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PhD Thesis

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Physical inactivity and current treatments of knee osteoarthritis

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PREFACE

This PhD thesis is based on the four original studies listed below. All studies originate from the Parker Institute, Copenhagen University Hospital, Bispebjerg and Frederiksberg. The studies were conducted from November 2015 to July 2018.

Original studies:

I. *Reliability and Construct Validity of the SENS Motion® Activity Measurement System as a Tool to Detect Sedentary Behavior in Patients with Knee Osteoarthritis*. Bartholdy C, Gudbergsen H, Bliddal H, Kjærgaard M, Lykkegaard KL, Henriksen M. Arthritis. 2018 Mar 1;2018:6596278.

II. *Association between weight loss and changes in physical inactivity in overweight/obese individuals with knee osteoarthritis: an 8-week cohort study*. Bartholdy C, Christensen R, Kristensen LE, Gudbergsen H, Bliddal H, Overgaard A, Rasmussen MU, Henriksen M. (submitted to a peer review journal)

III. *Changes in Physical Inactivity During Supervised Education and Exercise Therapy in Patients with Knee Osteoarthritis: A Prospective Cohort Study*. Bartholdy C, Skou ST, Bliddal H, Henriksen M. (submitted to a peer review journal)

IV. *Effectiveness of text messages for decreasing inactive behaviour in patients with knee osteoarthritis: a pilot randomised controlled study*. Bartholdy C, Bliddal H, Henriksen M. (submitted to a peer review journal)

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SUMMARY

Physical inactivity is a global problem and as time spent sitting or reclined increases the global health declines. Despite global strategies to stop this trend, analysis of recent data still suggest that time spent being physically inactive is increasing.

One subgroup in society that is predisposed to an inactive lifestyle is patients with knee osteoarthritis (OA) due to the symptoms accompanying the OA condition; pain and disability. Helping them reduce their time spent being physically inactive will not only improve their overall health and reduce the risk of developing co-morbidities related to knee OA and an inactive lifestyle, but also reduce their primary symptoms. The aim of this PhD thesis is therefore to increase knowledge regarding physical inactivity and its relation to current and new treatments for patients with knee OA.

Study one (article I) examined the reliability and construct validity of a new accelerometer (the SENS motion® activity measurement system, (SENS System)) in patients with knee OA. A standardised (observer recorded activities) and semi-standardised (patient reported activities) observational protocol was developed to assess the construct validity and repeated measures were used to assess reliability. A total of 24 patients with knee OA participated. Assessment of construct validity using the standardised protocol revealed a high average agreement between SENS system and objective observations (mean 97%, SD 7%) when splitting data into two groups; inactivity (sitting, reclined) and activity (standing, walking, other activity). When data was split into four categories (inactivity, standing, walking, other activity) the highest agreement was for inactivity (mean 99%, SD 3%) and lowest for walking (mean 28%, SD 18%). For the semi-standardised protocol, a mean agreement of 92% (SD 5%) was observed when using the two categories. When split into four categories the lowest agreement was found for other activities (mean 42%, SD 36%) and highest for inactivity (mean 94%, SD 5%). Average agreement between the repeated measures was 98% (SD 3%) when using the two categories. In the four categories the lowest agreement was mean 77% (SD 14%) for walking and the highest for inactivity (mean 96%, SD 8%). Overall the SENS system delivered valid and reliable recordings of time spent being physically inactive. Differentiation between different activities other than physical inactivity, standing and movement (walking, other activities) should be interpreted with caution. The SENS system was used to measure time spent being physically inactive in the next three studies.

Study two (article II) investigated if a spontaneous change in time spent being physically inactive occurred during an 8-week intensive dietary intervention, in overweight or obese patients with knee OA. A total of 124 participants were included in this observational cohort study. A

mean weight loss of 12.7 kg [95%CI -13.2 to -12.1; P<.0001] and significant reduction of all symptoms, measured with the knee injury and osteoarthritis outcome score (KOOS), was found after 8 weeks of intensive dieting with meal replacement. However, no significant change in average time spent being physically inactive was observed (mean change: 8.8 min/day [95% CI, -12.1 to 29.7]; P=0.41). Despite a substantial weight loss and significant improvement in knee OA symptoms, no spontaneous change in time spent being physically inactive occurred.

Study three (article III) investigated if a spontaneous change in time spent being physically inactive occurred following an education and exercise intervention in patients with knee OA measured with the SENS system. The study was designed as a pragmatic cohort including participants from local physiotherapy clinics that performed a widely used educational and exercise program (GLA:D®). A total of 32 participants were analysed and overall no changes occurred in average time spent being physically inactive (mean change: 16.2 min/day [95% -15.7 to 48.1]; P=0.31) from baseline to the last they of the program, but statistically significant improvements in KOOS function (mean change: 5.8 points [95% CI 1.9 to 9.7]; P=0.0046) and KOOS pain (mean change: 6.7 points [95% CI 2.3 to 11.0]; P=0.0032] were found. Despite education and exercise focusing on improving physical activity level and improvement of symptoms, no spontaneous change in time spent being physically inactive occurred.

In study four (article IV) motivational text messages were delivered over a 6-week intervention period to assess if three weekly messages could decrease time spent being physically inactive in patients with knee OA measured with the SENS system. The study was designed as a randomized controlled trial including 38 participants allocated to either motivational text messages (n=19) or no-attention control (n=19). No statistical significant difference between the two groups was found in the average change of time spent being physically inactive (mean difference: 13.2 min/day [95% CI -41.0 to 67.3]; P=0.63), neither were there any difference in change between the two groups in overall symptoms (KOOS). Motivational text messages sent three times per week for a 6-week period did not change time spent being physically inactive in patients with knee OA.

Overall this thesis found that reliable and valid measurements of time spent being physically inactive in patients with knee OA can be achieved over longer periods of time, but current treatments do not spontaneously affect time spent being physically inactive. Treatments that includes focus on reduced time spent being physically inactive should be developed to help assist this patient group to achieve a healthier lifestyle.

DANSK RESUMÉ (DANISH SUMMARY)

Fysisk inaktivitet (sidde, ligge i løbet af dagen) er blevet et globalt problem. Folk bruger mere og mere tid på at være inaktive, hvilket forringer helbredt og øger risikoen for tidlig død. På trods af globale strategier for at stoppe denne tendens viser ny data, at den mængde tid der bruges på fysisk inaktivitet fortsat er stigende. En undergruppe i samfundet, der er særligt inaktive, er personer med knæartrose. Den inaktive livsstil menes at skyldes de primære symptomer; smerte og nedsat funktion. Hvis denne gruppe kan reducere deres totale tid brugt på inaktivitet, vil det forbedre deres generelle helbred og reducere risikoen for at udvikle følgesygdomme relateret til en inaktiv livsstil. Samtidig vil det reducere deres primære symptomer. Formålet med denne ph.d.-afhandling er derfor at undersøge, om mængden af tid brugt på fysisk inaktivitet bliver påvirket i forbindelse med standardbehandlinger (vægttab, træning) eller ved nye behandlinger, hos personer med knæartrose.

Studie 1 (artikel I) undersøgte reliabiliteten og validiteten af et nyt accelerometer (SENS-systemet) hos personer med knæartrose. En standardiseret (observant registreret aktiviteter) og semistandardiseret (deltager registreret aktiviteter) observationsprotokol blev udviklet til vurdering af validiteten, og gentagende målinger blev brugt til at vurdere reliabiliteten. I alt deltog 24 personer med knæartrose. SENS-systemet blev vurderet til at have høj validitet ved den standardiserede protokol, når data blev opdelt i to grupper; inaktivitet (siddende, liggende) og aktivitet (gennemsnitlig enighed på 97%, SD 7%). Ved dataopdeling i fire kategorier (inaktivitet, stående, gang, og anden aktivitet), var der den højeste enighed for inaktivitet (gennemsnit 99%, SD 3%) og den laveste for gang (gennemsnitlig 28%, SD 18%). For den semistandardiseret protokol blev der observeret en gennemsnitlig enighed på 92% (SD 5%) ved anvendelse af de to kategorier. Ved dataopdeling i fire kategorier, blev den laveste enighed opnået for andre aktiviteter (gennemsnit 42%, SD 36%) og den højeste for inaktivitet (gennemsnit 94%, SD 5%). Enigheden mellem de gentagne målinger var gennemsnitligt på 98% (SD 3%) ved anvendelse af de to kategorier. Ved opdeling i fire kategorier var den laveste enighed på 77% (SD 14%) for gang og den højeste for inaktivitet (gennemsnit 96%, SD 8%). Samlet set leverer SENS-systemet både valid og reliabel data på fysisk inaktivitet. Ved yderligere opdeling af data var der stor usikkerhed.

Studie 2 (artikel II), undersøgte om en spontan ændring i fysisk inaktivitet målt med SENS-systemet opstod hos overvægtige personer med knæartrose, der gennemfører et 8 ugers intensivt diætprogram. I alt blev der inkluderet 124 deltagere i dette observationelle kohortestudie. Et gennemsnitligt signifikant og klinisk relevant vægttab på 12,7 kg [95% CI -13,2 til -12,1; P <.0001] og en signifikant reduktion af symptomer, målt med ”knee injury and osteoarthritis

outcome score" (KOOS), blev fundet efter gennemførelse af diætprogrammet. Den gennemsnitlige tid brugt på fysisk inaktive var uændret (gennemsnitlig ændring: 8,8 minutter/dag [95% CI, -12,1 til 29,7], P = 0,41). Et intensivt vægttab på 8 uger fører ikke til spontane ændringer i tid brugt på fysisk inaktivitet, til trods for et klinisk relevant vægttab og signifikant reduktion af symptomer.

Studie 3 (artikel III) undersøgte om en spontan ændring i tid brugt på at være fysisk inaktiv, målt med SENS-systemet, forekom hos personer med knæartrose ved deltagelse i et uddannelses- og træningsprogram. Studiet var et pragmatisk kohortstudie, hvor deltagerne blev rekrutteret fra lokale klinikker, der tilbød uddannelses- og træningsprogrammet (GLA:D®). I alt blev 32 deltagere analyseret og ingen ændringer i den gennemsnitlige fysiske inaktivitets blev observeret (gennemsnitlig ændring: 16,2 minutter/dag [95% -15,7 til 48,1]; P = 0,31), men statistisk signifikante forbedringer blev fundet på KOOS-funktionen (gennemsnitlig ændring: 5,8 point [95% CI 1,9 til 9,7]; P = 0,0046) og KOOS-smerte (gennemsnitlig ændring: 6,7 point [95% CI 2,3 til 11,0]; P = 0,0032]. Til trods for at deltagerne modtog uddannelse i vigtigheden af at opretholde et fornuftigt fysisk aktivitetsniveau, deltog i ugentlig træning og forbedrede deres symptomer opstod der ikke nogen spontan forandring i den totale tid brugt på fysisk inaktivitet.

I studie 4 (artikel IV) blev motiverende tekstbeskeder leveret over en 6 ugers periode for at vurdere, om 3 ugentlige SMS-meddelelser kunne reducere den totale tid, der blev brugt på fysisk inaktivitet hos personer med knæartrose, målt med SENS-systemet. Studiet var designet som et randomiseret kontrolleret forsøg, hvor 38 deltagere blev allokeret til motiverende tekstbeskeder (n = 19) eller en ingen ting (n = 19). Der var ingen statistisk signifikant forskel mellem de to grupper i den gennemsnitlige ændring af tiden brugt på fysisk inaktivitet (gennemsnitlig forskel: 13,2 min/dag [95% CI -41,0 til 67,3]; P = 0,63). Der var heller ingen forskel mellem de to grupper på forandringer i nogle symptomer (KOOS). Motiverende tekstbeskeder, der sendes tre gange om ugen i en 6-ugers periode, ser ikke ud til at reducere mængden af tid brugt på fysisk inaktivitet.

Reliabel og valid måling af fysisk inaktivitet er muligt hos personer med knæartrose. Nuværende behandlingstilbud (vægttab eller træning) til personer med knæartrose ser ikke ud til at påvirke den totale tid brugt på fysisk inaktivitet. Behandlinger der kan reducere fysisk inaktivitet, bør udvikles for at hjælpe personer med knæartrose med at opnå en sundere livsstil og reducere deres symptomer.

ABBREVIATIONS

ACR	American College of Rheumatology
CVD	Cardiovascular diseases
FITT	Frequency, Intensity, Time, and Type of activity
GLA:D	Godt Liv med Artrose i Danmark
HDL	High-density lipoproteins
HOMA- β	Homeostatic model assessment to assess insulin secretory function
HOMA-S	Homeostatic model assessment to assess insulin sensitivity
KL	Kellgren and Lawrence grading scale
KOOS	Knee injury and Osteoarthritis Outcome Score
LDL	Low-density lipoprotein
MET	Metabolic Equivalent
OA	Osteoarthritis
RA	Rheumatoid Arthritis
SENS system	The SENS motion® activity measurement system including the sensor and app
TKA	Total Knee Arthroplasty
WHO	World Health Organization

INTRODUCTION

Patients with knee osteoarthritis (OA) spend more time on sedentary behaviour than the healthy population[1]. Too much time spent sedentary leads to an increased risk of developing non-communicable diseases such as high blood pressure, coronary heart diseases, type 2 diabetes, and increased risk of early death[2-5]. Providing a treatment for patients with knee OA with a focus on decreasing time spent sedentary is therefore of great importance as it can reduce the risk of developing co-morbidities and early death, irrespective of time spent on moderate-to-vigorous physical activity[2 6-8].

Current guidelines recommend exercise and weight loss as primary treatment for knee OA[9 10]. These interventions are well-documented with beneficial effects on the primary symptoms; pain, disability, and quality of life[11]. However, it remains unclear if a secondary decrease in sedentary behaviour occurs subsequently to these recommended treatments. There are suggestions that the daily physical activity level does not change suggesting that sedentary behaviour remains the same[12 13] however, knowledge in this area is scarce[14]. With the increasing age of the general population the number of patients with knee OA will increase[15]. Proper treatment of this patient group is therefore vital not only to reduce their pain and disability and improve quality of life but also to improve their overall health.

Measuring sedentary behaviour is best performed by use of accelerometry[16]. An accelerometer is a small device that is placed, most typically, on the thigh of the participants to register movement or lack thereof. Such devices are constantly upgraded and improve to further optimize their monitoring abilities and improve user-friendliness. Today, measuring sedentary behaviour pattern continuously for several weeks is possible[17]. However, this creates a challenge as most research on sedentary behaviour is based on questionnaires and accelerometer data only assessing daytime activity[18-20]. With the possibility to assess physical activity patterns for 24-hours per day the term sedentary behaviour does not quite cover the data available as sedentary behaviour is defined as sitting or reclined during awake hours, typically measured in a 10 to 14-hour window[21-23]. Total time spent sitting or reclined, during 24-hour measurement (not confined to awake hours) will therefore be referred to as time spent being physically inactive in this thesis.

The aim of this PhD thesis is to assess the reliability and validity of a new accelerometer, to describe and document the level of physical inactivity before and after participation in recommended treatments for knee OA (exercise or weight loss) and investigate if motivational text messages can decrease daily time spent being physically inactive in patients with knee OA.

Specific objectives of this thesis are to;

1) determine the construct validity and reliability of a daily activity measurement system (The SENS motion® activity measurement system) and its accompanying algorithm for physical activity estimations,
2) evaluate the spontaneous change in physical inactivity in relation to weight loss among overweight/obese individuals with knee OA,
3) evaluate the spontaneous changes in physical inactivity during a supervised education and exercise program in clinical settings, and
4) investigate if motivational text messages following an education and exercise intervention would reduce time spent being physically inactive in patients with knee OA.

BACKGROUND

Definition of terms

The terms physical activity, physical inactivity and sedentary behaviour are used with different definitions throughout the literature to describe different movement behaviours. This complicates the interpretation of results across the literature and makes direct comparisons difficult. In the general literature the term sedentary behaviour is used to describe time spent sitting or reclined during wakening hours (10-14 hours) [21-23]. In the studies in this thesis I have measured physical inactivity (sitting or reclined during 24-hours). To avoid confusion, the term physical inactivity will be used instead of sedentary behaviour although not always with identical definitions. Furthermore, the accelerometer used in the studies in this thesis also measures time spent standing and moving which cannot be directly compared to studies reporting on physical activity that often also focus on intensity of activity. The different terms will be explained in more detail, in the following sections. Table 1 gives an overview of the different terms and their definition. If any alternative definition of the terms is used it will be stated.

Table 1. Overview of the different terms and their definitions. METs stands for metabolic equivalent and quantifies the energy expenditure used in addition to the resting metabolic rate during a specific activity.

TERM	DEFINITION
Physical inactivity	Time spent sitting or reclined during 24-hours
Standing	Standing up, and perhaps doing small activities with the arms, such as doing the dishes
Movement	Anything else than standing or being physically inactive
Physical activity	All movements performed with moderate-to-vigorous intensity
Sedentary behaviour	Any waking behaviour characterized by an energy expenditure ≤1.5 METs while in a sitting or reclining posture

Physical inactivity

In this thesis time spent physically inactive is the primary outcome and is defined as time spent sitting or reclined during 24-hours. The reasons for using this term throughout the thesis is based on; the results from study I, the clinically relevance of this outcome, developments in accelerometery allowing for 24-hour recordings, and the transparency of this outcome.

Previous studies that refer to the term physical inactivity use it to categorise those that do not meet the recommendations on physical activity (time spent on moderate-to-vigorous activity)[24]. It therefore does not inform us about the time spent sitting or reclined but about lack of time spent on moderate-to-vigorous activity. This way of defining the term will not be used in this thesis.

A term used to describe similar behaviour is sedentary behaviour defined by the Sedentary Behaviour Research Network as:

"*...any waking behaviour characterized by an energy expenditure ≤1.5 METs [Metabolic Equivalent] while in a sitting or reclining posture.*"[25]

There is a small difference between sedentary behaviour and physical inactivity in this thesis as time spent being physically inactive includes 24-hour recordings of sitting or reclined behaviour whereas sedentary behaviour refers to 10-14 hour recordings of sitting or reclined behaviour, typically during wakening hours[21-23]. In this thesis the term physical inactivity will be used to describe the existing literature and the results from the four studies despite the difference in measurement periods (24-hours vs 10-14 hours).

Standing

Another term that will be used in this thesis to describe the results from the studies is standing, defined as standing up, and perhaps doing small activities with the arms, such as doing the dishes. This term was determined based on the algorithm developed for the interpretation of data from the SENS system[17]. In the main scientific literature standing would typically fall into the category of light intensity activity but not fulfilling all the criteria for that category (see definition of light activity under physical activity) and will therefore not be used as such.

Movement

Due to the measurement properties of the accelerometer used in this thesis the physical activity term was valued counterproductive as the identification of different types of movements were related to some uncertainty[17] and overall not fitting the typical definition of the categories physical activity[26] or moderate-to-vigorous physical activity[27]. The output *movement* was defined as anything else than standing or being physically inactive (sitting or reclined) and will be used in the studies to describe data.

Physical activity

Physical activity is defined by WHO as:

"*Any bodily movement produced by skeletal muscles that requires energy expenditure.*"[26]

When physical activity is mentioned in studies it often tells us something about time spent in specific activity intensities, typically moderate or vigorous and in rarer cases also light activity[8 28 29].

The different categories; physical inactivity, light activity, moderate activity and vigorous activity, are defined using Metabolic equivalents (MET). MET is a unit quantifying the energy expenditure used in addition to the resting metabolic rate during a specific activity. One MET is defined as the energy expenditure at rest, usually equivalent to 3.5mL of oxygen uptake per kg per minute[30]. METs are typically used to assess if guidelines are being met[29]. Across the literature METs have been widely used to categorise different movements from questionnaires or to subgroup accelerometer data[30]. The physical activity categories often using METs are; light activity (standing, doing the dishes, walking around the house), moderate activity (biking, walking), and vigorous activity (running, spinning)[30]. Light activities correspond to an energy expenditure of 1.6 to 2.9 METs. Moderate activity corresponds to an energy expenditure of 3.0 – 5.9 METs. Vigorous activity corresponds to an energy expenditure of ≥6 METs[30].

When mentioning physical activity in this thesis, it refers to the way most studies have used the term; all movements performed with moderate-to-vigorous intensity[6 29 31].

Physical activity is not to be confused with the term exercise. Exercise is defined by WHO as:

"*is a subcategory of physical activity that is planned, structured, repetitive, and purposeful in the sense that the improvement or maintenance of one or more components of physical fitness is the objective*"[32].

This distinction is important when interpreting the literature and when assessing if guidelines for physical activity is being met. You can be physically active without exercising but you cannot exercise without being physically active. Guidelines on physical activity do not state that you should exercise, just that you need to perform 150 minutes of moderate activity or 75 min vigorous activity per week. Exercise is an easy and structured way of ensuring that you reach the demands of "enough" physical activity. However, if you bike to work every day with a minimum of 20 minutes in each direction you can also meet these demands.

It is relevant to underline that a low amount of time spent being physically inactive does not correlate to a high amount of time spent being physically active as the category light activity is not accounted for. It is therefore important to discern between physical inactivity and physical activity as they are two different predictors for health.

Physical inactivity

Physical inactivity (sitting or reclined) has been identified to have adverse health consequences not only for cardiovascular diseases[33] but also for: anxiety[34]; dementia[35]; overweight[36]; some cancer types[37 38] and all-cause mortality[2 6] - even when controlling for physical activity level (time spent on moderate-to-vigorous physical activity)[2 4 6]. Not all types of physical inactivity behaviours seem equally detrimental for health; there are some indications that TV-watching time is worse than physical inactivity time in social contexts[39].

Current guidelines in Denmark and from the World Health Organization (WHO) focus on the importance of performing moderate-to-vigorous physical activity[32]. However, no specific recommendations exist on what is too much time spent being physically inactive. The WHO statement on physical inactivity is:

"*Inactive adults or adults with disease limitations will have added health benefits if moving from the category of "no activity" to "some levels" of activity. Adults who currently do not meet the recommendations for physical activity should aim to increase duration, frequency and finally intensity as a target to achieving them.*"[26]

This statement indicates that any movement is better than no movement but no concrete recommendation on what it takes to be an inactive adult is formulated. Neither is amount of time needed to achieve a health benefit stated, making it difficult for the lay person to apply this in his or her daily life. The Australian Government Department of Health guideline on physical inactivity recommend to:

"Minimise the amount of time spent in prolonged sitting. Break up long periods of sitting as often as possible."[40]

This is also the case in the United Kingdom guidelines for physical inactivity[41]. These recommendations are somewhat more precise than WHO but still general, emphasizing the need for additional research to help improve recommendations for future generations.

Too much time spent being physically inactive is a growing problem as the development of technology increases time spent in front of a monitor, both during work and leisure time[32]. At this point no specific strategies exist for the reduction of time spent being physically inactive in a global level. If the general population is to benefit from the knowledge that exists, specific guidelines for the maximum amount of time being physically inactive needs to be determined as it is for time spent physically active[32]. Public information and advice on this matter should be communicated as clearly as it is for physical activity[42] to help guide future generations.

How much is too much time spent being physically inactive?

The question is then, what is too much time spent being physically inactive? A meta-analysis investigating the association between daily sitting time and all-cause mortality found that less than 7-hours of sitting per day did not increase the risk of all-cause mortality[2]. For every hour of increased sitting time beyond the initial 7-hours, the all-cause mortality risk increased by 5%, even after adjusting for physical activity level[2]. Another meta-analysis investigating the effects of physical activity as a moderator for the damaging effects of sitting found that the negative effects of sitting could be reduced if a minimum of 60–75 minutes of moderate intensity activity was performed per day[6] (figure 1). However, if a minimum of 5-hours of the total sitting behaviour was performed in front of the TV, not even 60-70 minutes of moderate intensity activity per day could eliminate the detrimental effects[6] (figure 1). In terms of how much is too much sitting, it seems that a maximum of 7-hours of physical inactivity[2] with less than 5-hours of TV viewing time[6] is the maximum amount of time per day you can be physically inactive without affecting your health negatively.

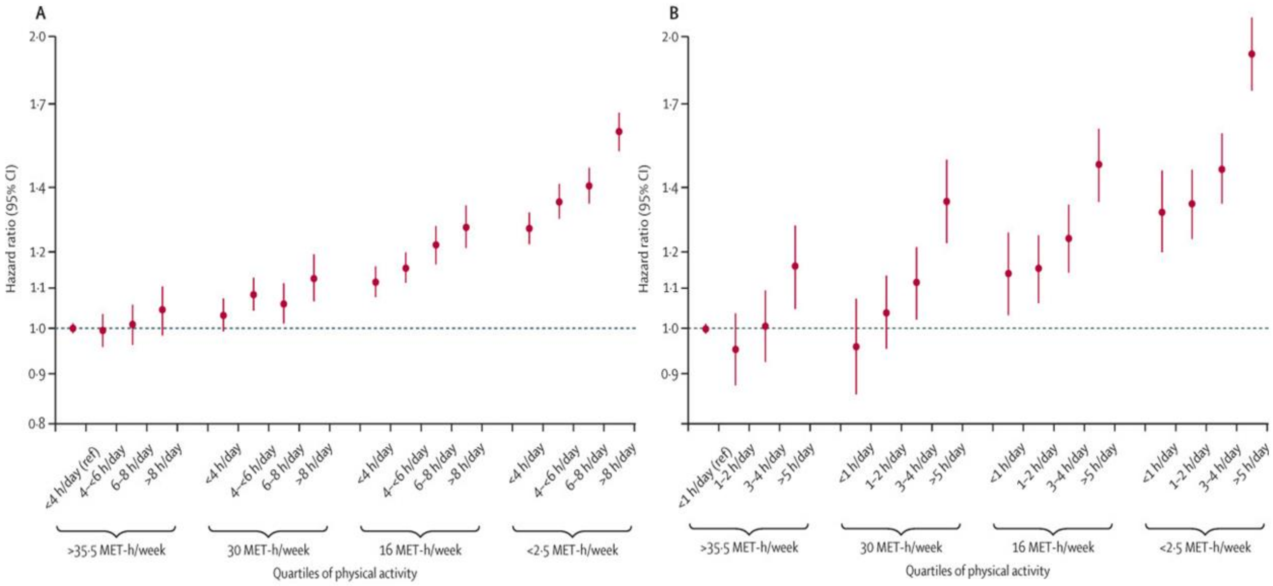

Figure 1. Modified from Ekelund et al. 2016, the Lancet[6]. Meta-analyses of the joint associations of sitting time and physical activity with all-cause mortality (A) and of TV-viewing time and physical activity with all-cause mortality (B). (A) Sitting time analysis, N=1 005 791. (B) TV-viewing time analysis, N=465 450. The reference categories are the groups with the highest levels of physical activity (>35·5 MET-h per week) in combination with <4 h/day of sitting (A) or <1h/day of TV-viewing (B). The median MET-h per week for the upper boundary for the first (lowest) quartile was 2·5 MET-h per week (equivalent to about 5 min of moderate intensity activity per day). Corresponding values for the second and third quartiles were 16 MET-h per week (about 25–35 min of moderate intensity activity per day) and 30 MET-h per week (about 50–65 min of moderate intensity activity per day), and the lower boundary for the fourth (top) quartile was 35·5 MET-h per week (about 60–75 min of moderate intensity activity per day).

If a person is too inactive and wishes to make a change, it is clinically relevant to know how large a reduction in time spent being physically inactive is needed to achieve health benefits. By switching 30 minutes of physical inactivity to light activity per day, a lowering of triglycerides (1.9%) and insulin (2.4%) levels is expected[43] as well as a 20% reduction in mortality risk at 5-year follow-up[44]. If 30 minutes of physical inactivity is switched with moderate-to-vigorous physical activity favourable changes in waist circumference (2.8% lower), HDL (high-density lipoproteins) cholesterol (4.6% higher), triglycerides (9.5% lower), glucose (1.3% lower), insulin (14.5% lower) and HOMA-S (insulin sensitivity) (11.5% lower) can be achieved[43]. In other words, the risk of developing non-communicable diseases, obesity and risk of dying is reduced if a 30 minutes reduction in daily time spent being physically inactive is achieved. In fact, a review has indicated that the most beneficial way of improving health is by reducing time spent being physically inactive, not by increasing time spent in moderate-to-vigorous activity[45]. Further, a reduction of 60 minutes in time spent being physically inactive has been suggested to reduce all-cause mortality[2 6].

The importance of reducing time spent being physically inactive in relation to health is still a fairly new discovery compared to the beneficial effect of regular physical activity[31]. The global strategies for better health currently focus on increasing time spent on moderate-to-vigorous activity[46] - not on reducing time spent being physically inactive.

Physical activity

The importance of regular and enough physical activity, especially moderate-to-vigorous physical activity, are old news, yet insufficient physical activity levels are still responsible for 6% of all premature death globally[27]. In fact, the WHO has issued a global strategy to help reduce the prevalence of insufficient physical activity by 10% in 2025[46] as insufficient physical activity is strongly linked to the development of non-communicable diseases[24]. Additionally, sufficient physically activity has beneficial effects on the onset of dementia[47 48], some cancer types[49-54], mental health and can help maintain a healthy weight[32 55].

A recent report on global physical activity with data from 1.9 million participants[56] revealed that approximately 25% of the global population do not meet the recommendation from WHO on minimum levels of physical activity needed to maintain a good health[32]. In fact, there has been an increase in people not meeting the recommended level of physical activity in high income countries (including Denmark) since 2001[56].

WHO recommends that adults should perform a minimum of 150 minutes of moderate aerobic physical activity throughout the week or a minimum of 75 minutes of vigorous aerobic physical activity[32]. Moderate aerobic physical activity for 150 minutes corresponds to spending 1.5% of the week’s total minutes performing some sort of activity such as biking or running slowly. In Denmark recommendations states that you should perform at least 30 minutes of moderate to high intensity physical activity every day, besides normal daily activities, and in addition also perform a minimum of 20 minutes of vigorous physical activity at least two times per week[57]. This corresponds to spending 2.5% of the total week’s minutes on moderate-to-vigorous physical activity.

In Denmark a total of 28.5% of the population (95% CI 22.7 – 35.0) do not meet the WHO recommendations for physical activity, despite both global and national reports emphasizing the importance of physical activity [32 57]. If the Danish standard for minimum amount of physical activity had been applied, this number would have been even higher further emphasizing the need for changes in the global populations physical activity habits.

Denmark is currently participating in the European network for the promotion of health-enhancing physical activity[42] and has done so since 2005. But the national level of physical activity is still too low.

How much is enough physical activity?

Based on the studies investigating the health-related problems arising from too little physical activity, following the guidelines from WHO will give an added health benefit[32]. In fact, is seems that there is a dose response relation between amount of physical activity and overall risk of all-cause mortality[28].

Studies on the impact of replacing physical inactivity with physical activity suggests that 30 minutes of additional light physical activity is enough to improve overall health with added benefits if the 30 minutes of additional physical activity are performed with a vigorous intensity[58]. Ultimately, it seems that some physical activity is better than none, and that the more time you can spend on physical activity, especially moderate-to-vigorous physical activity, the larger the health benefit (figure 1).

The detrimental effects of physical inactivity

Knee osteoarthritis

Both the onset and progression of knee osteoarthritis (OA) and level of disability can be linked to time spent being physically inactive irrespective of time spent on moderate-to-vigorous physical activity[59]. One of the explanations for the damaging effect physical inactivity has on the onset and progression of knee OA is that increasing body weight is linked to physical inactivity[36]. The risk of developing knee OA increases if you are overweight or obese and symptom severity seems to be linked to amount of overweight or obesity as well[60-62]. Secondly, time spent being physically inactive has been found to cause loss of cartilage volume in children[63] and immobile adults[64]. This suggests that time spent being physically inactive increases the risk of cartilage loss, which is linked to the development of knee OA[60]. Thirdly, lack of physical activity reduces overall muscle strength[65] and decreased strength increases the risk of developing knee OA[66]. Finally, physical inactivity is linked to increased inflammation[67] and a negative relation between development of knee OA and inflammation exist[68].

Metabolic heath

The negative association between low levels of physical activity or physical inactivity and health arises from the physiological responses to physical activity or lack thereof. When assessing health in high income countries Metabolic Syndrome biomarkers are often used[69]. The Metabolic Syndrome is a cluster of cardiovascular diseases (CVD) and diabetes risk factors including impaired glucose regulation, insulin resistance, hypertension, high blood lipids and central obesity appearing in conjunction with low levels of physical activity, physical inactivity, overweight and obesity[69]. Approximately 21% males and 15.5% females between 41-72 years have this condition in Denmark[70]. The Metabolic Syndrome biomarkers that are measured in studies are; waist circumference, systolic and diastolic blood pressures, high-density lipoprotein cholesterol, low-density lipoprotein (LDL) cholesterol, C-reactive protein, fasting triglycerides, plasma glucose, HOMA-S, insulin secretory function (HOMA- β)[43].

Time spent on physical inactivity is negatively associated with triglycerides, HOMA-β, and HOMA-S[43]. Strong associations between amount of moderate-to-vigorous activity and all the above-mentioned biomarkers have been found, except for blood pressure and LDL[43]. Performing light physical activity has a beneficial association with all biomarkers except systolic blood pressure[43]. Overall, in terms of reducing the risk of developing CVD or diabetes any change in overall movement pattern is of relevance whether it is a reduction in total time spent being physically inactive or an increase in amount of time spent on moderate-to-vigorous physical activity[43].

Mental health

Mental health can be positively affected by physical activity with exercise being the most commonly form of physical activity investigated[71]. Exercise in this relation is defined as a planned physical activity of moderate-to-vigorous intensity[32]. The specific mechanisms explaining why exercise is beneficial for mental health is limited, but both physiological and psychological factors are thought to play a role[71].

Specifically, for depression, regular exercise has been found to promote brain changes in the form of neural growth, reduced inflammation and feeling calm and well-being. Exercise is also known for the release of endorphins, which are powerful chemicals that makes you feel good. Furthermore, exercise also works as a distraction and gives the brain some “rest”[72].

Exercise has also been proven beneficial as an anti-anxiety treatment[71]. Besides the above-mentioned benefits[72], that also benefits the person with anxiety, exercise provides an attention condition allowing the brain to focus on a not-anxiety-provoking thing[72]. Furthermore, stress also benefits from exercise by reliving tension as well as resealing endorphins and creating some brain “rest” [71].

The amount of exercise needed to create these potential beneficial effects are individually determined, but evidence suggests that any mount of exercise is beneficial, and the more exercise performed the greater the benefit[73]. Interestingly, most studies have investigated the effects of exercise on mental health[71]. However, the link between physical inactivity and poor mental health suggests that simply reducing time spent being physically inactive can be beneficial[34 35].

Cancer

The physiological benefits of physical activity in relation to the risk of breast cancer and bowel cancer are thought to be; mediation of hormones, chemical messaging, lower inflammation and modulation of adipose tissue[74]. High physical activity levels are associated with a significant lower risk of developing these types of cancers[75]. The minimum amount of physical activity needed to achieve a change in these modifiable factors is hard to assess, but there seems to be a dose-response relation between risk of developing these types of cancers and physical activity[76]. Reducing time spent being physically inactive could potentially function as a preventive strategy[76].

Who are physically inactive?

In general, most of the Danish population spend too much time being physically inactive[77]. People especially predisposed to physical inactivity are those with disability[1]. Globally one of the largest groups that experience disability are people with OA[78] where knee OA is the most common lower limb OA conditions[79].

Direct comparisons of time spent being physically inactive between patients with knee OA and healthy age matched controls are scarce. The information that does exist indicates that knee OA patients spend more time being physically inactive than the healthy person[80] and that a negative relation between knee OA symptom severity and physical inactivity exist[23]. Studies investigating differences in total time spent on physical activity in patients with knee OA compared to healthy age matched controls have found mixed results[81-86].

The overall trend seems to be that the patients with knee OA are less physically active and spent more time being physically inactive than the healthy population albeit the difference may be small. Overall, this patient group needs to reduce their time spent being physically inactive and increase their time spent being physically active as this will benefit their overall health both mentally[34 35 73], physically[6 69 74] and limit the severity of OA symptoms[59-62].

Knee osteoarthritis

Epidemiology

Knee OA is one of the most common arthritic diseases with an estimated 3.6% of the global population living with the condition[87]. Knee OA is an age-related disease[88] and with the aging population[89] the number of persons with knee OA will increase. In Denmark approximately 60,000 patients with knee OA symptoms are referred to clinical practice each year [90].

Etiology and pathogenesis

The etiology is not fully understood but both genetic and non-genetic factors such as; gender, age, inactive lifestyle, obesity, overweight, occupation, joint injury, knee malalignment and low grade systemic inflammation are linked to the development of the disease[60 91].

Knee OA is a local joint disease that involves all structures of the joint including capsule, bone, ligaments, menisci, articular cartilage, bone, synovium, adipose tissue, and muscle[92]. The most commonly affected group is females aged >50 years, with the medial tibiofemoral compartment affected[93].

Diagnosis and classification

The diagnosis of knee OA is given if a person has three symptoms (pain, short-lived morning stiffness and functional limitation) and three signs on examination (crepitus, restricted movement and bony enlargement)[94]. In clinical trials the most commonly used classification criteria for knee OA are those developed by the American College of Rheumatology (ACR)[95]. Table 2 lists the classification criteria proposed by ACR and indicates that additional laboratory work can increase the specificity. Kellgren and Lawrence (KL) scoring is a measure on a radiograpic image of the affected knee on a scale from 0-4. The radiographic diagnose of knee OA is a KL grade score of ≥ 2 with osteophyte and possible joint space narrowing[96].

Table 2. The American College of Rheumatology criteria for the diagnose of knee OA. Adopted from Altman 1987[95].

Clinical[¤]	**Clinical and Laboratory**	**Clinical and radiographic**
Knee pain + at least 3 to 6 • Age > 50 years • Stiffness < 30 minutes • Crepitus • Bony tenderness • Bony Enlargement • No palpable warmth	Knee pain + at least 5 to 9 • Age > 50 years • Stiffness < 30 minutes • Crepitus • Bony tenderness • Bony Enlargement • No palpable warmth • ESR < 40 mm/h • RF < 1:40 • SF OA*	Knee pain + at least 1 to 3 • Age > 50 years • Stiffness < 30 minutes • Crepitus • + Osteophytes
92% Sensitive **75% Specific**	**91% Sensitive** **86% Specific**	**95% Sensitive** **69% Specific**

Abbreviations: ESR, erythrocyte sedimentation rate; RF, rheumatoid factor; SF OA, synovial fluid signs of OA.
*SF OA = clear, viscous, or white blood cell count < 2 000/mm^3
¤Alternative for clinical would be 4 of 6 for 84% sensitive and 89% specific

Clinical symptoms/patient complaints

Clinical symptoms are typically tenderness of the joint line, reduced movement, stiffness, instability of the joint, muscle weakness and crepitus[97] following the classification criteria from ACR (table 1). The most common complaints from patients with knee OA are pain and disability[97 98]. In the early stages of knee OA, the pain often occurs during specific activities, later rest or nightly pain also become a common symptom[97 99]. The disability complaints related to the disease include; reduced range of motion, impaired ability to perform household tasks, instability of the knee joint, and reduced strength[100].

Currently no clear relation between the clinical symptoms and radiographic changes has been found[101] and the pain triggering part of the condition is not fully understood[99].

Treatment for knee OA

Depending on the individual patient with knee OA a wide variety of treatments can be offered. Current guidelines recommend treatments that focus on symptom relief by exercise, weight loss, pharmacological treatments and in advanced knee OA surgery[9 102]. The primary treatment recommended is exercise and, for the overweight or obese patients with knee OA, weight loss[9 90].

Both treatment modalities are well document in terms of beneficial effect on the primary symptoms pain and disability[11 103].

A typical weight loss intervention consists of an intensive phase with education and in some cases meal replacement products during a period of approximately 8 weeks. After this, a period of several months follows where the participants have a few follow-up sessions to maintain or increase weight loss further, preferably for a year or more[104].

A typical exercise intervention lasts for 8 weeks with 3 exercise sessions per week[105]. The exercises performed varies from aquatic exercise to strength training to Thai Chi. All types of exercise interventions are beneficial in terms of reducing pain and improving function. Currently the most effective type of exercise intervention seems to be one that has a focus on either aerobic, quadriceps strengthening or lower extremity performance[106]. However, poor reporting standards of exercise interventions[105 107] limits our understanding of the roles that the individual components play in relation to optimal symptom relief.

Changes in physical inactivity following primary treatment

Hight amounts of time spent being physically inactive and limited time spent being physically active in patients with knee OA are thought to be caused by their primary symptoms pain (especially during movement) and disability[108 109]. Treatments that can provide symptom relief are therefore likely to lead to a spontaneous change in either time spent being physical inactive or physically active.

Links between obesity and physical inactivity[33] as well as limited physical activity[110 111] have been established. However, studies that have investigated changes in physical inactivity or physical activity following weight loss in patients with knee OA are scarce. One study that have investigated if a change occurs in time spent being physically inactive found that a weight loss above 4.5 kg over a 2-year period was associated with a minor reduction in time spent being physically inactive of 7.1 minutes/day. Whereas those that gained 4.5 kg or more over the 2-year period increased their time spent being physically inactive by 25.8 minutes/day[13]. This suggests that weight loss can change the time spent being physically inactive spontaneously, but further research is needed to explore this potentially positive relation between weight loss and physical inactivity.

There is limited evidence on the potential beneficial effects of exercise on physical inactivity and physical activity. The literature that exists mainly focus on changes in physical activity and have found a small change in self-reported physical activity after completing and exercise intervention[14 112]. Whether a spontaneous change in time spent being physically inactive following an exercise intervention occurs is unknown. A positive relation is thought to exist between completing an exercise intervention and time spent being physically inactive, as exercise has a positive effect on the primary knee OA symptoms, which are among the limiting factors found in inactive people including persons with knee OA[22 113 114].

Overall, little is known about the potential beneficial changes in time spent being physically inactive when participating in a weight loss or exercise intervention. Current knowledge indicates that no or small changes in physical activity may occur[13 14 112], but whether this is the same for physical inactivity is unknown. The primary treatments, weight loss and exercise, are not the sole interventions with beneficial effects on knee OA symptoms and potential beneficial effects on time spent being physically inactive. Interventions like self-management and education[115 116] or behaviour modification[14 117] for patients with knee OA are beneficial in terms of symptoms reduction and may have some beneficial effects on time spent being physically inactive.

Interventions targeting physical inactivity

Currently it seems that no studies have investigated the effects of targeted interventions to reduce time spent being physically inactive in patients with knee OA. Studies have investigated the effects of education or behavioural change strategies on time spent on moderate-to-vigorous physical activity[14 118]. The overall effect on time spent on moderate-to-vigorous physical activity after completing these interventions are moderate to low in the short term and low in the long-term. Two studies have investigated if total time spent physically active (light, moderate, and vigorous intensity) changes using education or behavioural change strategies with conflicting results[119 120]. One study found a significant increase on total time spent physically active[120] and the other found no increase in total time spent physically active[119].

Text messages as a behaviour modifier

As indicated in the previous section (interventions targeting physical inactivity) behavioural modification or education may have some effect on physical activity in patient with knee OA, but studies are scarce, and the effects are predominantly low to none[14 118-120]. Many types of intervention strategies can change behaviour[45 121 122], one of them is the use of a common and integrated communication form: text messages via mobile phones. Today most people own a mobile phone with text messages being one of the most frequently used services[123]. Using text messages to deliver an intervention have merits as it is a low-cost, easy to implement, and potentially effective treatment.

Changing behaviour is difficult and require an effort in the form of self-control, which is easily challanged[124], and this is why text messages may be effective. They can be employed on a regular basis assisting the individual with support reinforcing health behaviour[125] without the need for planning a meeting with a coach or counsellor.

A systematic review of systematic reviews found that for overall health improvement the majority of text-messaging interventions were effective at; addressing diabetes self-management, facilitate weight loss, increase physical activity and reduce physical inactivity, smoking cessation, and increasing medication adherence[126]. The individual characteristics of the included studies were too diverse to form a research based recommended intervention model, as the overall conclusion was based on multiple intervention setups covering a large range of conditions and a wide variety of people.

One study using a text-message intervention targeting change in time spent on physical activity in patients with knee OA reported no change in self-reported physical activity or objective measures total physical activity (both light, moderate, and vigorous) was found after 3 months. At 12 months both subjective and objective measures of total physical activity was in favour of the intervention group with a 24 minutes/day difference between groups[119].

The evidence indicates that text messages as an intervention for reducing time spent being physically inactive could have some merit in the treatment of patient with knee OA. However, whether a text-message intervention can reduce time spent physically inactive in patients with knee OA is yet to be determined.

Behaviour change theories

Changing behaviour is a complex process and many theories exist trying to conceptualise how best to change behaviour and the theories often overlap[127 128]. In research, wishing to change physical activity or physically inactive behaviour some of the most common theories used are: Theory of planned behaviour, social cognitive theory and transtheoretical model[45 122 129-131].

Theory of planned behaviour conceptualize that behaviour is guided by attitude, subjective norms and perceived behavioural control, which together form an intention that leads to a specific behaviour[132]. The strength of the intention is determinant for the chance of success, meaning that the stronger the intention, the more likely a person is to perform or change a specific behaviour[133]. Behaviour change techniques most often used when delivering a behaviour change intervention based on this theory are: persuasion, information, increasing skills, goal-setting, and rehearsal of skills[134].

Social cognitive theory is a theory that explains human behaviour in a reciprocal model in which personal factors, environmental influences, and behaviour constantly interacts. The concept of the social cognitive theory is that people learn through both own experiences but also from others and their actions. Behaviour change techniques most often used from this theory are: reinforcement, goal-setting, self-monitoring and behavioural contracting[125].

Transtheoretical model or stages of change propose that people are at different stages of readiness to adopt a healthy behaviour. The model can be used to assess the stage at which the individual is at, and use this in the planning of the intervention, thereby increasing the chances of success. The transtheoretical model as a heuristic model describes a sequence of steps: Precontemplation, Contemplation, Preparation, Action and Maintenance[135]. Behaviour change techniques that can be used when employing this model are: education, goal-setting, motivational sessions, self-evaluation, self-efficacy[136].

The above theories all consist of different elements, and interventions seldomly use all components; they rather use specific components of the main theories or base the design loosely on a theory[137 138]. There are some indications that health behaviour change has a greater chance of success if they are based in a specific behaviour change theory[129 139 140].

METHODOLOGICAL ASPECTS

Measuring physical inactivity

Assessing time spent being physically inactive are typically obtained by questionnaires or accelerometers[141]. Assessment of physical inactivity by use of questionnaire relies on the individual's ability to remember how much time they have spent on different activities during a predefined period back in time. Assessment of physical inactivity by use of an accelerometer is an objective way of assessing behaviour as the device is attached to the individual and records movements during the wear-time period[141].

The easiest and most common way of measuring physical inactivity is by questionnaire as it is a quick and low-cost method for obtaining data on a subject's habits especially in large population studies[16]. However, questionnaire-based data tend to over- or underestimation actual time spent on different behaviours[142 143]. Recent developments in technology have made measurements of physical inactivity by use of accelerometer feasible outside a laboratory and for longer periods at a time without too much interference with daily habits[16 141 144].

Accelerometer

An accelerometer is a device that measures the accelerations of the body during movement by capturing intensity, frequency and duration in relation to the position (in which plane)[145]. All this is done in a time stamped manner[145] allowing for a clear, objective way of assessing movement.

The device is typically attached to the thigh or lower back as this placement is close to the centre of mass and thus represents movement of the whole body[16 146].

The accelerometers used today typically measure acceleration in three planes (vertical, horizontal, and transversal)[146]. Based on the orientation of the accelerometer, the accelerations (the changes in the speed at which it is moved) and pattern of acceleration, a fairly precise estimation of the movement/activity performed can be made[144 147 148]. Figure 2 illustrates the raw accelerometer data outputs that comes from different movements performed in everyday life.

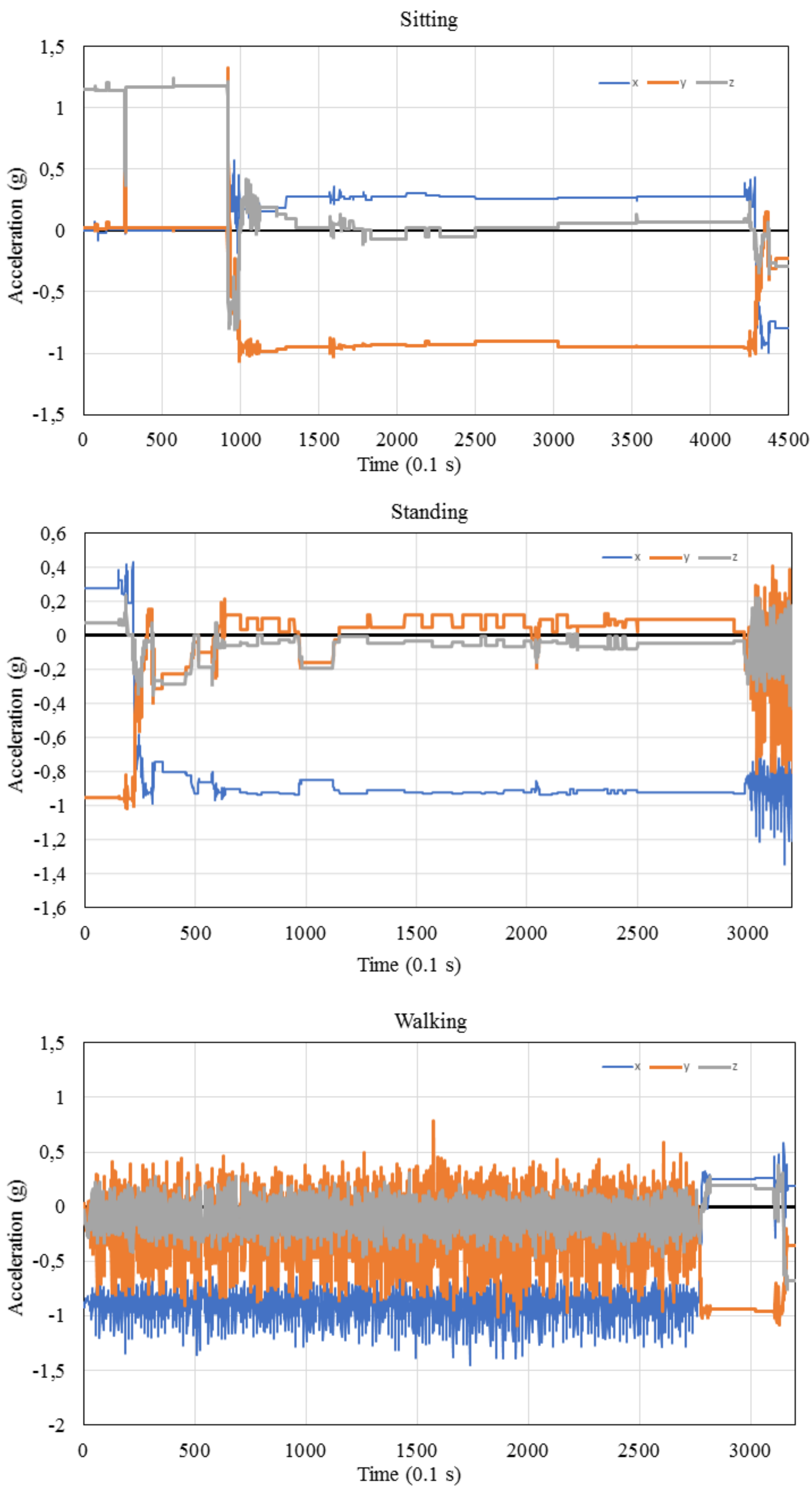

Figure 2. Raw data from this PhD thesis representing different types of movements measured with the SENS system. The three different lines on each graph represent the acceleration in the three planes.

Interpreting raw data like in figure 2 that is recorded for every 0.1 second during a measurement period is not feasible when measuring large groups for longer periods of time. To assist in interpretation of the recording, the accelerometer typically has a predefined algorithm that is applied to the raw data to reduce time spent interpreting data. Data is typically delivered with a numeric value—activity counts per unit of time—which can be translated into estimates of energy expenditure[149].

Energy expenditure is typically classified into two categories; moderate activity or vigorous activity[144]. These categories have been widely used to assess if a population meets the recommendation for physical activity level as these recommendations focus on the importance of performing different types of movement intensities for certain periods of time[32 57].

The assessment of intensity of movement is fairly precise if the same device is used but different accelerometers have different intensity thresholds making it difficult to compare data obtained with different accelerometers[144 146].

The SENS Motion® Activity Measurement System

The accelerometer used in this PhD thesis is the SENS motion® activity measurement system (SENS system). This accelerometer is a new, small, low cost, easy to use, water proof accelerometer embedded within a Band-Aid (Medipore™, 3M, Soft Cloth Surgical Tape on Liner). The SENS system consists of a triaxial accelerometer (50x21x5 mm, weight 8 g) sampling at 12.5 Hz with a range of ±4G that connects wirelessly (via Bluetooth) to a smartphone App (both Android and iOS) that automatically transmit data to a secure webserver when the phone is connected to a Wi-Fi signal. The raw data is recorded and stored on the accelerometer until connected with the app, then data is transmitted via the app to the secure webserver. Data is automatically transmitted form the accelerometer to the app every 10 seconds unless the app is out of reach, in that case 14 days of data can be stored on the accelerometer. The accelerometer has a battery lifespan of 20 weeks and with the waterproof feature it allows for long periods of recording without needing to change the accelerometer, provided the app is installed on the test person’s smartphone. The Band-Aid holding the accelerometer can be changed if necessary by the test person.

The raw data that is collected (figure 2) needs to be transformed into different movement categories. This is done by estimating orientation and acceleration of the accelerometer. Orientation is estimated by gravity vectors, defined as the average angle (with respect to gravity) of the average signal recorded over a 10 second period. The estimates range from 0 to $\pi/2$ (1.57) radians with 0 referring to a horizontal position and π/2 radians referring to a vertical position. The threshold between an upright (vertical) or seated/reclining position (horizontal) is 0.75 radians.

To assess the intensity of movement the device calculates a sum of the squared accelerations from all three axes (G^2) compensating for the static gravity component by averaging the maximum peak to peak amplitude in a 2-second window over a 10-second period. To differentiate between movements, the intensity of the acceleration is divided into three categories; below $0.3G^2$, between $0.3G^2$ and $1.3G^2$, and above $1.3G^2$. A value below $0.3G^2$ represents no movement and a value above $1.3G^2$ represents an intensity higher than walking.

In table 3 the different cut-off values is presented with the different categories. These categories are based on early observations done during algorithm development of the SENS system on healthy people. Ten-second intervals of transformed data can be extracted from the database allowing for summation of time spent in different movement categories.

Table 3. Algorithm for identification if the different body positions and movement[17].

	ORIENTATION < 0.75	**ORIENTATION >= 0.75**
ACCELERATION < 0.3	Seated/reclined	Standing
0.3 < ACCELERATION < 1.3		Walking
1.3 < ACCELERATION	Other activity	

Development of a new accelerometer system, albeit based on the same technology as used in other systems, require new assessment of reliability and validity as thresholds for different categories of movements are individual from accelerometer to accelerometer[149]. The results from the validity and reliability resting of the SENS system will be presented in chapter study I in this thesis.

Assessing validity and reliability of accelerometers

Validity

If a measurement is valid it measures close to what actually happened in the "real" world. The degree of validity is the probability that the device measures what it claims to measure. Different kind of validities exist; construct validity, content validity, face validity and criterion validity[150].

Construct validity assess to which degree a measurement measures a construct, an example could be to which degree an accelerometer measures the movement performed[150].

Content validity has limited use in clinical research as it typically is applied in educational context to assess if an education actually teaches participants in the subject of interest[150].

Face validity is a term used when assessing if a measurement actually expresses what we wish to measure. An example could be using a strength test (kg) to assess if a muscle has gotten stronger. If this measurement has high face validity it means that the what we, as a society, considers a valid expression of the outcome (muscle strength) can be expressed by how many kilos a person can lift/move. This type of validity assessment is typically performed when assessing different construct of a questionnaire[150].

Criterion validity is the most commonly used validity assessment in clinical research as is assess the agreement between two measurements. Typically, a commonly used measurement instrument is used as the standard to reach (gold standard) and results of this measurement instrument is compared to the new measurement instrument[150].

The type of validity assessment used in this PhD to assess if the accelerometer measured what we observed was construct validity as construct validity tells us whether the measured movements were equal to the observed movements[150].

If a measurement instrument has a high construct validity it means that what we observed equals or close to equals of what we measured[150]. To assess construct validity in accelerometers it is recommend that observations are performed in a controlled environment (structured recordings), in a timestamped manner to compare accelerometer data with observational data[151]. Furthermore, estimation of the device's ability to measure in non-controlled environments (outside the lab; semi-structured recordings) is equally important[151]. Here observations should be performed in the test persons home allowing for actives to be performed in their natural order[151].

The output obtained from the structured and semi-structured recordings should then be assessed in regards to the FITT concept; FITT stands for the Frequency, Intensity, Time, and Type of activity[152]. The individual FITT components applies to the overall description of movements and each of these components have different weights depending on, type of movement information, and population that is the desired target[151]. When assessing if patients with knee OA change their habitual behaviour for the better, total time spent being physically inactive (sitting or reclined) was deemed clinically relevant[2 4 6 59] and therefore sufficient as an outcome. This patient group is known to have an inactive lifestyle[80] that affects their knee OA health[59] and overall health negatively[2 4 6]. Achieving a reduction in total time spent being physically inactive would give a clinical meaningful outcome both to patients and clinicians.

Reliability

Reliability is a term used to assess if the same results are found using the same measurement under the same conditions but obtained from two or more different measurements. In clinical research inter-rater reliability, intra-rater reliability or test-retest reliability are often used[153]. Inter-rater reliability is used to assess if the same outcome is achieved by two or more raters using the same measurement. Intra-rater reliability is high if the same outcome is obtained when the same rater performs the measurement twice or more. Test-retest reliability is used to assess if the measurement delivers the same outcome when assessing the same results under the same conditions but at two different time points[153].

Assessing reliability in terms of the accelerometer used in this thesis is relevant as it is attached to the participants for long periods of time (several weeks) with a Band-Aid that only lasts between 1-7 days. This means that the participant needs to change the Band-Aid on their own with a high risk of moving the device from its original placement. If such a displacement of the accelerometer creates a discrepancy in the output, the reliability of the outcome is low. In other words, the device should give us the same results despite a Band-Aid change if the device is to be deemed reliable.

SUMMATION OF THE BACKGROUND AND RESEARCH QUESTIONS

Physical inactivity is becoming a common problem on a global scale[32]. Persons particularly disposed to this trend are those with disability such as patients with knee OA[59]. This group is thought to be predisposed due to their knee OA symptoms; pain and disability[23]. Reducing pain and disability symptoms are therefore thought to have an indirect and spontaneous effect on the amount of time spent being physically inactive. Evidence of this supposedly indirect effects of the primary treatments, weight loss and exercise, is limited and uncertain[13 112]. Understanding the level of influence the current treatments have on this patient group in relation to change in physical inactivity would improve the overall understanding of the treatments effects and could help optimizing treatment in the future.

Changing time spent physically inactive can be difficult and could require further motivation than the initial benefits that weight loss or exercise may give. Adding motivational text messages to a post-exercise intervention period could therefore potentially create a further reduction in time spent being physically inactive as text messages have been found effective at increasing time spent being physically active in previous studies[126].

Assessing changes in physical inactivity have largely been done by self-report[16]. However, this is known for underreporting actual time spent being physically inactive[142 143]. Over the last decades accelerometer technology has developed to become an easy, and low-cost method to assess physical inactivity[141 144].

The overall research question in this PhD thesis is therefore whether time spent being physically inactive is affected spontaneously by current treatments in patients with knee OA.

The specific research questions for each study that is sought answered are:

Study I: Is the SENS Motion® Activity Measurement System a reliable and valid tool to assess physical inactivity in patients with knee OA?

Study II: Does time spent being physically inactive change following a weight loss intervention for overweight/obese patient with knee OA?

Study III: Does time spent being physically inactive change following an education and exercise intervention for patients with knee OA?

Study IV: Can motivation text messages decrease time spent being physically inactive in patients with knee OA?

Each of the research questions will be sought answered in the individual studies, in the following thesis chapters.

STUDY I

Reliability and Construct Validity of the SENS Motion® Activity Measurement System as a Tool to Detect Sedentary Behaviour in Patients with Knee Osteoarthritis

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Note: this article uses the term sedentary to describe time spent sitting or reclined which will be referred to as time spent being physically inactive later in the thesis. Activity is used in this article to describe walking, and other activities, later the word movement will be used to cover this category.

STUDY II

Association between weight loss and changes in physical inactivity in overweight/obese individuals with knee osteoarthritis: an 8-week cohort study

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Running head: Weight loss and change in physical inactivity in knee osteoarthritis

STUDY III

Changes in Physical Inactivity During Supervised Education and Exercise Therapy in Patients with Knee Osteoarthritis: A Prospective Cohort Study

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Running Head: Exercise therapy and change in physical inactivity time

STUDY IV

Effectiveness of text messages for decreasing inactive behaviour in patients with knee osteoarthritis: a pilot randomised controlled study

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DISCUSSION

In this chapter a short discussion of each study, building on the already discussed subjects in the respective articles presented in the previous chapters, are followed by a collective discussion. This is accompanied by a section on the clinical relevance of the results, methodological considerations and overall strength and limitations.

Study I

A total of 24 patients with knee OA participated in this study, which assessed the construct validity and reliability of the SENS system and its accompanying algorithm for physical inactivity and specific movement estimations. The SENS system was deemed a reliable and valid tool for measuring physical inactivity, standing and movement in patients with knee OA.

The accelerometer delivered reliable and valid data on physical inactivity summed in minutes per day. Most studies assessing physical inactivity or physical activity uses METs to estimate time spent in different intensity categories[144 154]. When the goal is to assess time spent on moderate-to-vigorous physical activity this is relevant and useful. When the focus is on estimation time spent being physically inactive METs become irrelevant as the intensity of physical inactivity is the same for all types of inactive behaviour in all types of people[30]. If the SENS system had been able to estimate intensity of the different movements in a reliable and valid manner, using these as secondary outcomes would have been possible and interesting. If estimation of movement intensities had been possible it would had allowed for a more direct comparison with other studies. This would have provided a less hypothetical discussion though still having limitation regarding direct comparisons because the SENS system measures for 24-hours opposed to 10 to 14 awake hours in most studies[21-23].

The accelerometer was not estimated to have a high validity when assessing time spent walking or time spent on other activities. The general trend was that the upper limit of the agreement between observation and accelerometer output in the detection of walking was to “too low” and the lower limit agreement in detection of other activities was “too high”. This contradicting observation suggests that some of the other activities performed generated the same acceleration as walking thereby causing a misclassification of the data. When interpreting accelerometer data, the algorithm used two elements (acceleration and orientation) to categorize data. Perhaps an additional layer of interpretation should have been applied to the algorithm—patterns recognition[155]. This would have allowed for detection of different acceleration patterns that potentially could have increased the agreement between observations and accelerometer data[155].

When measuring the construct physical inactivity it is important to contemplate if the outcome, in this case total time in minutes per day, is relevant for this patient group (the FITT principle)[152]. Time spent being physically inactive was deemed relevant for this patient group as they spend most of their day engaged in inactive behaviour and because inactive behaviour irrespective of time spent being physically active have been found damaging to general and knee health[2 4 6-8 59].

Consequently, the SENS system was used in the subsequent three studies (Study II, II and IV) to assess time spent being physically inactive, with little emphasis on time spent in other activities.

Study II

This study included 124 overweight or obese patients with knee OA undergoing an intensive dietary intervention with meal replacements (800–1000kcal) for 8-weeks. Despite a substantial weight loss and a clinically relevant reduction in self-reported symptoms, no spontaneous change in time spent being physically inactive occurred. As mentioned in the chapter ‘Study II’ this could be a result of the diet restriction as the total calorie intake was just above starvation level[156]. Such low intake of calories could result in a feeling of low energy thereby reducing the likelihood of engaging in physical activity. However, the absence of an association between symptom reduction and change in time spent being physically inactive was still unexpected as severity of OA symptoms have been linked to decreased time spent being physically active[109] and amount of time spent being physically active is a predictor of future knee OA development[59]. Furthermore, the level of disability can be linked to an increased time spent being physically inactive[22 113] and pain can be linked to less time spent being physically active[157]. It was therefore surprising that no change in time spent being physically inactive was observed despite a large reduction in symptoms. The finding is similar to that of another study assessing changes in time spent being physically active (by self-report; questionnaire) concluding that changes in pain and symptoms at the end of an exercise intervention (3 months) and at 6 months was unrelated to a change in time spent being physically active[12].

The threshold for a clinical relevant change is suggested to be of 8-10 KOOS points[158]. A recent systematic review of the measurement properties of the KOOS instrument suggests that this might be too low a threshold for the clinically relevant change and they also conclude that the smallest detectable change was above 20[159]. The lack of spontaneous change in time spent being physically active found in this study, despite overall symptom reduction, might be explained by the fact that the changes on the KOOS questionnaire are too small. I might be that a larger change in symptoms could have had an influence in spontaneous change in time spent being physically inactive following a weight loss. However, the effect sizes of the weight loss and symptoms are comparable to previous studies on weight loss[160-162], and larger effects on symptoms from this kind of intervention is not likely.

A negative association between symptom severity and overall behaviour pattern (time spent being physically inactive and physically active) exists[23 81-86]. However, the lack of change in physical inactivity when symptoms are reduced could indicate that a reversal of the adopted behaviour does not occur spontaneously—in spite of symptomatic improvements. It seems that additional efforts are needed if a reduction in time spent being physically inactive is desired.

The lack of cohesion between self-reported change in symptoms and physical inactivity could be explained by the fact that the patients with knee OA, in addition to the two primary symptoms, also can experience fatigue[163] and can be affected by systemic inflammation[68]. An exercise and diet study found a relation between fatigue, chronic inflammation levels and physical activity with higher levels of fatigue and inflammation being related to lower levels of physical activity[164]. A decrease in these parameters was associated with a positive change in time spent being physically active. This could explain why a reduction in primary symptoms did not influences time spent being physically inactive. As fatigue and inflammation was not assessed in this study it is unknown if the weight loss intervention affected these too.

The results from this study coupled with existing literature indicates that there is no association between spontaneous change in physical inactivity or physical activity and change in symptoms in overweight or obese patients with knee OA when participating in an intensive weight loss intervention. Weight loss is generally health enhancing, and adding a specific intervention for reducing overall time spent being physically inactive could have potential additional beneficial effects on the knee health[59], overall health[2 4 6] and increase the chance of long-term weight loss success[13].

Study III

This study was designed as a pragmatic cohort including participants from local physiotherapy clinics that performed a widely used education and exercise program (Godt liv med Artrose i Danmark: GLA:D®)[112]. A total of 32 participants were analysed and no spontaneous changes in time spent being physically inactive were observed.

The lack of changes in time spent being physically inactive may be explained by the small, not clinically relevant, effect on function and pain measured by the KOOS questionnaire. Larger effects on symptoms might have changed the results as some studies have indicated that symptom severity and physical activity level are negatively related[109 113]. In study II large and clinically relevant reductions in function and pain (measured by KOOS) were observed, but time spent being physically inactive remained unchanged. This could indicate that larger effects of an education and exercise intervention would not induce spontaneous changes in time spent being physically inactive. Furthermore, the level of symptom reduction found in this study (study III) resembles that of other similar interventions[165-168]. Achieving a larger symptom reduction from interventions like the GLA:D® seems unlikely as the GLA:D® database[157 169] and existing literature of over 100 exercise trial consistently show similar low to moderate effects on knee OA symptoms[9-11]. Application and interpretation of the KOOS questionnaire in clinical research (and practice) is difficult as there are discrepancies between stated minimal clinically important differences (MCID) (between 8-10 KOOS points[158]) and the suggested measurement error for the KOOS instrument (above 20 for OA populations)[159]. The reported measurement error (>20 points) of KOOS in knee OA patients is based on one study[170] and the MCID for knee OA has not been established scientifically. The discrepancy means that the level of a clinically relevant change measured can be too low to allow for a distinction between true change and change due to performance or measurement error[171].

The difference between the intervention types in study II and study III could potentially have had different influences on time spent being physically inactive as the education and exercise intervention included information and encouragement to help participants become more physically active[112]. An intervention that targets physical activity through education and exercise was thought to have a greater indirect effect on time spent being physically inactive than a dietary intervention, as it teaches the patients the importance of moving enough and how to move without pain[112]. Despite these potential benefits from the intervention no change occurred.

Overall, it seems that the education and exercise program (GLA:D®) alone is unable to spontaneously affect the time spent being physically inactive emphasizing the need for additional treatment options to help this patient group reduce their time spent being physically inactive.

Study IV

This randomised controlled trial included 38 participants randomised equally (1:1) to an intervention group (motivational text messages) or control group found that motivational text messages delivered three times per week for 6 weeks subsequent to completion of a GLA:D®

program had no effect on time spent being physically inactive compared to a no attention control group.

The lack of change, both between groups and within groups (table 2 in chapter: study IV) could be explained by the simplicity of the intervention. The original idea was that the participation in an education and exercise program (GLA:D®) that is supposed to result in reduced pain, improved function, as well as giving the individual knowledge of the importance of moving regularly and therapeutic guidance in exercise that are knee friendly and health enhancing[112], would provide the tools needed to spend less time being physically inactive with just a small additional effort. The motivational text messages were meant to be supportive and reinforce healthy behaviour[125] to further reduce time spent being physically inactive. The idea for the intervention was based upon other interventions promoting physical activity in persons with disability as they typically employ social support with beneficial effects on the overall physical activity level in different groups[131] and physical inactivity[45].

The lack of reduction in time spent being physically inactive found in this study was disappointing as this intervention would have been a low cost and easy to implement intervention that could help this patient group improve their knee OA and overall health[2 4 6-8 59].

The study was designed to be able to detect a group difference of 60-minutes in total time spent being physically inactive. This can seem as a rather large difference, as previous text message interventions show smaller changes in time spent being physically active[118 126]. However, the 60-minute difference was based on the indications that a reduction of 60-minutes inactive time daily may have a significant impact on all-cause mortality[2 6]. Furthermore, this intervention was placed after completing a GLA:D® program, which was thought to give an added benefit as the GLA:D® program contains two components, education on the importance of being physically active and exercise sessions with a physiotherapist and reduces overall symptoms[112]. This was thought to give a beneficial start for the participants in this study, with a potential large (60 minutes) effect on total time spent being physically inactive. The assumption and study design were made before knowing the results of study II and study III.

Interventions to reduce physical inactivity are scarce and the few studies that exist have focused on increasing time spent physically active and report low to moderate effects[14]. If this intervention had been successful it would have been an easy addition to an already implemented treatment in the Danish health-care system (the GLA:D® program).

Changing behaviour, and in this case physical inactivity, appears to be no easy fix and alternative interventions are warranted. An intervention type that have had some success at increasing number of steps per day or time spent in moderate-to-vigorous activity are wearable activity trackers[172]. The basis of such devices is the same as the accelerometer used in this study allowing for real time recording of behaviour with the possibility for 'live' reports or feedback to the individual. This allows for constant personal feedback on physical activity or step counts employing a useful behaviour change strategy—self-monitoring of behaviour[125 131]. The SENS system is currently developing an App that would allow for individual goal setting and feedback. Designing an intervention that uses the accelerometer technology, not only to inform research, but also the patients, could potentially be effective at reducing time spent being physically inactive[172]. An intervention design that includes an accelerometer and feedback mechanism, such as an app, may allow for improved self-efficacy[125] on a regular basis and the possibility for self-monitoring giving positive reinforcement[125 131]. Furthermore, a few meetings with a therapist and/or patient peers might allow for social support by education[45] and increase the likelihood of success.

The rational of such an intervention is based on research investigating the effects of behavioural change strategies in other patient groups or with another outcome (time spent physically active)[45 126 130]. Overall it seems that multicomponent interventions using feedback from the app, goal-setting and therapeutic contact are effective interventions[130]. Whether the same strategies are effective at reducing time spent being physically inactive in patients with knee OA still needs further investigation[118].

Collective discussion

The lack of reduction in time spent being physically inactive in study II and III could be because the interventions inability to reverse the chronic disease; it "merely" reliefs symptoms. Despite pain reduction and improved function, the patients still have "bad" knees that limits their mobility. A treatment that removes the diseased knee joint, such as total knee arthroplasty (TKA), may be more effective at reducing time spent being physically inactive.

TKA is typically performed on patients with end stage knee OA as this is the most effective treatment for this group of patients[173]. During TKA surgery the diseased knee is replaced, thereby effectivity removing the chronic disease. TKA have larger effects both in the short and long-term on all knee OA related symptoms compared to exercise or weight loss[90]. It is therefore possible that this group of "former patients with knee OA" show a spontaneous reduction in time spent being physically inactive or increase their time spent being physically active, because the primary limitation (the knee) have been removed. Two systematic reviews have assessed both patient reported outcome and accelerometer data up to one year after a TKA and found that total time spent being physically inactive[174] and time spent being physically active[175] did not change. Despite removing the suspected main cause of their inactive behaviour, it did not facilitate spontaneous changes in physical inactivity nor physical activity. This further supports the results in this thesis—that the intervention provided works when assessing the core outcomes (body weight, pain and function), but the effects does not seem to spread further than that (no spontaneous change in time spent being physically inactive).

There exist many interventions designed to reduce time spent being physically inactive with different impacts[45]. The most promising interventions seem to be those that specifically targets physical inactivity using self-monitoring, employ problem solving and changes in the social or physical environment[45]. The mentioned elements of a successful behaviour change intervention can stem from several behavioural change theories (see behaviour change theories section) and overall it seems that the common denominator is that standing on a specific theory in the development of the intervention will increase the chance of success[129 139 140]. Using a behavioural change theory when planning study IV would likely have increased the chance of success of the intervention. As for study II and III the concept was to investigate if spontaneous changes in time spent being physically inactive occurred. Adding additional elements from behaviour change theories might have altered the outcome but would also have conflicted with the original purpose.

A patient group with similar pain and disability problems as the patients with knee OA are patients with rheumatoid arthritis (RA). RA is an inflammatory condition that affects most joint in the body and in contrast to OA medication can effectively halt the structural destructions of disease[176-178], although pain and disability may be a constant factor[179]. A randomised controlled trial of 150 patients with RA found that motivational counselling and text messages over a 16-week period reduced sitting time by 1.61 hours/day[180]. This suggests that a proper intervention with a clear target can be successful. The intervention group also reported significantly improvements in pain, function and quality of life. This study suggests that a behaviour change intervention in a group not too dissimilar to patients with knee OA, can be effective at reducing time spent being physically inactive. It also seems possible to achieve a reduction in physical inactivity that not only is significant but also clinically relevant for the overall health[2 4 6] and condition specific symptoms.

Clinical relevance

The results from study II and III indicates that the treatment that we provide today as primary treatment for patients with knee OA is effective at their primary goal; reducing pain and improving function. However, a secondary effect on time spent being physically inactive does not seem to occur.

In study II, III and IV inconsistencies were found between self-reported time spent moving and actual measured time spent moving. This lack of consistency between what the patients report and what occurs is not new knowledge[142 143]. The development of accelerometers such as the one in the SENS system allows us to investigate what the patient does when they are out of sight and creates the possibility for health-care professionals to adjust treatments according to objective data rather on patient reported experience. This may allow a better adjustment of treatments as the information quality is improved. The negative effects of the added information the accelerometer can provide is the typical lack of cohesion between what the patient perceives and what actually happens[142 143]. This can be mitigated by providing direct feedback to the patients.

Methodological perspectives

Study design

Study II and III were designed as observational cohort studies, which is a limitation as the results cannot confidently say something about causality. Randomised trials of high quality are the gold standard for assessing causal relationships. However, in randomised studies of weight loss and exercise, blinding is an inherent and difficultly managed source of bias, which reduces the RCT quality and assessment of causality. On the other hand, the results of study II and III are quite robust and the observed lack changes are quite confidently estimated. Hence, the lack of spontaneous changes in physical inactivity is quite confidently established in these studies.

Study IV was designed as a randomised controlled trial, which is a strength as causality can be assessed. However, the sample size was smaller than originally planned and a larger sample would have allowed for a more robust conclusion. On the other hand, the uncertainty of the estimated group difference was small and increasing the sample to the target of 50 participants would most likely have little effect on the estimated mean change in time spent being physically inactive.

Accelerometer as outcome

The potential beneficial effects of wearing the accelerometer should not be neglected as we cannot say anything about the participants' behaviour before the accelerometer had been placed on the participants. If the participants' physical inactivity level had been affected by wearing the accelerometer it would be attributable to the Hawthorne effect[181]. Such an effect would be expected to be detectable as a spontaneous change in outcome—at least during the first period of measurement when awareness was high. However, this was not the case (figure 3, next page). The lack of such an effect may be attributed to the discrete design of the accelerometer. It is small and can fit under clothes without being detected and does not need to be removed during bathing reducing the inconvenience related to wearing a 24-hour monitoring device. Further, studies that have investigated the potential influence of wearing an accelerometer concluded that they had little to no influence on the behaviour pattern[182 183]. Altogether, this could indicate that the participants' habitual physically inactive behaviour is not too different from that measured during the study participation.

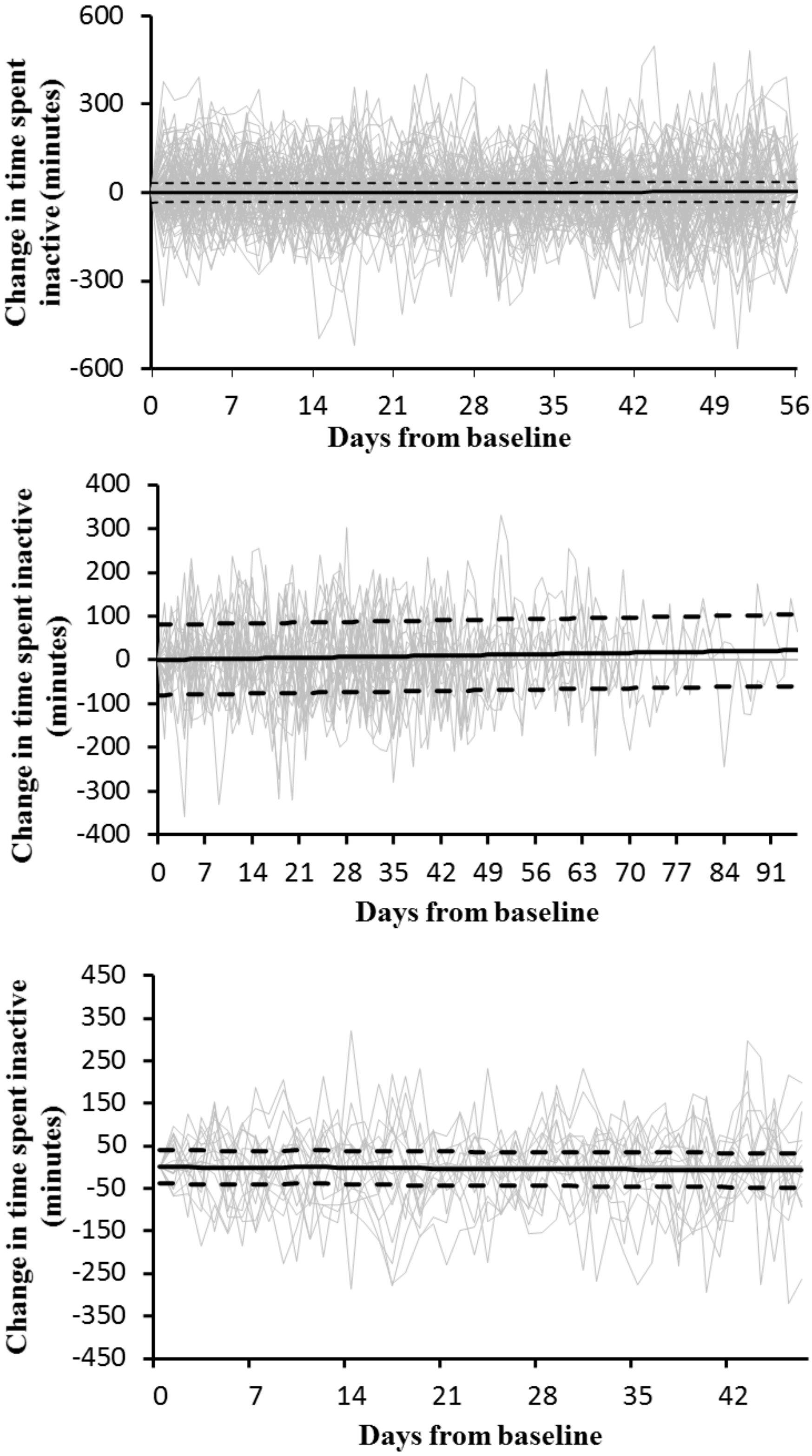

Figure 3. Illustration of the daily variations in time spent being physically inactive in study II (top graph), study III (middle graph) and study IV (bottom graph).

Validity assessment

Assessment of validity in study I was with a focus on the construct validity, i.e. to which degree a measurement measures a construct[150], in this case time spent in different activities, including physical inactivity. Construct validity was assessed as the percentage of agreement between observed (or self-reported) time spent in the different activities and the algorithm-based categorisation of the same activities. The observer/self-report included recorded time stamps (HH:MM) of the beginning and end of the 4 activity types (inactivity (reclined + sitting), standing, walking, other activities). The SENS system algorithm categorized the continuous data into the same activities in 10 second epochs. The time interval of a given activity in the observation/self-report was compared to the same time interval from the algorithm, and the percentage of agreement between the observed/self-reported activity and the algorithm was calculated for each observed/self-reported activity. As such the observation/self-report was considered a gold standard for assessing construct validity.

However, the different properties of validity can be interpreted differently[184] and it can therefore be discussed if the construct validity was assessed in study I. The Consensus-based Standards for the selection of Health Measurements Instruments (COSMIN) group have defined construct validity as:

> *"The degree to which the score on HR-PRO [health related patient reported outcome] instrument are consistent with the hypotheses (for instance with regard to internal relationships, relationships to scores of other instruments, or differences between relevant groups) based on the assumption that the HR-PRO instrument validly measures the construct to be measured."*[171]

While this definition related specifically to patient reported outcomes, the definition may be applied to other outcomes. If applied to the validity assessment of the SENS system, the property construct validity is incorrectly applied. Instead the property criterion validity should have been used to describe the type of validity assessment performed in study I. Criterion validity is defined by the COSMIN group as:

> *"The degree to which the scores of an HR-PRO instrument are an adequate reflection of a 'gold standard'."*[171]

This inconsistency between definition of properties when assessing validity can cause confusion and interpretations difficulties[184 185]. Furthermore, depending on the type of outcome that is to be measured, the type of validity property assessed previously may not hold true when using an instrument to assess a different outcome[184].

In study I only one validity property was assessed because this property was deemed most relevant when wishing to determine the SENS systems validity regarding the outcome time spent in different activities including being physically inactive. Other important properties, using the COSMIN taxonomy, such as responsiveness, construct validity or structural validity could also have been relevant properties to assess[171] to increase the generalizability of the SENS system to other components of the outcome time spent being physically inactive. However, the study design and properties of the data structure was not suitable for assessing all measurement properties. Finally, the assessment of the construct/criterion validity was deemed very relevant as measurement of physical inactivity is considered important based the known detrimental effects of physically inactive behaviour[2 4 6].

Placebo and blinding

In study IV the participants were not blinded to the purpose of the study nor to which group they were placed in as soon as the received the text messages. Blinding of participants might have been a possibility if sham text messages had been provided to the control group. The sham text messages would have had to contain some sort of information about physical activity to “deceit” the participants. Blinding the participants to the study purpose would be another option but that is considered unethical. Nevertheless, providing a sham intervention instead of a no attention control group would have improved the methodological quality of the study, by reducing the risk of performance bias[186]. Thus the lack of blinding may have biased the results[186], however as no change in any way was observed it is unlikely.

Ethical considerations

Approval from the Health Research Ethics Committee was sought for Study I-IV, but the committee ruled that the measurement of time spent being physically inactive during treatment was thought to be non-invasive and the studies were deemed exempt from health research ethical approval. The Danish Data protection Agency approved each study before commencement and all study protocols were registered in international databases. These approvals and registrations were performed to ensure transparency of the research and ensure patient integrity and safety.

The methods used to collect data on time spent being physically inactive were non-invasive and the only potential risk in participating in the studies was that the skin could get irritated or have an allergic reaction to the Band-Aid adhesive. If skin irritation occurred the Band-Aid was moved to the opposite thigh. If an allergic reaction was reported participation in the study would be stopped—this did not occur.

Knowledge among participants that were being monitored for physical inactivity may have induced a spontaneous decrease in time spent being physically inactive independent of treatment, which could be considered a threat to the results. However, this is not considered a health research ethical problem as decreased in time spent being physically inactive is recommended—not only for the population being studied but for the general population[26 40 41].

General strength and limitations

The limitations pertaining to the individual studies have been outlined in the individual chapters (see chapters: study I, study II, study III and study IV). A general limitation in this thesis is the applicability to other groups of patients with knee OA. As mentioned earlier, the number of participants were small, and all participants were included from the central and rural areas of Copenhagen. Whether the same results would occur in other patients with knee OA located in other places of the country or in other countries is unknown. As the definition of knee OA in clinical trials are largely the same across countries (ACR criteria is typically used)[11] reducing the likelihood of achieving a different result in another knee OA population.

The measurement of physical inactivity in study II, III and IV was commenced after inclusion in each study. Whether this reflects “real” behaviour patterns for the included participants is difficult to ascertain. Participants that volunteered already had decided for a change in behaviour, either by reducing food intake or by exercising. Whether this affected the results by changing the baseline physical inactivity level is uncertain. However, despite the possibility of a changed behaviour pattern at baseline, time spent being physically inactive was still (too) high. It was therefore possible to reduce time spent being physically inactive significantly during the intervention period.

The changes in time spent being physically inactive in study III and IV was based on an average of three days recording, as this is recommended as a minimum to estimate average behaviour[148]. This might be a too short period to accurately estimate changes in time spent being physically inactive[187]. Figure 3 illustrates the day-to-day variation in time spent being physically inactive and the overall trend was toward no change reducing the probability that adding additional days in the estimates of average time spent being physically inactive would change the results in study III and IV.

The last 3-day period of the measurements was close to or at the actual end of the individual interventions, therefore it is not possible to say anything about potential changes in time spent being physically inactive in the period after the intervention. It may be that the participants in study II, III and IV would have decreased time spent being physically inactive over time. However, this scenario seems unlikely as interventions assessing short and long-term effects on physical inactivity and physical activity in general finds that the best effects of an intervention is achieved at the end of the intervention[14 172 188].

Finally, all participants in the studies were volunteers with a desire to participate in the individual studies. This may represent selection bias[186] and is something that is unavoidable when depending on volunteers.

The strength of each study has been highlighted during the discussion of the individual studies and in chapter: study I, study II, study III and study IV. A strength across all the studies is the objective measurement method used. The accelerometer measured continuously during the entire intervention period reducing the likelihood of the patients changing their behaviour because they have to use the accelerometer for a short period of time[183]. Figure 3 illustrates data from study II, III and IV. It is evident by the continuous measurement that daily variations in time spent being physically inactive does occur and the overall change is null. The fact that the accelerometer was worn non-stop reduced the chance of the measurement being an expression of a specific period, strengthening the results in this thesis.

Study II and III were designed to investigate if spontaneous changes in time spent being physically active in patient with knee OA occur during current standard treatments. The use of already recommended and implemented treatments to assess changes in time spent being physically inactive increases the translational value of the studies. In study II and III the participants' main reason for participating in the interventions were to either lose weight or to exercise - not to reduce time spent being physically inactive. It is therefore likely that the study results resemble the general tendency for patients with knee OA that complete a weight loss intervention or an education and exercise intervention.

The effects of a treatment can be affected by the context[189]. Context effects are a multifactorial concept involving several elements such as physical environment, characteristics of participants, practitioner, and interaction between participants and practitioner[190-195]. Study III was placed in a clinical setting with a minimum of study visits, low additional contact with the participants and inclusion criteria matching those of the clinics to avoid influencing the context of which the intervention was delivered. This should reduce the risk of the outcome being influenced by the study setup. Likewise, study II was a part of a larger study with a pre-planned dietary intervention period. To avoid influencing the context the visits was placed in connection with the main study visits already planned. Study IV was also conducted with focus on having a minimal influence on the participants, other than what the motivational texts would provide, to increase the strength of the results in this study. Overall, this should increase the likelihood that the results found in the different studies (II, III, and IV) can be attributed to the interventions with limited influence from the context created by the study.

CONCLUSION

Objective estimations of physical inactivity and physical activity have improved, both in cost and measurement precision creating a possibility to better estimate time spent on specific behaviours within different groups in the population. Especially estimation of time spent being physically inactive has become a relevant and useful outcome as the global trend is that time spent being physically inactive is increasing steadily, ultimately having detrimental effects on the global and individual health. Some groups are predisposed to become inactive and helping them as part of the primary treatment is likely to become an important aspect of future treatment. Results from this thesis suggest that accelerometers are valid and reliable tools to assess time spent being physically inactive in patients with knee OA over longer periods of time. This thesis also found that the overall time spent being physically inactive was unaffected by the interventions currently recommended. Finally, a simple and cheap additional treatment in the form of general physical activity advice text messages was assessed as a potential add on to an existing treatment. However, no reduction in the time spent physically inactive occurred. The results of this thesis emphasise the need for additional treatment components or strategies that specifically targets physical inactivity to optimise the overall health of this patient group.

PERSPECTIVE FOR FUTURE RESEARCH

This thesis provides new data on how time spent being physically inactive changes during current treatments of patients with knee OA. The results underline that focus on the side effects of living with knee OA is important (increased time spent being physically inactive).

Current priorities in OA research are on increasing long-term adherence to treatment and investigation if potential benefits can be found in combining treatments[196 197]. This information coupled with the indications from this thesis, suggest that future research should include a focus on finding a behaviour change intervention that reduces time spent being physically inactive. This intervention should then be added to existing treatments options, thereby creating better all-round treatment for patients with knee OA.

Living with the chronic disease knee OA seems to be a lifelong process of adjusting and adapting different treatments to minimize the disease progression and keeping pain and disability at a minimum while maintaining a healthy lifestyle. Continuing exploring how best to treat the different symptoms and secondary effects of living with knee OA is needed as the age in the population is increasing[198] thereby increasing the number of people living with knee OA as well[79]. This creates a need for better treatment options for this patient group to improve quality of life for the individual and reduce the burden on society[15].

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APPENDIX

Appendix 1. Study protocol from study II.

Appendix 2. Unadjusted ANCOVA analysis from study III.

Appendix 3. The motivational text messages in Danish and English from study IV.

Appendix 4. Sensitivity analysis from study IV.

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The declarations are presented in study order starting with study I.

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This declaration concerns the following article:
Reliability and Construct Validity of the SENS Motion® Activity Measurement System as a Tool to Detect Sedentary Behaviour in Patients with Knee Osteoarthritis

The PhD student's contribution to the article: *(please use the scale (A,B,C) below as benchmark*)*	(A,B,C)
1. Formulation/identification of the scientific problem that from theoretical questions need to be clarified. This includes a condensation of the problem to specific scientific questions that is judged to be answerable by experiments	C
2. Planning of the experiments and methodology design, including selection of methods and method development	C
3. Involvement in the experimental work	C
4. Presentation, interpretation and discussion in a journal article format of obtained data	C

**Benchmark scale of the PhD student's contribution to the article*		
A. refers to:	*Has contributed to the co-operation*	*0-33 %*
B. refers to:	*Has contributed considerably to the co-operation*	*34-66 %*
C. refers to:	*Has predominantly executed the work independently*	*67-100 %*

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2. Planning of the experiments and methodology design, including selection of methods and method development	B
3. Involvement in the experimental work	C
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Title of PhD thesis:
Physical inactivity and current treatments of knee osteoarthritis

This declaration concerns the following article:
Changes in Physical Inactivity During Supervised Exercise Therapy in Patients with Knee Osteoarthritis: A Prospective Cohort Study

The PhD student's contribution to the article: *(please use the scale (A,B,C) below as benchmark*)*	**(A,B,C)**
1. Formulation/identification of the scientific problem that from theoretical questions need to be clarified. This includes a condensation of the problem to specific scientific questions that is judged to be answerable by experiments	C
2. Planning of the experiments and methodology design, including selection of methods and method development	C
3. Involvement in the experimental work	C
4. Presentation, interpretation and discussion in a journal article format of obtained data	C

**Benchmark scale of the PhD student's contribution to the article*		
A. refers to:	*Has contributed to the co-operation*	*0-33 %*
B. refers to:	*Has contributed considerably to the co-operation*	*34-66 %*
C. refers to:	*Has predominantly executed the work independently*	*67-100 %*

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DECLARATION OF CO-AUTHORSHIP

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Title of PhD thesis:
Physical inactivity and current treatments of knee osteoarthritis

This declaration concerns the following article:
Effectiveness of text messages for decreasing inactive behaviour in patients with knee osteoarthritis: a pilot randomised controlled study

The PhD student's contribution to the article: *(please use the scale (A,B,C) below as benchmark*)*	**(A,B,C)**
1. Formulation/identification of the scientific problem that from theoretical questions need to be clarified. This includes a condensation of the problem to specific scientific questions that is judged to be answerable by experiments	C
2. Planning of the experiments and methodology design, including selection of methods and method development	C
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