour and not to increase physical activity with MVPA. This does not support the evidence that the existing CWAT-based intervention strategies, included in **Chapter 4**, mainly target the motivation of conscious effort to physical activity (i.e. exercise) by reaching a daily MVPA goal or a daily step count with the aid of self-monitoring, goal setting and feedback. This is possibly due to the fact that most studies included CWATs as a supporting tool in a multicomponent intervention, where we used a CWAT-only group without any other motivational tools. In addition, half of the CWAT-only group increased their MVPA levels by 30 minutes per day, which means that this group includes responders and non-responders. Future studies with the aid of qualitative analyses should elucidate why some people benefit from using a CWAT as a single behaviour change component, while a large part of the population needs extra stimuli with the aid of additional motivational techniques.

Furthermore, our results of **Chapter 4** suggested that participant's gender, age and baseline physical activity levels were associated with the increase in physical activity outcomes (steps per day), which was also found in healthy adults [20]. Such findings indicate that different target populations respond diversely to CWAT-based interventions. Therefore, it is warranted to design population-specific interventions with different goals and motivational techniques targeting both physical activity and sedentary behaviour in future research in which the implemented CWAT-devices are of key importance.

The majority of the studies included pedometers (step counters) as CWAT-device. Interestingly, the contemporary CWATs used in **Chapter 5** and **Chapter 6** differ from the conventional pedometers as they are more sophisticated, provide real-time feedback on variables such as step count, physical activity intensity, calories burned, heart rate and may include a mobile or internet connectivity interface to provide personalised feedback reports [23]. With respect to behaviour change techniques, CWATs also include self-regulatory properties including goal setting and review of goals, feedback and information of discrepancies between behaviour

and set goals. In addition, CWAT companies are starting to enable personal files with family and friends and, thereby, supporting social support, competition and cooperation [24]. From this pallet of CWAT-properties, people can choose their personal corresponding CWAT options and features. These important CWAT-features will all contribute to further increases of physical activity levels. This is in accordance with a recent systematic review from Li *et al.* who showed that the more recent and sophisticated CWATs had a significant larger effect on daily steps compared to pedometer-based interventions [20].

Interventions Targeting Sedentary Behaviour

It is somewhat surprising that interventions described above and especially targeting physical activity alone, or in combination with sedentary behaviour, appeared to be less effective in reducing sedentary behaviour, compared to solely focusing on reducing sedentary behaviour [25, 26]. This suggests that sedentary behaviour in itself needs to be targeted in these interventions instead of interventions focusing on physical activity, sometimes with some degree of focus on reducing sedentary behaviour. In this respect, Prince *et al.* showed in a systematic review that interventions solely focussing on sedentary behaviour resulted in much greater reductions in sedentary time compared to the physical interventions [26]. In our study (**Chapter 5** and **Chapter 6**) we found that a CWAT-device in combination with motivational interviewing (multicomponent intervention) significantly reduced time spent in sedentary behaviour and increased physical activity of any intensity including standing, LPA and MVPA. Interestingly, the reduction in total sedentary time was accompanied by a significant decrease in prolonged sedentary bouts of more than 60 minutes, which is known to be an important contributor to impaired cardiometabolic health [27]. This makes the multicomponent CWAT+ intervention also effective with regard to NCD development. This could be confirmed by data from The Maastricht Study, which showed that each additional hour of sedentary time was associated with increased odds of 22% for type 2 diabetes and of 39% for the metabolic syndrome, independent of MVPA [28]. In contrast, the monocomponent intervention (CWAT-only group) was not able to significantly reduce sedentary time, despite a reduction of 30 minutes per day and increased MVPA of 15 minutes per day. Although this indicates that CWATs may not be effective for all individuals, they

do appear to have substantial benefits for some. For example, data from the 2005–2006 National Health and Nutrition Examination Survey (NHANES) showed that for every 30 minutes of sedentary behaviour that was reallocated to physical activity there was a 2-25% improvement in cardiometabolic health [29]. With our results we support the existing evidence that an intervention solely focusing on sedentary behaviour (CWAT+ intervention) outperformed interventions targeting both sedentary behaviour and physical activity (CWAT-only intervention). Therefore, we propose a sedentary behaviour counselling approach to effectively reduce sedentary time.

This means that CWATs on its own are not effective enough, at least for most participants, to reduce sedentary time and additional behaviour change techniques focusing on sedentary behaviour are necessary. This could also be confirmed by a randomised controlled trial from Kozey Keadle *et al.,* who showed that an intervention focusing on both physical activity and reducing sedentary time caused increases of time spent in MVPA in a similar amount as sedentary time was reduced [22]. Only the group who solely focused on sedentary behaviour resulted in reduction in sedentary time that exceeded the increase in physical activity [30]. In addition, Ellingson *et al*. also performed a study in which they investigated the additional influence of motivational interviewing, next to CWAT-use. However, they solely focussed on increasing physical activity and found no improvements in sedentary behaviour in all groups, even in participants who improved their physical activity level [31]. Importantly, the device used did not provide feedback on sedentary behaviour, which was in contrast with our CWATs. In addition, they used a single, low-dose of motivational interviewing, which could also be a reason why no effects were found.

Furthermore, the diversity of behaviour change components included into an intervention are of importance. Gardner *et al.* proposed self-monitoring, goal setting, providing knowledge about the independent health risks of sedentary behaviour, and motivational counselling as important 'active ingredients' to reduce sedentary behaviours [32]. We also included these components with motivational interviewing as most important ingredient. This way of building motivation for behaviour change has been shown to be effective and is also recommended by the American Heart Association as an effective approach for low-intensity

interventions to promote physical activity and dietary changes [33]. In addition, it has already been shown in large intervention trials and a systematic review that motivational interviewing positively influences physical activity [34-36]. Based on our results we suggest that motivational interviewing is also an effective behaviour change strategy to reduce sedentary behaviour. Motivational interviewing is not based on a particular theory but a "collaborative, person-centered form of guiding to elicit and strengthen motivation for behaviour change" [37]. In addition, a lack of research on the most important components of interventions containing motivational interviewing has made it difficult to draw conclusions with respect to the processes by which motivational interviewing contributes to behaviour changes [36].

Moreover, these results are also in accordance with the current literature showing that CWATs may be more effective in combination with additional behaviour change strategies, such as coaching or motivational counselling [38]. This means that CWATs are facilitators and not drivers of a behaviour change intervention to reduce sedentary behaviour [39]. Thus, for a successful sedentary behaviour intervention with motivational interviewing, CWATs are an essential component.

Sedentary Behaviour, Physical Activity and Cardiometabolic Health

We observed that reducing sedentary time and increasing physical activity led to significant beneficial effects on cardiometabolic health (**Chapter 4-6**). More specifically, increasing physical activity with interventions targeting physical activity was linked to reduced levels of waist circumference, systolic blood pressure and low-density lipoprotein cholesterol in patients with NCDs (**Chapter 4**). In addition, healthy adults showed improvements in body weight, percentage body fat, waist circumference, insulin sensitivity, triglyceride concentration and cardiac autonomic function after the multicomponent CWAT-based intervention in free-living conditions (**Chapter 5** and **Chapter 6**). This was in line with a recent meta-analysis of Hadgraft *et al*. who also showed beneficial effects of sedentary behaviour reductions on body anthropometrics, blood pressure and glucose and lipid metabolism [40]. However, they included no information with regard to physical activity intensity (LPA may be more important for metabolic health and MVPA more important for cardiovascular health) and pattern (frequently interrupting

sedentary time improves metabolic health), of which we have shown in **Chapter 5** and **6** to be important for improvements in metabolic and cardiovascular health.

The CWAT+ group significantly increased time spent in standing behaviour, LPA and MVPA, which resulted in improvements of cardiometabolic health outcomes. We found that an increase in LPA was significantly associated with metabolic health, including improved anthropometrics, insulin sensitivity and triglyceride concentration (**Chapter 5**). In contrast, MVPA was only associated with cardiovascular health, reflected by cardiac autonomic function (**Chapter 6**). These results are in line with a study of Duvivier *et al.* who found that replacing sedentary behaviour with standing and LPA had a positive effect on insulin sensitivity, glycaemic control and circulating lipids, whereas one continuous bout of MVPA improved circulating markers of endothelial dysfunction under equicaloric conditions [41, 42]. However, we found no significant improvements in endothelial markers, which could be attributed to the duration and intensity of MVPA. In our study, MVPA was increased with 20 minutes, compared to the control group, to a total of 50 minutes per day which should probably be at least one hours per day [41]. This can also be confirmed by **Chapter 4**, in which we showed that engaging in at least 60 minutes of MVPA may be viable to protect the potential harms of prolonged sitting. In addition, MVPA includes a wide range of physical activity intensities and, therefore, it might be the case that individuals in the study from **Chapter 5** and **Chapter 6** have performed more physical activity on moderate intensity (brisk walking) compared to vigorous intensity (exercise). On the other hand, we showed that 50 minutes of MVPA were enough to increase HRV, an indicator of cardiovascular health status [43]. These results are in line with a cross-sectional study from Kiviniemi *et al.* who found a positive association between the root mean square of successive differences between normal heartbeats (RMSSD) and time spent in MVPA. I expect that the increase in MVPA leads to an increased cardio-respiratory fitness, which is a major determinant of HRV [44]. Although no association was found between prolonged sedentary time (sedentary bouts > 60min) and MVPA, it seems that longer periods of MVPA are necessary to improve HRV. Furthermore, it has been shown that the positive health effects of MVPA can be mitigated by the negative health effects of sedentary behaviour during the rest

of the day [45]. This implies that frequently interrupting sedentary behaviour with standing and LPA could reinforce the positive effects of MVPA on HRV.
The pattern of sedentary behaviour seems to be more important within the context of improving metabolic health. We showed in **Chapter 5** that the increase in LPA was inversely correlated with prolonged sedentary bouts of more than 60 minutes, whereas MVPA was not. In addition, we also found that LPA was significantly associated with cardiometabolic health outcomes. Therefore, we expect that these hourly, or even less, interruptions of sedentary time were of key importance for the improvements in cardiometabolic health. This is in line with a systematic review that compared the effects of breaking up prolonged sitting with bouts of physical activity throughout the day versus continuous sitting. They found that the use of physical activity breaks attenuated post-prandial glucose, insulin and triglyceride concentrations [46]. These results suggest that interrupting sedentary behaviour by spreading physical activity over the entire day seems to beneficially affect metabolic health. However, future research is necessary to investigate the effects of the number, duration and intensity of physical activity breaks. Taken together, it is suggested by our results, and confirmed by other research, that interrupting prolonged periods of sedentary time with LPA improves metabolic health, while there is no evidence to support the effect of this intensity in providing positive changes in cardiovascular risk factors within healthy sedentary adults. Although the physiological plausibility of reducing and interrupting sedentary behaviour for cardiometabolic health has been strengthened by both observational and experimental studies, further research regarding the specific dose-dependent relations and pattern effects of these movement behaviours on cardiometabolic health.

Methodology

Information Bias

Physical activity and Sedentary behaviour

In **Chapter 3, 5 and 6** we used the ActivPAL™ accelerometer, which is a valid instrument to measure time spent sedentary (sitting and lying), standing and physical activity [47]. It is often used as the gold standard due to the measurement of body postures [47-50], which is not the case in most other accelerometers used in

research regarding physical activity and sedentary behaviour. Therefore, a strength of this dissertation is that we were able to discriminate sitting from standing. Furthermore, although the ActivPAL™ is not able to discriminate waking time from sleeping time (time in bed), which is necessary for correct estimations of sedentary time and total daily physical activities during the waking period, we correctly define waking time using a validated automated algorithm that was developed using a subsample of The Maastricht Study, an observational prospective population-based cohort study [51]. However, a limitation is that although the ActivPAL™ properly classifies lower physical activity intensities, it underestimates step count during high cadence running and cycling [52]. This leads to an inaccurate estimation of physical activity intensity at higher intensities. Therefore, novel and more precise measurements are being developed and need to be integrated in future experimental and observational studies. For example, studies would benefit when using an accelerometer in combination with heart rate monitors. With the considerable increase in CWAT development, these devices will make a significant contribution in future research within the field of physical activity monitoring.

Endothelial function

We measured endothelial function with the aid of the EndoPAT® device, a non-invasive measurement of the arterial beds in the fingertip using peripheral arterial tone (PAT) measurement [53]. This measurement has an increased measurement error compared to flow-mediated dilation (FMD), which is referred as the golden standard for measuring endothelial function [54]. However, the PAT-signal is significantly correlated (r = 0.55) with the FMD measurement [55].

Selection Bias

In this dissertation we selected both highly trained athletes (**Chapter 3**) and healthy sedentary adults (**Chapter 5** and **Chapter 6**). Although the inclusion of highly trained athletes was necessary to investigate whether spending high amounts in MVPA (for a couple of years) could mitigate the detrimental effects of sedentary time on cardiometabolic health, our findings are not generalizable to the general population. Therefore, further research is necessary to investigate

whether the same conclusions could be found within the general population with lower levels of MVPA.

Furthermore, the inclusion of sedentary adults was based on objectively measured sedentary time and is therefore a strength of this dissertation. Although this way of inclusion has been done in only a few clinical trials in the current literature, most studies included participants based on physical (in)activity levels, which not guarantees a sedentary population, especially when a population should be included within the field of sedentary behaviour research. However, to make a translation to the general population, future studies should also include adolescents, NCD populations and more active adults. However, when the multicomponent CWAT-based intervention has positive effects on sedentary adults, we can assume that this intervention is able to improve sedentary behaviour and physical activity levels in this healthier population.

Study Design

Although cross-sectional studies have some advantages, such as time efficiency, this type of studies are not able to provide evidence with respect to causality. In the cross-sectional study from **Chapter 3** we examined possible associations between sedentary behaviour, physical activity and cardiometabolic health with the aid of objective measurements. However, long-term randomised controlled trials with a high number of participants from the general population (healthy subjects and individuals with NCDs) are necessary to investigate any causalities between these behaviours, cardiometabolic health and NCD development. Furthermore, the randomised controlled trials used in this dissertation were of high quality, except for the fact that blind the assessors was not achievable. Therefore, it is warranted in future studies to include lifestyle coaches as well as assessors who are fully blinded to reduce performance bias.

This means that both long-term cohort studies and randomised controlled trials are proposed to determine the cardiometabolic health effects after interventions with regard to sedentary behaviour and physical activity.

Concluding Remarks and Future Perspectives

This dissertation first investigated the modifying effects of moderate-to-vigorous physical activity (MVPA) on the association between sedentary behaviour and cardiometabolic health within highly active adults. For the majority of the population these high volumes of MVPA are not achievable due to lack of money, time and/or motivation [56], since at least 27% of the global population is not able to reach the recommended levels of MVPA per day. As a result, they are more prone for an impaired cardiometabolic health and increased risk for developing NCDs such as type 2 diabetes mellitus and cardiovascular diseases. Therefore, we focussed on the efficacy of CWAT-based interventions, including mono- and multicomponent behaviour change techniques, to reduce sedentary behaviour and increase physical activity levels for both NCD management and reducing the risk of developing NCDs. In addition, we also investigated whether improvements in sedentary behaviour and physical activity leads to clinically relevant changes in cardiometabolic health.

In conclusion, the results suggest that in highly active people high volumes of MVPA can eliminate the association between sedentary behaviour and cardiometabolic health (**Chapter 3**). However, these data were based on a cross-sectional study and therefore, longitudinal studies with objective measurements of physical activity and sedentary behaviour (with posture-discriminating devices usually placed on the thigh) at multiple time points are necessary to gain better insight in the temporal sequence and dose-response association of various levels of physical activity, sedentary behaviour, cardiorespiratory fitness and cardiometabolic health within different ages and ethnicities. In addition, since movement behaviours are finite across a 24-hour period, changing the time spend in one behaviour will inevitably affect the time in at least one other behaviour. Therefore, more sophisticated analysing techniques such as compositional data analyses are necessary to take this feature into account.

For people who are not able to reach these high volumes of MVPA, a 12-week multicomponent behaviour change intervention, consisted of a consumer wearable activity tracker and motivational interviewing, appears to be effective to reduce sedentary behaviour and increase the amount of both standing time, LPA and MVPA (**Chapter 4-6**). In this respect, future research should attempt to establish

a 'knowledge base' with regard to the development of sedentary behaviour interventions. From this, the most effective interventions to reduce sedentary time will be found. For example, are more additional behaviour change techniques better, or should we target occupational or leisure time sedentary behaviour? This should then be followed by testing feasibility, efficacy, and subsequent effectiveness of these programmes in both the general population and clinical settings. Although we showed that motivational interviewing can significantly reduce sedentary time, it has also been shown that environmental change interventions were highly effective (i.e. sit-stand desks) [57]. Therefore, the combination of these two intervention strategies could possibly lead to an even higher reduction in sedentary time. Whereas these findings suggest that CWAT-based interventions may have potential to improve sedentary time and physical activity in the short term, there is still a need to evaluate the long-term impacts of these interventions. In addition, since we are one of the first that included more sophisticated CWATs into our intervention trials, more research is necessary to investigate the efficacy of these CWATs instead of pedometer use.

As a result, these changes in sedentary behaviour and physical activity improve cardiometabolic health in sedentary adults and NCD populations (**Chapter 5** and **chapter 6**). In addition, it seems that the intensity (LPA or MVPA) and pattern of physical activity have differential effects on metabolic and cardiovascular health, where LPA is more beneficial for metabolic health and MVPA for cardiovascular health. These results provide a useful direction for future mechanistic studies to unravel the underlying molecular mechanisms with regard to glucose metabolism, mitochondrial function, lipid metabolism (especially lipoprotein lipase activity) and endothelial function. This will substantially improve the understanding on both metabolic and cardiovascular health attributes of standing, LPA and MVPA in the near future.

Furthermore, we know from this dissertation that sedentary behaviour can be interrupted in different ways (high levels of MVPA and/or more frequent interruptions with standing and/or LPA). This leads to various patterns of physical activity behaviours consisting of a combination of total sedentary time, frequency of sedentary bouts and the dose, frequency and intensity of physical activity. In this respect, it is not fully known yet what combinations of physical activity

behaviour characteristics have an optimal influence on cardiometabolic health outcomes. To evaluate the optimal physical activity behaviour patterns, dose-response studies should be performed in such a way that we have to go towards an integrated physical activity profiling as we, for example, showed with the CoDa approach. In addition, artificial intelligence, including machine learning and deep learning techniques, may become increasingly important to model the cardiometabolic health effects of various physical activity behaviour patterns.


LDL
HDL

Addendum

Valorisation

Clinical implications

Non-communicable diseases (NCDs) are a worldwide rising problem, requiring new strategies to reduce the risk of developing these chronic diseases. According to the World Health Organization, it is estimated that each year more than 36 million people die from NCDs (63% of global deaths) [58]. Therefore, there is high priority to address these NCDs, of which the importance is now highlighted by the WHO in the Global action plan for prevention and management of NCDs [58]. They stated that one of the most important ways of reducing deaths from NCDs is to control unhealthy lifestyle choices that lead to their development. As a results, they have also developed a new global action plan to help countries scale up policy actions to promote physical activity [59].

Within the research field, the evidence-based support with respect to the importance of an active lifestyle for optimal cardiometabolic health has grown exponentially. In addition, the inter-relation between physical activity and sedentary behaviour is increasingly being addressed within the current public health guidelines and policies [60]. Several countries and healthcare organisations have already started with providing general recommendations to replace sedentary behaviour with physical activity of any intensity. The general message 'sit less and move more', as stated in the current WHO guidelines for physical activity and sedentary behaviour, is a first step towards targeting both sedentary behaviour and physical activity. Nevertheless, no written plans with regard to both effective and cost-effective ways to decrease sedentary behaviour are proposed. Although the new guidelines encourage to reduce sedentary behaviour and increase physical activity, physicians, governmental agencies and companies should take responsibilities to implement the current guidelines into our daily life. Especially in primary care physicians should encourage people to reduce sedentary behaviour by tailoring to individuals' context and circumstances. However, findings indicate that the prevalence of sedentary behaviour counselling is low, where only 10 percent of the patients in a primary care setting receive specific recommendations to reduce their sedentary behaviour [61]. Therefore, we should focus on a stepwise approach to modify physical-activity behaviour on initial changes in sedentary behaviour. Here, primary care physicians and the government have the potential to play an important role in modifying sedentary behaviour within healthy inactive populations and patients with NCDs. Instead of

the well-known recommendations to achieve at least 150−300 minutes of MVPA per week, recommendations should be more personalized in which people can adopt a cocktail of sedentary behaviour and physical activity, based on differences in frequency and intensity, that works best for them.
In addition, as dieticians give advice and help people to make correct healthy lifestyle and diet choices, lifestyle/physical coaches should be trained to advise individuals regarding their sedentary and physical activity behaviours. Based on this dissertation, CWATs in combination with motivational counselling related to sedentary behaviour may need to place greater emphasis on addressing the association between sedentary behaviour and cardiometabolic health, especially for patients with NCDs and physically inactive people. Thus, starting with a focus on sedentary behaviour may be more effective on long-term behaviour change and subsequent improvements in health outcomes.
Although we found no significant benefits to reduce sedentary time and improve cardiometabolic health in sedentary adults with a CWAT on its own, I believe that these devices, as facilitators of a behaviour change intervention, will have both individual and public health implications in future NCD self-management and progression. Here, newly developed self-monitoring technologies should be able to monitor sedentary behaviour in addition to physical activity levels to support people in setting goals to reduce sedentary behaviour. With the increasing popularity of these CWATs, a formal adoption in public health practice has to be made in such a way that CWATs support continuous health monitoring, provide knowledge, give feedback and encourage a healthy behaviour. This will reduce the number of health care visits due to personalized on-demand interventions.

Furthermore, reducing sedentary behaviour and increasing physical activity normally resulted in an increased CRF. Here, CRF is a physiological measure reflecting a combination of genetic predisposition, physical activity behaviour and functional health of various organ systems [62]. As a result, CRF will improve when sedentary behaviour is reduced and physical activity increased. Therefore, CRF could be a surrogate marker for the measurement of physical activity, sedentary behaviour and cardiometabolic health in clinical practice. In this dissertation we used a cardiopulmonary exercise test using an electronically braked cycle ergometer, which is the gold standard for measuring CRF. In this way, physicians

are able to quickly and reliably estimate CRF and related physical activity behaviours, cardiometabolic health and the risk of developing NCDs.

Socioeconomic impact

The increased prevalence rates of NCDs and related comorbidities have led to a major economic burden for the global health care systems, as well as for patients themselves. The cumulative output loss due to the four major NCDs together with mental disorders is estimated to be 47 trillion US dollars [58]. These socioeconomic costs make the prevention and management of these diseases a major challenge for the 21st century. Here, the inexpensive and easy to access strategies presented within this dissertation may contribute to a reduction in this global economic burden. Reducing sedentary behaviour and increasing physical activity is freely accessible and inexpensive for the general population. In addition, the low costs of CWATs make them an attractive tool to facilitate monitoring of sedentary behaviour and physical activity. Moreover, primary care physicians may play an important role in modifying movement behaviours of their patients, since their advice is often respected and they have the ability to motivate their patients to change unhealthy behaviours [63]. However, due to lack of time and reimbursement, most physicians do not provide such physical activity counselling programmes. Instead, they can develop methods to incorporate feedback using CWATs into their interventions. There is also an important role for healthcare providers, who might simply advise their patients to use CWATs by reimburse or compensate these devices. In addition, they could reward people who make the effort to increase their physical activity and reduce sedentary behaviour with the aid of personalized insurance premiums.

Modifying sedentary behaviour and physical activity will probably also affect the use of transportation and related costs and, at the same time, this will have a positive effect on the emission of greenhouse gasses with respect to the urgent matter of climate change.

Furthermore, recent data from the UK's Office for National Statistics highlight that of the 131 million working days lost to sickness, important contributing factors are back, neck and muscle pain and stress, which can, for a large part, be found within office-based occupations [64]. Therefore, approaches to avoid sedentary time at work are required as potential mediating factor, of which the strategies used in

this dissertation could perfectly be implemented. Moreover, this will also improve work productivity, quality and efficiency. All these suggestions will ultimately provide cost savings to both the health care systems and employees.

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LDL
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Appendices

Summary

During the last decades, Western societies live in an environment that is characterized by passive forms of transportation, sedentary jobs and modern communication techniques. These changes have contributed to a predominantly physically inactive lifestyle in which a vast majority of our waking hours is spent in a seated position. Insufficient physical activity, defined as not meeting the minimum international recommendations for regular physical activity (>150 of moderate-to-vigorous intensity physical activity [MVPA] min/week), is a major contributor to the development of non-communicable diseases (NCDs), such as chronic respiratory diseases, type 2 diabetes mellitus, cardiovascular diseases and cancer. Despite the significant health benefits of MVPA, adherence to these physical activity guidelines is poor. In addition, it appears that even the recommended levels of MVPA do not always fully protect against cardiometabolic risk factors and the development of NCDs. As such, next to the time spend in MVPA, an additional factor that also appears to determine cardiometabolic health and NCD development is sedentary behaviour. In fact, during the past decade, emerging evidence clearly disclosed that, even in the presence of regular MVPA, prolonged sedentary behaviour is an independent contributor to cardiometabolic health. In keeping with this line of reasoning, it has been suggested that both physical inactivity and a sedentary lifestyle should be targeted as they independently affect cardiometabolic health.

Although MVPA has recognized as an important factor to improve cardiometabolic health, it is less clear whether high amounts of MVPA are able to combat the detrimental effects on cardiometabolic health due to spending in high volumes of sedentary time. Therefore, it could be questioned if the inverse association between sedentary time and cardiometabolic health could be attenuated or even eliminated in individuals engaging in high amounts of MVPA. In this respect, in **Chapter 3**, we investigated the modifying effects of MVPA on the association between sedentary behaviour and cardiometabolic health using objective accelerometer-derived measures within highly active adults. Here, associations between various movement behaviours (i.e. sleeping, standing, light intensity physical activity [LPA] and MVPA) and biomarkers of glucose tolerance and lipid metabolism were analysed using a compositional data analyses approach to account for all behaviours. In this study, we observed that, despite spending in

high levels of sedentary behaviour (7−13 hours/day), high levels of MVPA were able to mitigate the inverse association between sedentary behaviour and cardiometabolic health. These results suggest that engaging in at least 60 minutes of MVPA may be viable to protect the potential harms of prolonged sitting. In addition, the cardiorespiratory fitness (CRF) was significantly correlated with both sedentary time and MVPA. From this, it could be suggested that people with a high CRF may provide favourable effects against the deleterious consequences of prolonged sitting.

Although we proposed a minimum of one hour of MVPA per day to counteract the detrimental effects of sedentary behaviour on cardiometabolic health, the majority of the population is not able to reach these high levels of MVPA and spend the largest part of the day in sedentary behaviours. Unfortunately, no pragmatic/realistic strategies involving a more holistic 24-hour approach targeting both interacting behaviours have been proposed so far. Therefore, interventions to reduce sedentary behaviour and increase physical activity levels are necessary to combat the increased risk of NCD development in the general population.
It has already been shown that consumer wearable activity tracker (CWAT)-based multicomponent interventions are able to improve physical activity within healthy adults and positively affects the risk of NCD development. Next to the decreased risk, physical activity plays also an important role in the progression and management of NCDs. Therefore, in **Chapter 4** we systematically reviewed the effects of CWAT-based interventions on physical activity and cardiometabolic health in populations with NCDs. In this study, we observed that populations with chronic diseases significantly increased their daily step count using CWATs only, or as part of a multi-component intervention. This increase in physical activity resulted in significant improvements in cardiometabolic health such as a reduced waist circumference, systolic blood pressure and low-density lipoprotein cholesterol concentration.

Given the fact that both physical activity and sedentary behaviour should be targeted, we subsequently investigated in **Chapter 5** and **Chapter 6** the efficacy of CWATs, as self-monitoring (CWAT-only) and as part of a multicomponent behaviour change strategy (CWAT + motivational counselling), to reduce

sedentary time, increase physical activity and improve cardiometabolic health in healthy sedentary adults.

In **Chapter 5**, we investigated the effectiveness of CWAT-based efficacy of a single component CWAT-only intervention and the added value of a multicomponent (CWATs + motivational interviewing) behaviour change intervention to reduce sedentary behaviour, increase physical activity and improve anthropometrics, body composition, glucose tolerance and lipid metabolism within sedentary adults. This study showed that the multicomponent intervention (CWAT-use + motivational interviewing) significantly reduced sedentary behaviour and increased physical activity, whereas the single component (CWAT-only) intervention did not. Moreover, the reduction of sedentary behaviour was accompanied by an improvement in body weight, waist circumference, fat mass, triglyceride concentration and enhanced insulin sensitivity. In addition, most favourable effects were found when LPA was increased instead of standing or MVPA. These results are promising for people who fail to reach the recommended levels of MVPA to improve cardiometabolic health and a delayed onset of chronic diseases.

In **Chapter 6**, we investigated the efficacy of self-monitoring (CWAT-only) and multiple behaviour change techniques (self-monitoring + motivational counselling) to reduce sedentary behaviour and improve cardiometabolic health and vascular function in sedentary adults. Health outcomes measures included anthropometrics, body composition, lipid metabolism, heart rate variability (cardiac autonomic function), vascular endothelial function and markers of systemic low-grade inflammation and microvascular endothelial function. Self-monitoring in combination with motivational interviewing effectively reduced sedentary time, increased physical activity and improved serum lipids (triglyceride concentration) and heart rate variability, whereas self-monitoring on its own did not. Moreover, regression analyses showed that MVPA was significantly associated with cardiac autonomic function, which indicates that MVPA is more important for cardiovascular health.

Overall, the studies described in this dissertation were designed to investigate the modifying effects of MVPA on the association between sedentary behaviour and cardiometabolic health, and to study novel approaches to improve sedentary behaviour, physical activity, cardiometabolic health and vascular function. Taken together, high amounts of MVPA can eliminate the association between sedentary behaviour and cardiometabolic health. For people who are not able to reach these high amounts of MVPA, a multicomponent behaviour change intervention, consisted of a CWAT and motivational interviewing, seems a promising way to effectively reduce sedentary behaviour and increase the amount of both standing time, light-intensity physical activity and MVPA. These effects lead to improvements of both metabolic and cardiovascular health.


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Appendices

Samenvatting

De laatste decennia leeft de westerse bevolking in een omgeving die wordt gekenmerkt door passieve vormen van vervoer, sedentair werk en moderne communicatietechnieken. Deze veranderingen hebben bijgedragen tot een overwegend fysiek inactieve leefstijl, waarbij een overgroot gedeelte van de dag zittend wordt doorgebracht. Onvoldoende fysieke activiteit, gedefinieerd als het niet voldoen aan de internationale minimum aanbeveling van de Wereldgezondheidsorganisatie voor regelmatige lichaamsbeweging (> 150 min/week matig tot zwaar intensief bewegen), is een belangrijke oorzaak van de ontwikkeling van chronische aandoeningen, zoals chronische luchtwegaandoeningen, diabetes mellitus type 2, hart- en vaatziekten en kanker. Ondanks dat we weten dat matig tot intensieve fysieke activiteit aanzienlijke gezondheidsvoordelen oplevert, worden de huidige richtlijnen zeer slecht opgevolgd. Bovendien biedt de aanbevolen hoeveelheid van fysieke activiteit niet altijd volledige bescherming tegen cardiometabole risicofactoren, zoals het suiker- en vetmetabolisme, en de ontwikkeling van chronische aandoeningen. Daarom is sedentair gedrag, naast onvoldoende matig tot intensieve fysieke activiteit, een bijkomende factor die ook invloed lijkt te hebben op de cardiometabole gezondheid en de ontwikkeling van chronische aandoeningen. Gedurende de afgelopen tien jaar is steeds meer bewijs geleverd dat, zelfs in aanwezigheid van regelmatig matig tot intensieve fysieke activiteit, langdurig zitten een onafhankelijke bijdrage levert aan de cardiometabole gezondheid. Dit betekent dat zowel onvoldoende fysieke activiteit als een sedentaire leefstijl aangepakt dient te worden.

Hoewel matig tot intensieve fysieke activiteit erkend wordt als een belangrijke factor om de cardiometabole gezondheid te verbeteren, is het onduidelijk of grote hoeveelheden matig tot intensieve fysieke activiteit de nadelige effecten op de cardiometabole gezondheid kunnen tegengaan als gevolg van langdurig zitten. Wellicht kan de inverse associatie tussen zittijd en cardiometabole gezondheid worden afgezwakt, of zelfs volledig teniet worden gedaan, wanneer personen een grote hoeveelheid aan matig tot intensieve fysieke activiteit per dag spenderen. In **Hoofdstuk 3** is beschreven of een hoge mate van matig tot intensieve fysieke activiteit de schadelijke gevolgen van langdurig zitten op de cardiometabole gezondheid ongedaan kan maken. In deze studie is waargenomen dat, ondanks

langdurig zitten (7-13 uur/dag), een hoge mate van matig tot intensieve fysieke activiteit (minstens 60 minuten per dag) de potentieel schadelijke gevolgen van langdurig zitten op de cardiometabole gezondheid teniet kan doen. Daarnaast is ook aangetoond dat de cardiorespiratoire fitheid (conditie) significant gecorreleerd is met de hoeveelheid matig tot intensieve fysieke activiteit. Dit betekent dat een hoge cardiorespiratoire fitheid een gunstig effect heeft op de schadelijke effecten van langdurig zitten.

Hoewel één uur matig tot intensieve fysieke activiteit gezondheidsvoordelen met zich meebrengt, is een groot deel van de bevolking niet in staat om deze hoge mate van fysieke activiteit uit te oefenen, en brengen deze mensen het grootste gedeelte van de dag zittend door. Tot op heden bestaan er nog maar weinig effectieve strategieën die zowel de fysieke activiteit verhogen als het zitgedrag kunnen reduceren. Deze interventies zijn evenwel nodig om het risico op de ontwikkeling van chronische aandoeningen binnen de populatie te verlagen. Multicomponent interventies met activity trackers hebben eerder aangetoond dat deze de fysieke activiteit van gezonde mensen op een effectieve wijze kunnen verhogen en het risico op chronische aandoeningen kunnen verlagen. Naast deze risicoreductie is fysieke activiteit van belang in relatie tot de progressie en management van chronische aandoeningen. In **Hoofdstuk 4** is met een literatuurstudie onderzocht wat de effecten van multicomponent interventies met activity tracking op de fysieke activiteit en cardiometabole gezondheid zijn bij personen met een chronische aandoening. Deze studie toonde aan dat bij populaties met een chronische aandoening het aantal stappen per dag significant verhoogd kon worden met behulp van activity trackers, soms als onderdeel van een multicomponent interventie. De verhoging van fysieke activiteit resulteerde daarnaast in een verbetering van de cardiometabole gezondheid, waaronder de buikomtrek, de systolische bloeddruk en de cholesterolconcentratie in het bloed.

Om zowel de fysieke activiteit te bevorderen als het zitgedrag te veranderen is vervolgens in **Hoofdstuk 5** en **Hoofdstuk 6** onderzocht of de inzet van activity trackers, met en zonder extra motivationele technieken, het zitgedrag effectief kan reduceren, de fysieke activiteit kan verhogen en de cardiometabole gezondheid kan verbeteren.

In **Hoofdstuk 5** is de effectiviteit van activity trackers, met en zonder extra motivatie, op het reduceren van zitgedrag onderzocht, en of het verminderen van zitgedrag invloed heeft op de metabole gezondheid zoals het suiker- en vetmetabolisme, en lichaamssamenstelling. De resultaten tonen aan dat activity trackers met toevoeging van extra motivationele technieken het zitgedrag significant kunnen verminderen en de fysieke activiteit kunnen verhogen, waar het gebruik van alleen activity trackers niet voldoende is. Deze veranderingen van beweeggedrag resulteerden in een verlaging van het lichaamsgewicht, de vetmassa, de concentratie vetten in het bloed en een verbetering van de insulinegevoeligheid. De meest gunstige effecten werden gevonden wanneer het zitgedrag frequent werd onderbroken door lichte fysieke inspanning (wandelen en huishoudelijke taken). Deze resultaten zijn veelbelovend voor personen die niet in staat zijn om de aanbevolen dagelijkse hoeveelheid matig tot intensieve fysieke activiteit uit te oefenen en op deze manier het risico op chronische aandoeningen te verlagen.

In **Hoofdstuk 6** is onderzocht of activity trackers, met of zonder extra motivationele technieken, het zitgedrag kan reduceren en de cardiometabole gezondheid en vasculaire functie kunnen verbeteren in sedentaire volwassenen. Activity tracking in combinatie met extra motivationele technieken resulteerde in een daling van het sedentair gedrag en een stijging van de fysiek activiteit van elke intensiteit. Bijkomend gevolg was een verbetering van de cardiale autonome functie, dat gemeten werd middels de hartslagvariabiliteit. Ook toonde dit onderzoek aan dat de verbetering van de cardiale autonome functie grotendeels een gevolg is van een verhoging van matig tot intensieve fysieke activiteit. Dit betekent dat matig tot intensief bewegen belangrijk is voor de cardiovasculaire gezondheid en laag intensieve fysieke activiteit meer verantwoordelijk is voor een verbetering van metabole gezondheid.

De studies beschreven in dit proefschrift zijn opgezet om te onderzoeken wat de invloed van een hoge mate van matig tot intensief bewegen op de cardiometabole gezondheid is, die normaal verslechtert na langdurig zitten. Daarnaast zijn nieuwe innovatieve manieren onderzocht om het zitgedrag te reduceren, en of de

vermindering van zitgedrag leidt tot een verbetering van de cardiometabole gezondheid en vasculaire functie.

Afsluitend kan gesteld worden dat een hoge mate van matig tot intensief bewegen de schadelijke gevolgen van langdurig zitten op de cardiometabole gezondheid teniet kan doen. Voor personen die niet in staat zijn om deze hoge mate van intense fysieke activiteit te bereiken, lijken activity trackers in combinatie met motivationele technieken een veelbelovende methode om het zitgedrag te reduceren en de fysieke activiteit van verschillende intensiteiten (staan, lichte intensiteit en matig tot intensieve intensiteit) te verhogen. Deze veranderingen leiden tot zowel een verbetering van de metabole als de cardiovasculaire gezondheid.


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Appendices

Curriculum Vitae

Wouter was born on the 22th of June in 1990 in Maastricht, The Netherlands. He attended the secondary school at Bonnefantencollege in Maastricht and graduated in 2008. He first studied Biometrics at Hogeschool Zuyd in Heerlen and subsequently studied Biomedical Sciences at Maastricht University and Hasselt University where he graduated cum laude in 2018. His master thesis was entitled "Cardiac function in adolescents with obesity: cardiometabolic risk factors and impact on physical fitness" within the research group of prof. dr. Dominique Hansen. In February 2018, Wouter started as a joint PhD candidate within the research cluster Rehabilitation of Cardiopulmonary and Internal Diseases at the Department of Rehabilitation Sciences of Hasselt University and the Department of Nutrition and Movement Sciences of Maastricht University Medical Centre + (The Netherlands), under supervision of prof. dr. Bert Op 't Eijnde and prof. dr. Hans Savelberg. His research focusses on the associations between sedentary behaviour, physical activity and cardiometabolic health in healthy and diseased populations. Within this research field, an important part of his research focusses on targeting sedentary behaviour with the aid of sophisticated consumer wearable activity trackers. His work has been presented at various national and international symposia and conferences.

Appendices

List of Publications

- **Franssen WMA**, Beyens M, Al Hatawe T, Frederix I, Verboven K, Dendale P, Eijnde BO, Massa G, Hansen D. Cardiac function in adolescents with obesity: cardiometabolic risk factors and impact on physical fitness. *International Journal Of Obesity (Lond)*. 2019 Jul;43(7):1400-1410.
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- Van Ryckeghem L, Keytsman C, De Brandt J, Verboven K, Verbaanderd E, Marinus N, **Franssen WMA**, Frederix I, Bakelants E, Petit T, Jogani S, Stroobants S, Dendale P, Bito V, Verwerft J, Hansen D. Impact of continuous vs. interval training on oxygen extraction and cardiac function during exercise in type 2 diabetes mellitus. *European Journal of Applied Physiology*. 2022 Jan 17.
- **Franssen WMA**, Nieste I, Vandereyt F, Savelberg HHCM, Eijnde BO. A 12-week consumer wearable activity tracker-based intervention reduces sedentary behaviour and improves cardiometabolic health in free-living sedentary adults: a randomised controlled trial. *Journal of Activity, Sedentary and Sleep Behaviors.* 2022
- Nieste I, **Franssen WMA**, Duvivier BMFM, Spaas J, Savelberg HHCM, Eijnde BO. Replacing sitting with light-intensity physical activity throughout the day versus 1 bout of vigorous-intensity exercise: similar cardiometabolic health effects in Multiple Sclerosis. A randomised cross-over study. *Disability and rehabilitation*. 2022

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- **Franssen WMA**, Jermei J, Savelberg HHCM, Eijnde BO. The potential harms of sedentary behaviour on cardiometabolic health are mitigated in highly trained athletes. Submitted
- **Franssen WMA**, Nieste I, Joris PJ, Vandereyt F, Savelberg HHCM, Eijnde BO. The efficacy of a consumer wearable activity tracker-based behaviour change intervention to reduce sedentary behaviour and improve cardiovascular health in sedentary adults: a randomised controlled trial. Submitted

Appendices

Dankwoord

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