From Department of Medicine Solna
Karolinska Institutet, Stockholm, Sweden

DIABETES, CARDIOVASCULAR EVENTS, AND LIFESTYLE – FROM EPIDEMIOLOGY TO CLINIC

Madeleine Hummel

Karolinska Institutet

Stockholm 2024

Published by Karolinska Institutet.
Printed by Universitetsservice US-AB, 2024

ISBN 978-91-8017-280-6
Cover illustration: by Caroline Öhling, 2024

Diabetes, cardiovascular events, and lifestyle – from epidemiology to clinic

Thesis for Doctoral Degree (Ph.D.)

By

Madeleine Hummel

The thesis will be defended in public at the lecture hall Ljung at Academic Specialist Center, 4th floor, Solnavägen 1E, Stockholm, April 18th, 2024, at 10:00 am.

Principal Supervisor:
Associate Professor Ylva Trolle Lagerros
Karolinska Institutet
Department of Medicine Solna
Division of Clinical Epidemiology

Co-supervisor(s):
Associate Professor Stephanie Bonn
Karolinska Institutet
Department of Medicine Solna
Division of Clinical Epidemiology

Professor Marie Löf
Karolinska Institutet
Department of Biosciences and Nutrition

Professor Rino Bellocco
University of Milano-Bicoocca
Department of Statistics and Quantitative Methods
Karolinska Institutet
Department of Medical Epidemiology and Biostatistics

Opponent:
PhD Karin Hellgren
Karolinska Institutet
Department of Medicine Solna
Division of Clinical Epidemiology

Examination Board:
Associate Professor Ing-Mari Dohrn
Karolinska Institutet
Department of Neurobiology, Care Sciences and Society
Division of Physiotherapy

Associate Professor and Professor em Mats Eriksson
Karolinska Institutet
Department of Medicine Huddinge
Division of Endocrinology and Diabetes

Associate Professor Andreas Stompy
Linköping University
Department of Health, Medicine and Caring Sciences
Division of Prevention, Rehabilitation and Community Medicine

To my sons August & Henning

Abstract

Today, the health care system plays an important role in the prevention of diseases, not least through support of a healthy lifestyle, including being physically active. Given the development of digital tools together with the importance of healthy lifestyle habits in prevention of most diseases, mHealth with self-management interventions has the potential to play a greater role than ever before. The growing implementation of digital solutions in health care shows a need for flexible and remote support as a complement to regular visits to the health care provider.

Physical activity (PA), a modifiable lifestyle factor, has been shown to be associated with a decreased risk of cardiovascular disease (CVD) in previous epidemiological studies. Some have suggested that PA affects the risk of CVD in women and men differently, and different types of PA may have different effects. Type 2 diabetes (T2D) and CVD share several characteristics including risk factors. Following an aging population and increases in risk factors ascribed to lifestyle, the prevalence of T2D is expected to arise in the coming decades. Currently, there is a rapid development in lifestyle promoting smartphone apps and devices for self-management targeted to persons with T2D. However, few previous app interventions in persons with T2D have targeted objectively measured daily PA alone. Moreover, an elevated blood pressure (BP) is the leading risk factor for CVD, and a common comorbidity in persons with T2D. Hence, a normotensive BP in persons with T2D is of great importance, who are also likely to use digital devices for self-measurement.

This thesis aims to study the association between total physical activity (TPA) and leisure time physical activity (LPA), and risk of stroke and myocardial infarction (MI) in women and men **(study I)**, to study if a smartphone app intervention promoting PA by daily steps can improve time spent in moderate-to-vigorous intensity physical activity (MVPA), Health Related Quality of Life (HRQoL), and several other clinical variables in persons with T2D **(study II-III)**, and to validate two automatic BP monitors with a Bluetooth function against manual BP monitoring in persons with T2D **(study IV)**.

Study I was a prospective cohort study based on the Swedish National March Cohort (SNMC), following 31,580 individuals from 1997 to 2016. TPA and LPA were

self-reported in the baseline questionnaire and outcomes of incident cases of MI and stroke were derived from national registers. A 22% lower risk of MI was seen in women in the highest tertile of TPA compared to the lowest tertile (HR: 0.78; 95% CI: 0.63–0.97). Among men, being in the highest tertile of LPA was associated with a lower risk of MI compared to belonging to the lowest tertile (HR: 0.78; 95% CI: 0.62–0.98), and a lower risk of stroke was seen among men in the highest tertile compared to the lowest (HR: 0.78; 95% CI: 0.61–0.99).

Study II-III was based on data from the DiaCert-study, a two-armed randomized controlled trial including 181 women and men with T2D. The intervention group was given access to the step promoting smartphone app DiaCert at baseline and 3 months onwards in addition to standard care, while the control group received standard care only. Outcomes of objectively measured MVPA (min/day) using accelerometers (primary outcome), BP, body mass index (BMI), waist circumference, HbA1c, blood lipids, and HRQoL (secondary outcomes) were assessed at baseline and at follow-ups at 3 and 6 months. The intervention had a positive effect and showed improvements in three HRQoL health concepts; role limitations caused by physical health problems, (-16.9; 95% CI -28.5 to -5.4), role limitations caused by emotional problems (-13.9; 95% CI -25.8 to -2.1), and emotional well-being (-5.7; 95% CI -10.4 to -1.0), in the intervention group compared to the control group after 3 months of intervention. No effect was observed on neither the primary outcome MVPA after 3 months, nor any of the clinical variables measured at 3 and 6 months.

In **Study IV**, two automatic BP monitors were validated against manual BP monitoring using baseline data from the DiaCert-study. The mean difference between the automatic monitor Beurer BM 85 and the manual BP monitor was 11.1 (SD 11.2) mmHg for systolic BP and 8.0 (SD 8.1) mmHg for diastolic BP. For the automatic monitor Andersson Lifesense BDR 2.0, the corresponding mean difference was 3.2 (SD 10.8) mmHg for systolic BP and 4.2 (SD 7.2) mmHg for diastolic BP.

In conclusion, our results highlight potential differences regarding LPA and TPA on the risk of MI and stroke between the sexes. The step promoting app intervention DiaCert showed an effect on health concepts reflecting both physical and emotional HRQoL, but no effect was found for MVPA or any of the cardiometabolic markers measured. Hence, future research is needed to conclude what type of mHealth solution that would not only improve HRQoL, but also be effective in

supporting PA and improve cardiometabolic factors in this patient group. The validation of the two automatic BP monitors showed that one of the monitors differed in measurements within what could be clinically acceptable (Andersson Lifesense BDR 2.0), while the other did not (Beurer BM 85). Taken together, our results show that evaluation of the efficacy of mHealth PA interventions and validation of automatic BP monitors for home management are of importance to ensure the quality of the care, before implementing those in the health care system.

List of scientific papers

I. **Hummel M**, Hantikainen E, Adami HO, Ye W, Bellocco R, Bonn SE, Lagerros YT. Association between total and leisure time physical activity and risk of myocardial infarction and stroke - a Swedish cohort study. BMC Public Health. 2022 Mar 18;22(1):532. doi: 10.1186/s12889-022-12923-5. PMID: 35303845; PMCID: PMC8932168.

II. Bonn SE, **Hummel M**, Peveri G, Eke H, Alexandrou C, Bellocco R, Löf M, Trolle Lagerros Y. Effectiveness of a Smartphone App to Promote Physical Activity Among Persons With Type 2 Diabetes: Randomized Controlled Trial. *Accepted for publication in Interact J Med Res*.

III. **Hummel M**, Bonn SE, Trolle Lagerros Y. The effect of the smartphone app DiaCert on health related quality of life in patients with type 2 diabetes: results from a randomized controlled trial. Diabetol Metab Syndr. 2022 Dec 17;14(1):192. doi: 10.1186/s13098-022-00965-z. PMID: 36528609; PMCID: PMC9759853.

IV. **Wetterholm M**, Bonn SE, Alexandrou C, Löf M, Trolle Lagerros Y. Validation of Two Automatic Blood Pressure Monitors With the Ability to Transfer Data via Bluetooth. J Med Internet Res. 2019 Apr 17;21(4):e12772. doi: 10.2196/12772. PMID: 30994459; PMCID: PMC6492059.

Contents

List of abbreviations

BMI	Body mass index
CI	Confidence Interval
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
EASD	European Association for the Study of Diabetes
FPG	Fasting plasma glucose
GEE	Generalized estimation equations
HbA1c	Hemoglobin A1c
HDL	High-density lipoprotein
HR	Hazard ratio
HRQoL	Health Related Quality of Life
ICD	International classification of disease
LDL	Low-density lipoprotein
LPA	Leisure time physical activity
MCS	Mental component summary
MET	Metabolic equivalents
MI	Myocardial infarction
MPA	Moderate intensity physical activity
MVPA	Moderate-to-vigorous intensity physical activity
NDR	National Diabetes Register
OGTT	Oral glucose tolerance test
PA	Physical activity
PCS	Physical component summary
QoL	Quality of life
RCT	Randomized controlled trial
SBP	Systolic blood pressure
SD	Standard Deviation

SNMC	Swedish National March Cohort
T2D	Type 2 Diabetes
TPA	Total physical activity
VPA	Vigorous intensity physical activity

Introduction

Lifestyle is an umbrella term for how we choose to live our life, which in turn affect our health. The modifiable lifestyle factor physical inactivity is a known risk factor for type 2 diabetes (T2D) and cardiovascular disease (CVD) morbidity and mortality (1-4). Hence, physical activity (PA) is a keystone in both preventing and monitoring cardiometabolic risk factors. The World Health Organization (WHO) has declared that integration of both primary and secondary prevention is crucial to advance health care (5).

However, encouraging and supporting patients in the self-management of risk factors is known to be challenging for the health care provider (6). An increasing prevalence of T2D and the severity of cardiovascular events call for up to date knowledge that can be useful when supporting patients in self-care towards a healthier lifestyle, including optimal type of PA. Evidence-based and validated mHealth solutions that are easy-to-use can be an effective method to impact modifiable lifestyle factors, and could near the gap between clinic based care and home based self-management.

This doctoral thesis includes studies of the effect of an mHealth intervention promoting PA among persons with T2D, validation of home blood pressure (BP) monitors that can be used in mHealth solutions, and moreover, investigates different types of PA and their impact on the risk of cardiovascular events.

1 Literature review

1.1 Type 2 Diabetes

Diabetes was first described by the Egyptians in 1500 BC as "too great emptying of the urine". The word "diabetes", meaning "to pass through", was used by the Greeks around 250 BC, and "mellitus" or "from honey" referring to the sweet taste of the urine of a person with diabetes was added in the 1600s by the physician Thomas Willis (7). Diabetes is one of the first diseases being described. Today, T2D is the most common chronic metabolic disease and is increasing globally, with a prevalence of 537 million in 2021 and expecting to rise to 783 million in 2045 (8).

In Sweden, the prevalence of T2D in the adult population is estimated to be 5.5% according to the Swedish National Diabetes Register (NDR) (9), while the International Diabetes Federation estimates the prevalence among adult Swedes to be 7.0% (10). T2D stands for almost 90% of all diabetes, hence, being the most common type of diabetes (9). However, the true prevalence of T2D is probably underestimated as the disease develops gradually with slowly rising blood glucose levels over time and can be remained undetected at onset due to few symptoms.

Today, we know the importance of heredity and that T2D develops in genetically predisposed individuals, but which genes that are involved is not yet fully recognized (11, 12). It is also known that lifestyle factors, such as physical inactivity and overweight, have an impact on the development of the disease, by reducing insulin sensitivity (1-3, 13). Thus, T2D is a heterogeneous disease with both genetic and lifestyle factors influencing the glucose metabolism. The elevated levels of blood glucose, hyperglycemia, in persons with T2D most often develop due to insulin resistance, that is reduced insulin sensitivity in which the ability of insulin to assist glucose uptake into the cells is decreased. Several tissues can become insulin resistant including adipose tissue, liver, and skeletal muscle. As the insulin demand increases with hyperglycemia, insulin secretion is first increased to compensate this demand. With a rising demand, a simultaneous insufficient insulin secretion from the beta cells in the pancreas and later a beta cell dysfunction leads to diabetes. The molecular mechanisms behind these deficiencies remain partly unknown (13, 14).

The mean age among persons with T2D in Sweden is 68.7 years and the mean diabetes duration among persons with T2D is 10.4 years (15). Old age is a known risk factor of T2D, but for those with a diagnose onset early in life, the risk for

complications is the highest (9, 16-18). There are several complications of diabetes affecting both physical and mental health. Both macrovascular and microvascular complications are common (e.g., hypertension, coronary heart disease, stroke, nephropathy, retinopathy, and neuropathy) (19), but also depression (20, 21) and impaired Health Related Quality of Life (HRQoL) (22).

1.1.1 Diagnostic criteria

The diagnostic criteria for T2D are presented below. Today, three tests are available for screening and diagnosis of glucose perturbations: fasting plasma glucose (FPG), Hemoglobin A1c (HbA1c), and oral glucose tolerance test (OGTT).

As the name implies, a blood sample is taken after overnight fasting for the analysis of the biomarker FPG. HbA1c refers to glycated hemoglobin and reflects the glycemic history. Hemoglobin is a protein within the erythrocytes (red blood cells) that carries oxygen in the blood. Hemoglobin irreversibly interacts with glucose in the blood, formatting the glycated hemoglobin (HbA1c) which is a normal physiologic function. However, when the average blood glucose increases, so does the amount of HbA1c. Since the erythrocytes have a life-span of about 120 days, we are able to measure the average blood glucose concentration for the previous 3 months, of where the previous 30 days decides 50% of the HbA1c, the previous 30-90 days decides the 40%, and the previous 90-120 days decides 10% of HbA1c (23). HbA1c, as a measure of long-term glycemic control, is together with FPG, not only biomarkers used in the diagnosis of diabetes, but also the golden standard for diabetes control. Moreover, HbA1c is related to the risk of diabetes complications (24).

When performing an OGTT, the concentration of glucose in plasma is taken two hours after an intake of 75 grams of glucose. OGTT can detect impaired glucose tolerance in individuals with pre-diabetes and T2D that are not always found with FPG or HbA1c (25). The diagnostic criterion of diabetes is based on blood glucose levels above levels known to cause microvascular complications as retinopathy and nephropathy. However, macrovascular complications are known to arise earlier (26).

The diagnostic criteria for T2D according to European Association for the Study of Diabetes (EASD) and the American Diabetes Association (ADA) (5, 27) guidelines is the following:

• A FPG of 7.0 mmol/l or higher (and a confirmatory test of FPG, HbA1c, or OGTT at a different occasion).

or

• A HbA1c of 48 mmol/mol or higher (and a confirmatory test of FPG tested at the same time or FPG, HbA1c, or OGTT at a different occasion).

or

• OGTT of 12,2 mmol/L or higher (capillary) or 11.1 mmol/l or higher (venous) (and a confirmatory test of FPG, HbA1c, or OGTT at a different occasion).

or

• A random non-fasting plasma glucose of 12.2 mmol/l or higher (capillary) or 11,1 mmol/l (venous) and symptoms of diabetes.

1.2 Cardiovascular disease

Cardiovascular disease (CVD) is the number one cause of death worldwide. In 2019, it was estimated that 17.9 million people died from CVD, of which 85% were due to myocardial infarction (MI) or stroke (28). MI is most often due to a rupture of an atherosclerotic lesion in a coronary artery, leading to a formation of a blood clot that plugs the coronary artery and stops the blood flow and thereby the oxygen supply to the heart, which in turn leads to myocardial cell death (29). Stroke is caused by inadequate blood flow to the brain. It can either occur due to formation of a local blood clot or a circulating blood clot occluding a blood vessel in the brain i.e., ischemic stroke, or because of a rupture of a cerebral vessel leading to bleeding, i.e., hemorrhagic stroke (30).

MI is the leading cause of death in Sweden, while stroke is the third (31, 32). Risk factors associated with CVD, including age, heredity, smoking, diabetes, hypertension, blood lipid disturbance, overweight, and physical inactivity, are today well-known. In the past 20-30 years, prevention regarding modifiable risk factors together with progress in acute health care, have contributed to a decrease in CVD mortality. However, this positive development is somewhat

counterbalanced by an aging population and alarming increases in risk factors ascribed to lifestyle (17, 31).

1.2.1 Cardiovascular disease in persons with type 2 diabetes

T2D and CVD share several characteristics including risk factors. Both diseases have a genetic predisposition which act together with environmental factors in the development and progression of the disease. CVD is the major cause of morbidity and mortality in the diabetes population (33). A diagnosis of diabetes means on average a 2 to 4-fold increased risk of macrovascular events (34). Due to these macrovascular events, persons with diabetes have an 8 years decreased life expectancy (35). Furthermore, the life expectancy has been shown to be reduced by 12-15 years in people aged 60 years with diabetes and previous MI, stroke, or both (36). Moreover, about two in three persons with CVD have glucose perturbations (37-39).

Hypertension is one of the strongest risk factors for CVD, and a common comorbidity in persons with T2D. In Sweden, almost 80% of the T2D population are prescribed BP lowering medication (15). In a large cohort including patients from the Swedish NDR, overall mortality for a follow-up of 4.6 years was 17.7% in the group with a diagnosis of T2D compared to 14.5% in the control group, and CVD mortality was 17.9% among people with T2D versus 6.1% among controls (16). In another cohort study including patients from the NDR, no additional risk of death, MI, or stroke was found when all of the following risk factors: high HbA1c, high BP, elevated LDL-cholesterol level, albuminuria, and smoking, were within the recommended target ranges (40).

Prevention targets of CVD in persons with T2D are, in addition to glucose management, the same as for the population without T2D; BP, blood lipids, microalbuminuria, and lifestyle factors as smoking, obesity, and physical inactivity. However, most cut-offs for diagnosis and treatment targets are more strict for persons with T2D than for persons without diabetes. For example, in persons with hypertension the cut-off for diagnosis of hypertension with BP measured at the health care clinic is ≥140 in systolic blood pressure (SBP) and/or ≥90mmHg in diastolic blood pressure (DBP), according to Swedish guidelines. The European Society of Cardiology (ESC) together with EASD presented new guidelines in 2019 on treatment targets for persons with T2D and hypertension, with a goal of SBP between 120-130mmHg and of DBP between 70-80mmHg, if tolerated. In people older than 65 years and with no albuminuria the SBP goal is 130-139mmHg (5).

1.2.2 Knowledge gap – blood pressure

For diagnosis and control of hypertension, the standard method used today is repeated measurements at a health care clinic with a manual BP monitor at the upper arm while the patient is sitting. However, 24-hour ambulatory BP monitors and automatic monitors for home measurement of BP are becoming increasingly common. They have not only shown to predict the risk of complications (41), but BP measurement at home has also shown to increase compliance to BP medication (42). Moreover, home-measurement can provide more reliable measurements regarding white coat hypertension (i.e., high BP only when measured at the health care clinic) and masked hypertension (i.e., high BP when measured in a home setting, but normal when measured at the health care clinic), with the latter known to be common in persons with T2D (43).

With new technology, some automatic BP monitors have the ability to transfer data to e.g., a smartphone app, facilitating self-measurement and BP control for the patient and could possibly be shared with the health care provider. However, this requires validated monitors. Therefore, we have validated two commercially available automatic BP monitors in **study IV**.

1.3 Physical activity

PA is defined as "any bodily movement produced by skeletal muscles that results in energy expenditure" (44). In epidemiological studies, PA is often measured using metabolic equivalents (METs), representing the intensity expressed as energy cost, of a specific activity. One MET-hour is defined as the ratio of work metabolic rate to a standard resting metabolic rate of energy expenditure of 1 kcal per kg body weight per hour. One MET corresponds to the energy cost for 1 hour of sitting quietly (45, 46). PA levels can be categorized on the basis of METs with light intensity corresponding to 1.5 – 2.9 METs (e.g., slow walking), moderate intensity (MPA) corresponding to 3.0-5.9 METs (e.g., brisk walking) and vigorous intensity (VPA) of 6 or more METs (e.g., running).

1.3.1 Measuring physical activity

In epidemiological studies, different measurements of PA are used, including self-reported questionnaires and objective measurements with for example accelerometers. The benefits of questionnaires includes that they are easy to administer, convenient to use, can reach a great number of study participants to

a low cost, and can tell us what type of activity is done. Therefore, they are often the method of choice in large epidemiological studies.

Accelerometers can objectively measure movement in different planes, and intensity, duration, and frequency of the movement can be assessed. Today's accelerometers are most often wrist-worn, instead of hip-worn as the earlier versions, making them more convenient for the user and enable measurement during sleep. Moreover, the earlier versions of accelerometers were uniaxial, but today's accelerometers can measure movement in three axes (47).

1.3.2 Physical inactivity, morbidity, and mortality

A lack of PA, i.e., being physically inactive, has shown to be a risk factor of global morbidity and mortality, with an increased risk of several diseases, including T2D and CVD. Physical inactivity and low PA are by the WHO considered to be the fourth most important risk factor for disease (48), and are considered accountable for 3.2 million deaths globally every year (49). Further, physical inactivity has been estimated to cause 6% of the MI disease burden and 7% of T2D worldwide (4). Based on self-reported data, two in three adults meet the Swedish national guidelines for recommendation of PA (50), however, when measured objectively this number is only 7% (51).

Being physically active is central in both primary and secondary prevention of T2D and CVD (17). An inverse association between PA and CVD has been shown by several studies (52-54). In a meta-analysis, a risk reduction of 34% and 24%, respectively, was shown for CVD in individuals with vigorous or moderate level of leisure time physical activity (LPA) compared to individuals with low level of LPA. A similar dose-response relationship was seen for PA and CVD when MI and stroke were studied separately (55). In a large case-control study including both sexes, regular involvement in LPA showed a 14% lower risk of MI and 31% lower risk for stroke (56, 57). PA has a positive effect on numerous risk factors for CVD, e.g., a review of 27 RCTs including persons with hypertension showed that regular PA on moderate-to-vigorous intensity level (MVPA) reduced the BP by a mean of 11/5mmHg (58).

In people with T2D, regular PA leads to an increase in insulin sensitivity, due to for e.g., less fat mass, more muscle mass, and cellular changes (including an increase of glucose transporters GLUT4 resulting in improved glucose uptake in the skeletal muscles). Together this is shown to improve HbA1c (59, 60). The effect of increased insulin sensitivity remains even in rest after PA, but declines after 48

hours. Therefore, the guidelines for PA in persons with T2D includes, not only the preferred intensity and duration, but also frequency, with the recommendation to perform PA at least every second day (61-63). Moreover, PA has an impact on several other risk factors for CVD, such as reduced abdominal obesity, improved BP, and blood lipids, in addition to increased insulin sensitivity. In observational studies, higher levels of PA in persons with T2D have been associated with lower risk of complications as macro- and microvascular disease (64, 65). Moreover, an association between PA and improved HRQoL has been shown in persons with T2D (66-69).

In addition to PA, several studies suggest that sitting time is associated with risk of negative health outcomes (70). A meta-analysis showed that sitting time independently of PA was associated with an increased risk of both incidence of T2D and CVD mortality (71).

1.3.3 Physical activity recommendations

It is known that there is a curvilinear dose-response relationship between PA and health, where dose includes intensity, duration, and frequency of the PA. In the Swedish guidelines for PA in the prevention and treatment of disease (FYSS) (63), the recommendations for aerobic PA to prevent the risk of all-cause mortality, and also for prevention of CVD and T2D, for all adults including people with T2D are the following:

• Aerobic PA on a moderate intensity level (corresponding to 3.0-5.9 METs) for ≥150 – 300 min/week with a frequency of 3-7 times/week,

or

• Aerobic PA on a vigorous intensity level (corresponding to 6.0-8.9 METs) for ≥75-150 min/week with a frequency of 3-5 times/week,

or

• A combination of moderate and vigorous intensity with a duration of ≥ 90 min/week (30 minutes, 3 times/week).

The recommendations also include muscle-strengthening PA at least 2-3 days/week. In addition, it is encouraged that sedentary time is decreased. These recommendations are in line with the recommendations on PA published by the WHO (72).

A goal of "10,000 steps" per day is often used as a strategy to increase PA. It has been shown in a previous study (73) that participants walked more when recommended 10,000 steps a day compared to a 30-minute walk a day. About 7000-8000 daily steps corresponds to the lower range of the recommended doses described above when 3000-4000 of those daily steps equals to the recommended 150 minutes per week on a moderate intensity level. 10,000 steps per day corresponds to aerobic PA on a moderate intensity level for 300 min/week (74).

1.3.4 Knowledge gap – physical activity

There is convincing evidence that PA contribute to a lower risk of CVD with a curvilinear dose-response relationship, i.e., with greatest gain for those who increase their activity from being inactive (75). However, few studies have investigated the relationship in men and women separately, but some studies suggest that the impact is different between the sexes with a stronger association among women (76, 77). Moreover, most studies have focused on a single domain such as e.g., LPA, and thereby not provided an overall picture of PA. Few studies assess total physical activity (TPA) that includes occupational activity. It could be assumed that more men have strenuous occupations, and studies have shown that there might be a "physical activity paradox" with occupational PA being a risk factor for CVD (55, 78). This may contribute to a difference between sexes. Thus, we have in **study I** investigated the relation between TPA and LPA, on the risk of MI and stroke in both women and men.

1.4 mHealth

WHO defines eHealth as "the use of information and communication technologies for health", and mHealth as "medical or public health practice that is supported by mobile devices" (79). In recent years, eHealth and mHealth have been rapidly growing areas in medical research and health care. Early on, the use of health practice technology consisted of websites and mobile phones with short text message service, but today, mHealth is often focused on applications (apps) developed for smartphones. With more people having access to smartphones, the use of mHealth, can be a new strategy to support patients. Today, more than 90% of Swedes, independent of socioeconomic status, have a smartphone (80). Digital services for healthcare are used by 8 out of 10 (81). With new technology and with a growing user demand, the number of health-related apps is continuously

increasing. However, despite their popularity the efficacy of the apps is rarely evaluated.

There are apps targeting lifestyle behaviors including PA, that have been studied and shown to be successful (82-86). App features including a user-friendly design, goal-setting, feedback, and self-monitoring have been suggested to improve effectiveness in attaining health behavior change (82, 87). The impact of apps on health outcomes has been studied among persons with T2D (83, 84, 88, 89). However, most of the apps are heterogeneous in the functions and number of functions that they provide, which may include tracking blood glucose, weight, diet, PA etc. Only a few apps primarily target PA with change in PA as the primary outcome (85, 86). In a review, apps providing a single function more often showed significant improvements in health outcomes than apps with multiple health behavior interventions (82).

1.4.1 Knowledge gap - mHealth

PA has beneficial effects on glycemic control and is known to reduce the risk of several cardiometabolic risk factors (90). However, PA interventions for persons with T2D have been proven to be difficult to implement in today's health care (91). Compliance to PA recommendations is generally low among persons with T2D as a group (65). Walking may be the easiest applicable form of PA in daily life and has shown to be effective in improving glycemic control, BP, body mass index (BMI) etc. (92). Today, there are numerous commercial apps targeting lifestyle, making it difficult both for the patient and the care giver to choose the most suitable app to use. Moreover, the effect of the apps on PA and cardiometabolic risk factors are rarely scientifically studied, and few of them primarily target PA in persons with T2D. With the aim to provide healthcare professionals and patients with a scientifically evaluated tool targeting daily walking, a smartphone app intervention promoting daily steps in persons with T2D is studied in **study II and III**.

1.5 Health Related Quality of Life (HRQoL)

There is no clear definition of the various terms Quality of Life (QoL) and health related QoL (HRQoL). However, the latter of the two is most commonly measured with self-reported questionnaires as physical, emotional, and social well-being related to health (94). During the last decades, the awareness concerning the importance of the patient's perspective of her own health have made HRQoL an

important goal in disease management, which is reflected in today's international guidelines for treatment of several diseases including T2D.

1.5.1 HRQoL in persons with type 2 diabetes

Impaired HRQoL has been shown among persons with T2D compared to healthy individuals (96). Diabetes complications are known risk factors to worsen HRQoL (22, 95). In addition, a greater difference in HRQoL has been seen between persons with T2D and the general population, compared to persons with type 1 diabetes and the general population (97).

1.5.2 The questionnaire RAND-36

The RAND-36 is a widely used, generic, self- reporting questionnaire that measures HRQoL. The 36-item Short Form Health Survey (SF-36) was developed within the RAND Medical Outcomes Study (MOS) to measure HRQOL in the study participants. The 36 items in SF-36 were selected from considerably more items answered by the participants in the MOS, resulting in the short form questionnaire. Hence, the name Short Form-36 (98). The 36 items were developed at RAND Corporation, a nonprofit research organization. It is today distributed by them as the RAND-36 and publicly available. The questionnaire was first published in 1992 as SF-36 (99), and one year later as RAND-36 (98). The RAND-36 is translated into several languages, including Swedish, and has been used among persons with T2D in previous studies (100-103).

1.5.3 Knowledge gap - HRQoL

PA is known to impact HRQoL in persons with T2D. There are only a few mHealth studies evaluating the effect on HRQoL with inconsistent results (86, 88, 89). Therefore, in **Study III**, we have studied a smartphone app intervention with support in daily walking on the effect of HRQoL in persons with T2D.

1.6 From epidemiology to clinic

To summarize, the studies included in this thesis investigated what type of PA that benefits the person the most in terms of prevention of CVD, the validation of two automatic BP monitors to support self-measurement and control of hypertension, and if a step promoting app intervention could support persons with T2D towards improved PA, cardiometabolic risk factors, and HRQoL.

As a general practitioner at a primary health care clinic, I meet the patient from the general population with risk factors for cardiovascular events, as well as the patient with a diagnosis of T2D on a daily basis. My job includes both primary and secondary prevention of T2D and CVD. Therefore, lifestyle is always on the agenda. I inform the patient about PA guidelines and recommendations, and together we talk about expectations, goals, and worries. For the patient with T2D, PA is always prescribed in combination with medication. However, supporting patients in lifestyle habits takes time and resources are limited. Moreover, as a health care provider in primary care you might only see your patient once a year. Therefore, I see the need for support of a healthy lifestyle between routine visits at the clinic. Digital solutions for self-measurements and self-management interventions could engage the patients in their own care. However, it is known that supporting patients in self-management is challenging, and today, there is a "jungle" of smartphone apps and tools for self-care. Most of them are not studied or validated, making it challenging for the health care provider in terms of recommendations. Hence, evidence-based methods are needed.

2 Research aims

This thesis aimed to extend previous knowledge about the association between lifestyle, including physical activity and the use of mHealth, and cardiovascular disease and type 2 diabetes, that could be useful for preventing cardiovascular events and improving health in persons with type 2 diabetes.

More specifically, the aims of this thesis were:

Study I: To study the association between total physical activity and leisure time physical activity, and risk of myocardial infarction and stroke in both men and women in a large Swedish cohort

Study II: To investigate if use of a smartphone app that promotes physical activity by daily steps, can improve moderate-to-vigorous physical activity and the clinical cardiometabolic variables body mass index, waist circumference, blood pressure, HbA1c, and blood lipids in persons with type 2 diabetes

Study III: To evaluate if use of a smartphone app promoting physical activity by daily steps impacts Health Related Quality of Life in persons with type 2 diabetes

Study IV: To validate two automatic blood pressure monitors with the ability to transfer data via Bluetooth, against manual blood pressure monitoring, in persons with type 2 diabetes

3 Materials and methods

3.1 Study designs

Epidemiology is "the study of the distribution and determinants of disease frequency" (104). By identifying the occurrence of disease in a population from descriptive epidemiology and risk factors, prevention targets, and disease treatment from observational and intervention studies, epidemiology gives us valuable information for medical and public health.

The evidence-based medicine pyramid is a hierarchic visualization of evidence based on the study design with the highest quality of evidence at the top. Reviews and meta-analyses are found at the top of the pyramid. Then, randomized controlled trials (RCT's) and cohort studies, in that order, are found below, followed by case-control studies and case-reports at the base (105). However, when deciding on what study design to use when to answer a clinical research question depends on several factors, including the prevalence and incidence of the outcome studied, along with ethical, financial, and practical challenges.

This doctoral thesis includes three types of study designs: cohort study (Study I), RCT (study II-III), and validation study (study IV).

In a prospective cohort as study I, the exposure of interest is measured at baseline in a population that has not experienced the specific outcome of interest at the start of the cohort. The participants are then followed for a specific time period to assess the incidence of outcomes, which is then compared among the exposure groups.

Study II and III in this thesis are based on an RCT. In an RCT, the participants are randomly assigned to either an intervention or no intervention (the control group), to study the effect of the intervention while minimizing the impact of confounding factors.

Study IV is a validation study, that is, a study that compares the accuracy of a measure with the measure of the available diagnostic standard. Study designs are further discussed under "Methodological considerations" in the Discussion.

Table 1. Overview of study designs, data sources, data analyses, and participants of the included studies in the thesis (106, 107).

	Study design	Data source	Statistical analysis	Participants included in the analysis
				n
Study I	Cohort study	Swedish National March Cohort	Cox proportional hazard models	31,580
Study II	Randomized Controlled Trial	DiaCert-study	Linear mixed models	156
Study III	Randomized Controlled Trial	DiaCert-study	Generalized estimation equations	166
Study IV	Validation study	DiaCert-study	Spearman rank correlation coefficients & Bland-Altman method	180

3.2 Study I

Research question: Does total physical activity and leisure time physical activity have an impact on the risk of myocardial infarction and stroke, and does the effect differ in men and women?

Study design

Study I was based on data from the population based prospective Swedish National March Cohort (SNMC) with linkage to National Registers.

The Swedish National March Cohort (SNMC)

In September 1997, the Swedish Cancer Society organized a national 4-day fund-raising event. Besides fundraising galas, the event included the possibility of taking part in a walk named "the National March" and other local activities in 3,600 cities and villages around Sweden. By taking part in "the National March" the participants donated 50 Swedish crowns to cancer research. During the event, all participants were also given the opportunity to donate "one hour for research" by answering a 36-page questionnaire covering medical and lifestyle history, including PA exposure information (fig. 1-3).

A total of 43,880 participants completed the questionnaire. The participants gave informed consent to use their national registration numbers for linkages to Swedish National Registries. The SNMC was formed of the people who took part in the event, with the aim to study the associations between lifestyle factors and disease morbidity and mortality (107).

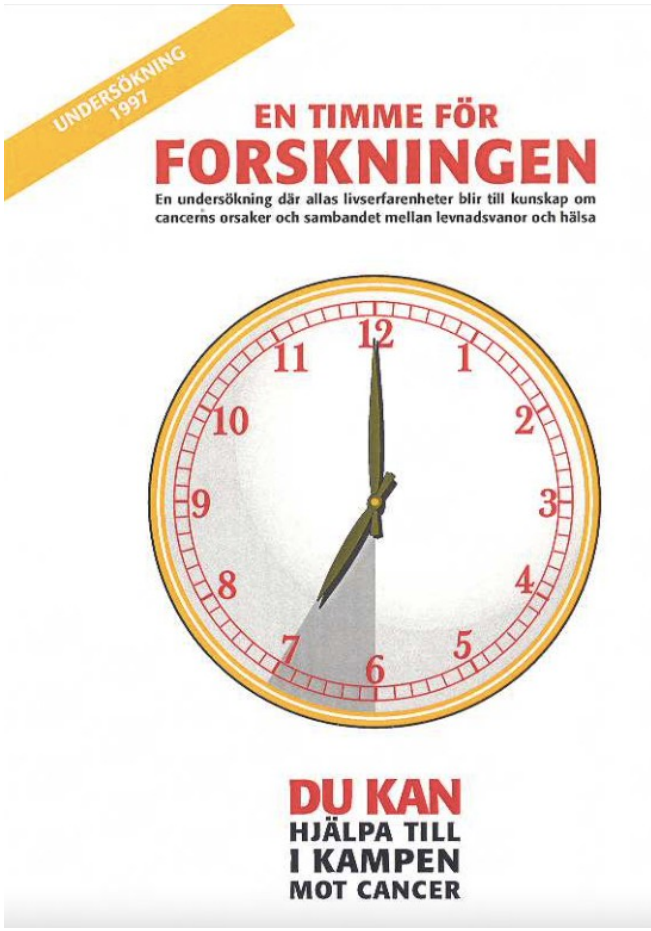


Figure 1. The front page of the 36-page questionnaire used in the Swedish National March Cohort. Published with permission from the Lukas Production.

National registers

Sweden has a long history of personal national registration numbers and population health registration systems with a high coverage, making register-based medical research possible through record-linkage (108).

The National Board of Health and Welfare holds several registers, including the National Inpatient and Outpatient Register and the Cause of Death Register, which were linked to the SNMC, with the latest updates made in 2016. The National Inpatient and Outpatient Register covers hospital discharge diagnoses since the 1960s (with full national coverage since 1987) and outpatient specialist care since 2001 (with primary care not yet registered). The Cause of Death Register covers all deaths in Swedish citizens from 1969. In the Swedish health care system, diagnoses are since 1987 coded according to the international classification of disease (ICD), and the registers are mandatory to report to (109, 110). The validity of MI and stroke recorded in the National Inpatient and Outpatient Register has previously been evaluated. For MI, 98-100% of cases were found correct and for stroke the corresponding numbers were 68.5- 98.6% (111).

Study population

Before analyses, we excluded all participants with incorrect national registration numbers, who were younger than 18 years old, and who moved from Sweden or died before the start of the follow-up. Furthermore, we excluded participants who had experienced a previous cardiovascular disease or a diagnosis of cancer. Finally, we excluded those who had missing data in the questionnaire regarding TPA (n=3,674) or LPA (n=10,843) from the questionnaire. After these exclusions, the final cohort consisted of 31,580 participants for the analyses on TPA and 24,211 participants for the analyses on LPA.

Exposures

Figure 2 and 3 shows the questions from the validated questionnaire used to assess the exposures TPA and LPA, respectively (112). As illustrated in figure 2, to assess TPA, participants reported time spent at each of nine PA intensity level by answering the question "How physically active are you on an ordinary weekday?", summing up to a total of 24 hours. Each level was assigned a MET value between 0.9 (time spent sleeping/resting) and 8 METs (the most strenuous activity level) (46). All levels were summarized; hence, TPA was measured as the total energy expenditure during a 24-hour weekday and expressed as MET-hours/day.

When the number of hours in a day was underreported and did not make it up to 24 h, we multiplied the missing hours with a MET value of 0.9, i.e., time spent sleeping or resting. If the sum exceeded 24 h, we assumed that the overreporting of time was independent of the intensity level, and the value of each intensity level was multiplied by 24 and divided with the reported number of hours.

LPA was measured in the questionnaire by reporting the weekly average number of hours dedicated to sports/exercise/athletics/outdoor life divided into three levels corresponding to 3, 6, and 10 MET during summer and winter, respectively. See figure 3. The MET-value for each level was then multiplied with the number of hours spend on each intensity level, and finally summed up to the total MET-h spend on LPA.

How physically active are you on an ordinary day-and-night weekday?
In the table below there are 9 levels (degrees) of strains. In order to understand what each level means there are examples of activities that are just that strenuous. Try to estimate how long time during 24 hours that you totally devote to each level. Start with level A and state the time with one cross per level.

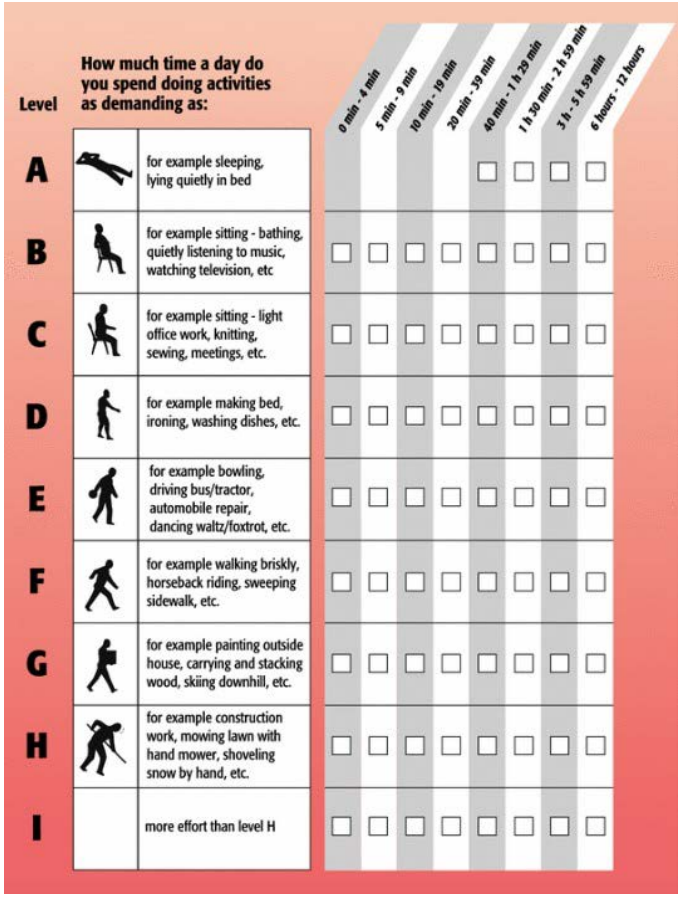


Figure 2. The total physical activity questionnaire used in the Swedish National March Cohort questionnaire.

How much time per week, in average, during the last 12 months have you devoted to athletics/exercise/sports/outdoor life?

		Hours per week 0	0-1	2	3	4	5 or more
Light exercise, like taking a walk	Summer	☐	☐	☐	☐	☐	☐
	Winter	☐	☐	☐	☐	☐	☐
Strenuous exercise, like speedy walk, jogging or swimming	Summer	☐	☐	☐	☐	☐	☐
	Winter	☐	☐	☐	☐	☐	☐
Hard training or competition	Summer	☐	☐	☐	☐	☐	☐
	Winter	☐	☐	☐	☐	☐	☐

Figure 3. The leisure time physical activity questionnaire used in the Swedish National March Cohort questionnaire.

Outcomes

The outcomes studied were incident cases of nonfatal and fatal MI or stroke obtained from national registries. We followed participants through record-linkages from October 1, 1997, to the time of a first MI or Stroke, death, emigration, or to the end of the follow-up on December 31, 2016. Nonfatal events were ascertained in the Swedish National Inpatient and Outpatient Register. Fatal events were ascertained in the Swedish Cause of Death Register, identified using the ICD-codes; 410 (ICD-9), and I21 (ICD-10) for MI; 430, 433, 434, 436 (ICD-9), and I60, I61, I63.0-I63.5, I63.8-I63.9, I64 (ICD-10) for stroke. Emigration status was received from the Population Register. The mean follow-up time was 17.9 years.

Statistical analyses

First, we categorized the TPA and LPA into sex-specific tertiles named "low", "medium", and "high". We selected tertiles to ensure an adequate number of cases when comparing groups, especially in the sex stratified analyses. We then reported the baseline characteristics of the study population as mean (standard deviation, SD) and n (%) for continuous and categorical variables, respectively, in the three levels of TPA. To test potential differences between groups at baseline we used the one way analysis of variance (ANOVA) test to test the difference of means of continuous variables. The Chi-square test was used for categorical variables, which compares the distribution of a variable between groups.

For analyzing survival data, we fitted Cox proportional hazards regression models, which takes into account the unequal lengths of time that each participant is followed and models the risk of the event up to each point in time. We analyzed the time from September 1997, when the participants filled out the baseline questionnaire, until the occurrence of first MI or stroke. The incidence of MI and stroke among low, medium, and high TPA and LPA, respectively, were then compared, with the lowest level of physical activity of each domain used as the reference category. Additionally, we also fitted models with TPA and LPA as continuous variables. Crude and multivariable adjusted Cox proportional hazard ratio (HR) models and the 95% confidence interval (CI) (i.e., with a 95% confidence that the interval will contain the population mean HR) were fitted, with age as the underlying time scale, since age in our study is a stronger determinant of MI and stroke than the time from baseline to follow-up. The crude model further included adjustments made for sex.

Potential confounders for the multivariable adjusted models were carefully selected based on known risk factors for MI and stroke and included: cigarette smoking, alcohol consumption, level of education, and BMI, of which all were self-reported in the questionnaire. Finally, the analyses were adjusted for: hypertension, diabetes, and lipid disturbance, since they may be confounders, or they may be mediators on the causal pathway between the exposures and outcomes studied (fig. 4). For example, when evaluating the effect of PA on the risk of MI and stroke, PA is associated with lipid levels (e.g., a diagnosis of hyperlipidemia might affect the PA level due to PA recommendations received from the health care giver) and lipid levels are associated with the risk of MI independent of PA, i.e., a confounder. However, one mechanism for the effect of PA on risk of MI may be that it is partly mediated by changes in lipid levels, i.e., an intermediate step on the causal pathway. Yet, it could also be of interest to assess the extent to which PA has an effect on MI and stroke by other mechanisms than lipid levels, hence, being managed as a confounder.

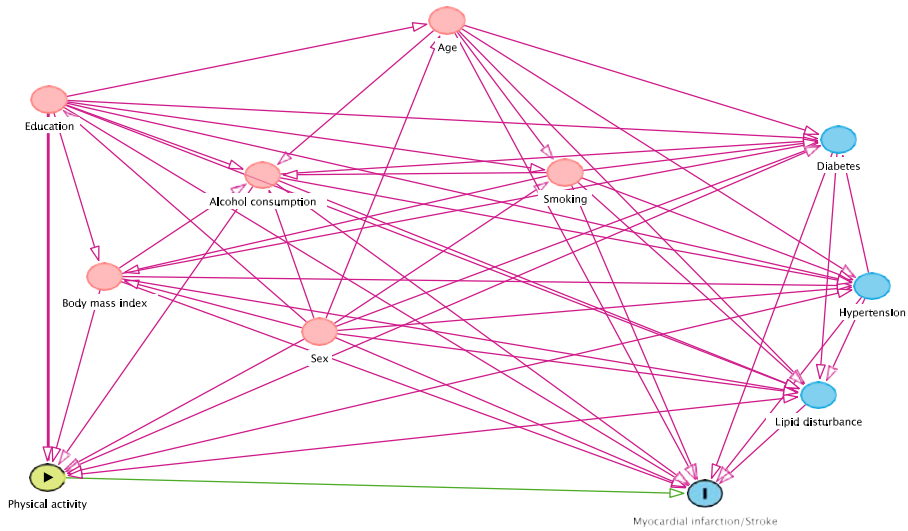


Figure 4. A Directed Acyclic Graph (DAG) between physical activity and myocardial infarction/stroke.

The proportional hazards assumption states that the HR between the groups studied is constant over time. We used Schoenfeld's residuals to test if the proportional hazards assumption was violated. To further assess a potential linear

relationship between exposures and outcomes, we conducted a linear trend test. To do so, the exposures were handled as continuous variables by using the median values of each physical activity tertile. We also used restricted cubic splines to investigate the dose-response relationship between our continuous exposure and the outcomes.

Furthermore, we investigated the role of sex (female, male), age (< 60 years, ≥ 60 years), BMI (≤ 25 kg/m², > 25 kg/m²), smoking (never, former, current), and alcohol consumption (low, medium, high) as potential effect modifiers, i.e., to assess if the association between TPA/LPA and MI/stroke varied by levels of these factors.

To investigate potential sources of bias that affect the outcome, we did four types of sensitivity analyses. Having a MI or stroke will most probably make the participants change their activity level, thus, first we tested for reverse causation bias. To do so, MI and stroke cases during the first two years after enrollment was excluded. Secondly, since we only had baseline data of the exposure and no information of possible changes in PA during the follow-up time, which could affect the occurrence of the outcomes studied, we limited the follow-up time to 10 years to see if the association was affected. Thirdly, to test the effect of extremely high versus extremely low PA, we ordered the exposure into 9 groups and repeated the main analyses. Lastly, waist circumference was a potential confounder to adjust for. However, since as many as 8,986 participants had missing values on waist circumference, this would have drastically reduced the size of our main study sample, specifically for the sex stratified analyses. Therefore, we adjusted for this in a sensitivity analysis.

Finally, since we had missing values on exposures and covariates, we performed a multiple imputation analysis under the assumption of data missing at random, which means that we replaced missing data by generating possible values based on the relationship between the variable with missing data and other observed variables in our data. By replacing missing data with multiple different possible values, we were given multiple data sets with replaced missing data to analyze. The resulting multiple estimates were then combined to one result, as a way to reduce the chance of drawing an inaccurate conclusion of the missing value.

The limitation of multiple imputation is that it can be argued that we make up data. However, analyzing only complete cases would result in a smaller sample with results limited to participants with complete data.

3.3 Study II

Research question: Does the DiaCert intervention promoting steps for 3 months have an effect on physical activity and cardiometabolic markers in persons with T2D?

Study design

Study II is based on data from an RCT; The DiaCert-study (106). Figure 5 shows a flow-chart of the study design.

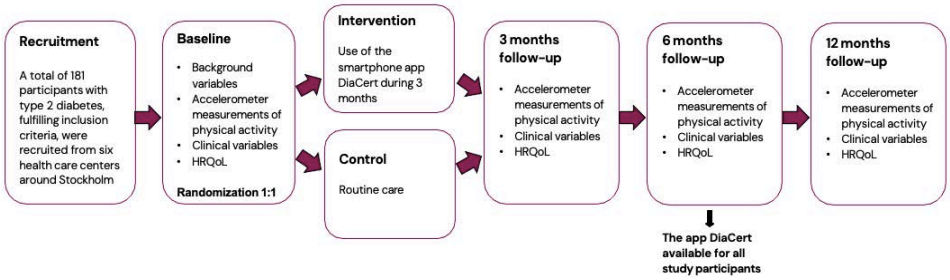


Figure 5. Flow-chart of the DiaCert study design.

The DiaCert-study

The DiaCert-study was a two-armed RCT of persons with T2D, mainly completed within primary health care. The study participants were recruited from five primary care centers and one specialized medical center around Stockholm, Sweden. Baseline data was collected continuously between February 2017 and June 2018, and the data collection was ended in June 2019.

At baseline, the participants were randomly allocated (1:1) into either the use of the smartphone app DiaCert for 3 months in addition to clinical routine care (intervention arm), or to clinical routine care only (control arm) prescribed by their regular primary care physician and diabetes nurse. Randomization was done using a random allocation sequence list generated in Stata 14.0. We randomized men and women separately in blocks of ten within each care center, to obtain an even distribution in the two study arms. This was made continuously as participants were included in the study, and they were informed about their allocation at the baseline meeting.

The intervention group got access to the DiaCert app one week after the baseline meeting, when the baseline accelerometer measurement of PA was finished. At the 3-month follow-up, participants in the intervention arm removed the app from their phones. All the participants, in both study arms, were then offered access to the app again at the 6-month follow-up. Hence, no participants received the intervention between the 3-month and the 6-month follow-up. We followed participants for 1 year with a final 12-month follow-up. The intervention effect was only studied after 3 and 6 months, respectively, since both groups could use the app after the 6-month follow-up.

The intervention

The smartphone app DiaCert encouraged daily walking by several features. With an individual daily step-goal of at least 1,000 steps and at most 10,000 steps, the participant could see if the goal was reached in the app with the daily steps shown in numbers as well as visually being displayed by a circle gradually being filled from white to blue. The average number of steps per day during the last week was presented and a bar chart with one bar representing each day was shown, where the bar went from red to green if the goal was reached (fig. 6). Moreover, an automatic positive feedback message was received in the app when the daily goal was met.

The participants chose their own individual step-goal together with the study personnel at baseline, based on the participant's usual activity level. With connection to a digital platform, the daily steps were shared with study personnel allowing for the possibility to follow the participants activity. The study personnel contacted the participants every second week to ask if the step-goal should be increased or decreased by an even 500 steps and with a maximum goal of 10,000 steps. Furthermore, the result of the user's HbA1c that was measured at baseline and at follow-ups were also displayed in the app. The app was compatible with both iOS (version 9.2 and higher) and Android (version 4.1 and higher).

Figure 6. Screen shots of the DiaCert smartphone app. Adapted from Bonn et al (113).

Study population

We included men and women diagnosed with T2D, who were 18 years or older, who had the ability to read and understand Swedish, who were able to walk, and had access to and were able to use a smartphone. In total, we recruited 181 men and women.

Prior to the study started, power calculations were performed to ensure sufficient power to detect a clinically significant difference in MVPA after 3 months. To ensure an 80% power with a p-value of 0.05, based on the ability to detect a difference in MVPA of 8 min/day between the study arms at 3 months, our calculations resulted in a sample size of at least 100 participants completing the study in each arm. In total, we planned to recruit 250 participants to cover for a 20% dropout rate. However, the recruitment ended after 2.5 years, due to practical reasons linked to the continuous work with updating the app to run with the current iOS and android versions.

Participants with complete baseline data for each specific outcome were included in the analysis, i.e., analysis of intervention effect were made following the intention-to-treat approach. Hence, participants were studied according to their assigned group whether or not they adhered to the intervention. This ensures the randomization and thereby limits that the intervention effect is biased by confounding, however, it may underestimate the effect due to dropouts, non-adherence to the app etc. A total of 156 participants had valid accelerometer data on PA at baseline. They were therefore included in the analysis of intervention effect of the primary outcome (MVPA at 3 months of follow-up).

Outcomes

The primary outcome of objectively measured physical activity (MVPA, min/day, at 3 months of follow-up) was investigated, along with the secondary outcomes BMI, waist circumference, BP, HbA1c, and blood lipids. The primary and secondary outcomes were assessed after the 3-month long intervention and at the 6- and 12-month follow-ups. We followed participants for 12 months, however, the intervention effect was only studied after 3 and 6 months, respectively, since both groups had the possibility to use the app after the follow-up at 6 months.

To measure the primary outcome MVPA, the accelerometer Actigraph wGT3x-BT (Actigraph Corporation, www.actigraph.com) was used. The participants wore the accelerometer on their non-dominant wrist for seven subsequent days (including nighttime) at baseline and at each follow-up. Handling of accelerometer data was performed using the open-source R-package GGIR.

We included data for participants with valid wear time of at least 4 days (including at least one day during the weekend) and 16 hours per day. Non-wear time was set to 4x15 minutes and imputed averaged activity from the same time the other days were used for non-wear time. The default threshold for MVPA was 100 milligravity and sessions of at least one minute with consistent activity were included (47).

Physical activity at baseline was further assessed with two validated self-reported PA questions. One question addressing the total time spent exercising during one week and one question were the participants were asked to add together the total time spent doing other types of LPA than exercise in ≥10 minutes during a week. (114).

BP (mmHg), waist circumference (cm), height (cm), and weight (kg) were measured by study personnel, and BMI was then calculated based on the latter two (kg/m²). Blood samples were taken for the analysis of the biomarkers HbA1c (mmol/mol), total cholesterol (mmol/l), high-density lipoprotein cholesterol (HDL) (mmol/l), low-density lipoprotein cholesterol (LDL) (mmol/l), and triglycerides (mmol/l).

Statistical analysis

Descriptive statistics were computed and stratified by study group. Potential differences between the groups were determined using Student's t test for continuous variables. It compares the mean of a variable between groups, and Chi-square tests for categorical variables, which compares the distribution of a variable between groups.

To study the intervention effect when having repeated measures, we used Linear mixed models to assess any change in outcomes at 3 and 6 months of follow-up, respectively, between the groups. All participants with complete data at baseline for each specific outcome were included in the analysis of intervention effect, i.e., intention-to-treat analyses. Since missing MVPA data at baseline was missing equally much in both study groups, we assumed that it was missing at random. However, as the primary outcome MVPA did differ significantly between the two study groups at baseline, we conducted a sensitivity analysis adjusting the models for baseline levels of MVPA using the methods described by Twisk et al (115). Moreover, we also performed post-hoc sensitivity analyses with data on PA from the self-reported questionnaire, using multiple imputation and thereafter fitting linear mixed models using the imputed data (116). This was carried out since the study participants were aware of their study arm, i.e., whether they were randomized to be a control or would get active intervention, which might have affected their baseline PA assessment.

3.4 Study III

Research question: Does the DiaCert intervention promoting steps impact HRQoL in persons with T2D?

Study design

Study III is based on data from the same intervention as study II. See Study II for more detailed information on study design.

Study population

A total of 181 eligible women and men were recruited to the DiaCert-study. See study II for inclusion criteria. Before analysis were performed in study III, we further excluded 15 individuals who did not have complete baseline data on the outcome HRQoL. After these exclusions, 166 participants were included in the analyses.

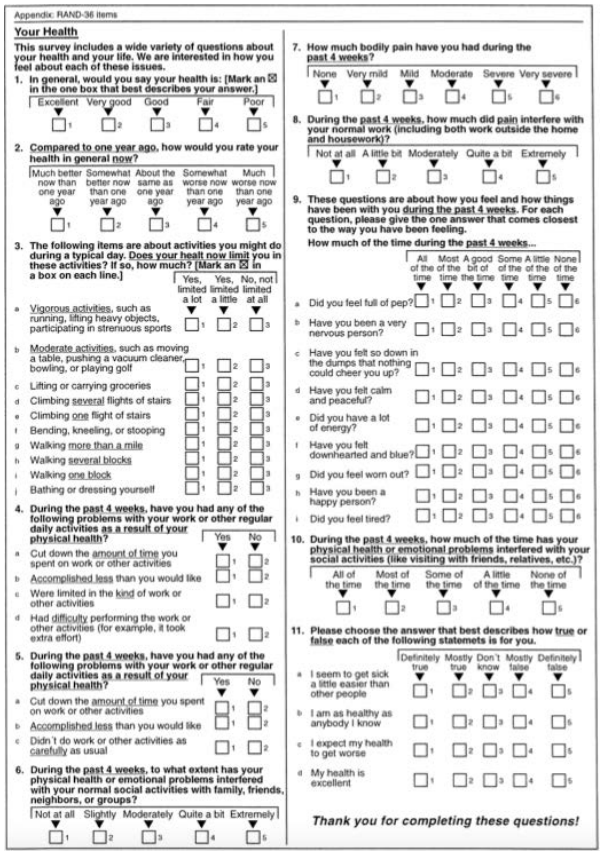
Outcome

The secondary outcome HRQoL was assessed with the questionnaire RAND-36 and studied in study III. The study participants filled out the RAND-36 at baseline and at each follow-up.

The RAND-36 questionnaire includes 36 questions about physical and emotional health (fig. 7). The questions cover eight health concepts: physical functioning, role limitations caused by physical health problems, role limitations caused by emotional problems, social functioning, emotional well-being, energy/fatigue, bodily pain, and general health perceptions. One additional question measure change in perceived health status today compared to one year ago (98, 117). The questionnaire RAND-36 is publicly available (118).

When scoring the RAND-36, each question gives a score between 0 to 100 where the score represents the percentage of a maximum score of 100. Questions in the same health concept are then averaged together. A higher score means better HRQoL (117, 119).

If there was missing data on a singular question, health concept scores were based on the average for all answered questions included in that specific health concept. Only participants with baseline data on all health concepts were included in the analysis. Fifteen participants were excluded due to incomplete data on RAND-36 health concepts at baseline.



Appendix: RAND-36 items

Your Health

This survey includes a wide variety of questions about your health and your life. We are interested in how you feel about each of these issues.

1. In general, would you say your health is: [Mark an ☒ in the one box that best describes your answer.]

Excellent 1 | Very good 2 | Good 3 | Fair 4 | Poor 5

2. Compared to one year ago, how would you rate your health in general now?

Much better now than one year ago 1 | Somewhat better now than one year ago 2 | About the same as one year ago 3 | Somewhat worse now than one year ago 4 | Much worse now than one year ago 5

3. The following items are about activities you might do during a typical day. Does your healt now limit you in these activities? If so, how much? [Mark an ☒ in a box on each line.]

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	1	2	3
b Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	1	2	3
c Lifting or carrying groceries	1	2	3
d Climbing several flights of stairs	1	2	3
e Climbing one flight of stairs	1	2	3
f Bending, kneeling, or stooping	1	2	3
g Walking more than a mile	1	2	3
h Walking several blocks	1	2	3
i Walking one block	1	2	3
j Bathing or dressing yourself	1	2	3

4. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	Yes	No
a Cut down the amount of time you spent on work or other activities	1	2
b Accomplished less than you would like	1	2
c Were limited in the kind of work or other activities	1	2
d Had difficulty performing the work or other activities (for example, it took extra effort)	1	2

5. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	Yes	No
a Cut down the amount of time you spent on work or other activities	1	2
b Accomplished less than you would like	1	2
c Didn't do work or other activities as carefully as usual	1	2

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

Not at all 1 | Slightly 2 | Moderately 3 | Quite a bit 4 | Extremely 5

7. How much bodily pain have you had during the past 4 weeks?

None 1 | Very mild 2 | Mild 3 | Moderate 4 | Severe 5 | Very severe 6

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all 1 | A little bit 2 | Moderately 3 | Quite a bit 4 | Extremely 5

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling.

How much of the time during the past 4 weeks...

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
a Did you feel full of pep?	1	2	3	4	5	6
b Have you been a very nervous person?	1	2	3	4	5	6
c Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
d Have you felt calm and peaceful?	1	2	3	4	5	6
e Did you have a lot of energy?	1	2	3	4	5	6
f Have you felt downhearted and blue?	1	2	3	4	5	6
g Did you feel worn out?	1	2	3	4	5	6
h Have you been a happy person?	1	2	3	4	5	6
i Did you feel tired?	1	2	3	4	5	6

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time 1 | Most of the time 2 | Some of the time 3 | A little of the time 4 | None of the time 5

11. Please choose the answer that best describes how true or false each of the following statemets is for you.

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a I seem to get sick a little easier than other people	1	2	3	4	5
b I am as healthy as anybody I know	1	2	3	4	5
c I expect my health to get worse	1	2	3	4	5
d My health is excellent	1	2	3	4	5

Thank you for completing these questions!

Figure 7. Image of the RAND-36 questionnaire. Reprinted with permission (118).

The history of RAND-36 is presented under Literature review. The RAND-36 and the SF-36 includes the same questions. However, the scoring of the two questionnaires differs in two of the health concepts: general health and bodily pain. The difference has been considered negligible (98). Still, direct comparison between the two questionnaires is often not recommended without recalculation of bodily pain and general health first (120).

The health concepts, covering different aspects of health status, are sometimes further divided into two summary measures: the physical component summary (PCS) and the mental component summary (MCS). This is primarily seen in studies using the SF-36. However, different methods for the computation of the summary measures can be found in the literature, including which health concept that should be comprised in which of the two (or both) summary measures as well as different scoring algorithms (118). There is no specific scoring system for the RAND-36 and the RAND Corporation does not supply recommendation on which

method for computing summary measures, if any, to use (121). Furthermore, the manual for the Swedish RAND-36 does not support calculating summary measures (120).

For example, in one of the scoring methods seen in the literature, each of the eight health concepts affects both the PCS and the MCS. The concepts physical functioning, role limitations caused by physical health problems, bodily pain, and general health mainly reflect physical health positively, while the concepts emotional well-being, role limitations caused by emotional problems, social functioning and energy/fatigue mainly reflect mental health positively. However, energy sometimes reflects both the physical and mental health. High physical health concept scores generate a high PCS, and concurrently affect the MCS negatively. Thereby it lowers the MCS, even if the individual does not score low on the mental health concept scores, and vice versa (118, 122). In another scoring method, the health concepts physical functioning, role limitations caused by physical health problems, bodily pain, and general health only measure PCS and the other four health concepts only measure MCS. PCS do not affect MCS in either a positive or negative way, and vice versa. Since there is no recommended scoring algorithm for calculating PCS and MCS of the RAND-36, we did not use the summary measures.

Statistical analysis

First, to test if there were any statistically significant differences between the baseline characteristics of the study groups, the Mann–Whitney test were performed for continuous and Chi-square test was performed for categorical variables.

Within-group differences between baseline and follow-up in study III, were tested using the Wilcoxon signed rank-test. It is based on ranks and performed when two groups of measurements are dependent on each other, e.g., pre and post intervention in the same individual. To study the intervention effect when having repeated measures, we used the Generalized estimation equations (GEE) (106). At follow ups, the between group difference was assessed, while taking the within-subjects differences into account. The intervention effect was expressed in terms of change in HRQoL from baseline to follow-ups between the two study groups. Analysis of intervention effect were made following the intention-to-treat approach. We also performed sensitivity analyses where we only included participants (n=126) with complete RAND-36 data at baseline and at follow-ups.

3.5 Study IV

Research question: Do the two automatic BP monitors, Beurer BM 85 and Andersson Lifesense BDR 2.0, with the ability to transfer BP data via Bluetooth, measure BP as good as the available diagnostic standard of manual BP monitoring?

Study design

In study IV, baseline data from the DiaCert study was used. Two home BP monitors with the mHealth solution of transferring BP data via Bluetooth were validated with data collected at baseline in the DiaCert-study. More detailed information on study design is described under study II and III.

Study population

Both BP monitors validated, Beurer BM 85 Bluetooth and Andersson Lifesense BDR 2.0, are automatic monitors with a Bluetooth function allowing for data transferring to digital instruments.

The procedure of the BP measurements at the DiaCert baseline meeting was the following: the BP was first measured using a manual BP monitor. Then, BP was measured at the upper arm using Beurer BM 85 and Andersson Lifesense BDR 2.0 with no specific order, by the study personnel and after the participant had been sitting down with their legs uncrossed for at least 5 minutes.

Of the 181 participants recruited in the DiaCert-study, one participant did not have data on manual BP, 11 participants did not have data on Beurer BM 85, and 25 participants did not have data on Andersson Lifesense BDR 2.0 (due to larger arm circumference than recommended for the cuffs or due to battery discharge). In total, 169 participants had BP measurements from Beurer BM 85 and 155 participants from Andersson Lifesense BDR 2.0. See Study II for more detailed information on study population.

Statistical analysis

The characteristics of the study population at baseline were stratified into low BP (<140/<90mmHg) or high BP (≥140/or ≥90mmHg). Then, the statistical tests Student's t tests and Chi- square test were performed to assess any potential significant differences between the participants with low versus high BP.

We subtracted the manual measurement from the automatic measurement for each monitor to calculate any differences in SBP and DBP, respectively. Then, we categorized the participants into four groups classified by the differences in SBP and DBP according to whether they were within 5, 10, 15, or more than 15mmHg.

The Spearman rank correlation coefficient was used. It tells us the strength of the relationship between the two measurement methods. It ranges from -1 to 1, with -1 or 1 being a perfect negative or positive correlation and equals to 0 if there is no correlation. Spearman's rank correlation is based on rank and non-parametric. A high correlation does not by definition mean that the two measurement methods agree. If one measurement always increases when the other increases (but no need to increase exactly as much), the rank correlation will be 1, i.e., there is a perfect rank correlation. If one measurement decreases when the other increases, the Spearman correlation coefficient is negative. A correlation of zero means that there is no tendency for one measurement to increase nor decrease when the other increases.

Further, a Bland-Altman plot was conducted. The Bland-Altman plot gives us a visual assessment of the association with a graph, by plotting the differences in BP between the automatic monitor and the manual monitor for each individual (on the y-axis), against the mean BP of the two measurements (on the x-axis).

We also performed a sensitivity analysis with the measurements from Beurer BM 85 where we included only the 155 participants in whom BP also was measured using Andersson Lifesense BDR 2.0.

3.6 Ethical considerations

The ethical considerations relevant to study I-IV are described below and are based on the four ethical principles for medical research involving humans: autonomy, justice, beneficence, and non-maleficence. The latter two refers to "to help and do no harm", while autonomy simplified refers to that all persons have the right to decide for themselves, and justice is generally interpreted as fair treatment of persons. All studies comply with the Declaration of Helsinki (123).

In Study I, we used data from several registries with nationwide coverage (including Swedish Population Register, National Inpatient and Outpatient Register, and Cause of Death Register). The participants were informed about the aims of the study, including linkages to national registers, so that they could make an independent decision before providing consent to participate in the study. When signing the written consent, they also filled in their national registration numbers, acting as personal identifiers for Swedish residents. Thereby, follow-up of participants was enabled by linkages to Swedish national registries allowing for the identification of diagnosis, death, emigration etc. The fact that the participants gave their written consent at baseline in 1997, and that the follow-up was in 2016 when several linkages had been added, may be a potential threat to autonomy. However, when the participants gave written consent prior to participating, they were informed about the prospective nature of the cohort and the aim of studying several diseases. To participate was entirely voluntary, with the possibility to resign at any time. All data was stored in de-identified databases at Karolinska Institutet.

Similarly, in the DiaCert-study (study II-IV), the participants provided written informed consent before participating. All data including questionnaires, blood samples, and measurements of body composition, BP etc. was transferred to a data file where the data was provided with a code, i.e., all data has been unidentified, and then stored anonymously at Karolinska Institutet. This ensures that the information is not made available to unauthorized persons. Furthermore, since anonymized data are compared between groups within a large study sample as the general population in study I and persons with T2D in study II-IV, it would be virtually impossible to trace data to individual participants. The results will only be displayed at a statistical group level. Thus, the participants' right to integrity is assured when the data is published.

In study I, the 36-page questionnaire filled out by the participants at baseline were in Swedish only, and participation could therefore only be offered to those who could read and understand Swedish. Similarly, the inclusion criteria of the DiaCert-study included ability to read and understand Swedish. Furthermore, they included being able to walk, and having access to and being able to use a smartphone. Those who did not have access to a smartphone were not offered participation in the studies. This can be perceived as unfair since smartphones for lending was not offered. For persons who were unable to walk, no registration of any other form of PA was offered, thus preventing their participation. Furthermore, the app was not offered in a language other than Swedish, hence the inclusion criteria of being able to read and understand Swedish. All ethical problems described above can be assigned to "the principle of justice" i.e., it is perceived as unjust to be excluded from participation in a study due to Swedish language difficulty, no access to a smartphone, or not being able to walk. However, who is offered to participate in the study must be based on the purpose of the study. Since the aim was to evaluate a step promoting app, the principle of justice can be considered insignificant.

Since the DiaCert-study is a clinical trial with a 1:1 randomization at baseline, only the intervention group had access to the smartphone app DiaCert at baseline. However, all participants, including the controls, were given the opportunity to use the app after the 6-month follow-up. The advantage of choosing an RCT as the study design should be weighed against the injustice of not being able to access the app until after 6 months. The advantage of obtaining more useful results will ultimately benefit the research interest, the public interest, and the participants.

Participation in the DiaCert-study was, in general, a low risk. However, it could be so that participation might have increased the stress levels of the participant, if he or she felt a great pressure of increasing the daily PA. Moreover, increased PA decreases the glucose levels. Participants using insulin have the highest risk for hypoglycemia. Participants may have felt pressured to participate in the study when asked by their regular physician or diabetes nurse. However, those interested were then contacted by study personnel who also met the participants at baseline and at each follow-up. The participants could resign at any time.

Measurements of anthropometrics and clinical variables were made at baseline and at follow-ups. Regular controls and measurements are common practice in this patient group, but it is done at different frequencies depending on well-being,

blood sugar control, BP etc. For some participants, the measurements were done more often than usual when participating in the study, with e.g., more occasions with discomfort of venous sampling. Thus, this can be related to the "non-maleficence principle". However, the harm can be considered to be relatively minor, both in terms of harm occurring and its size. Also, the participants may see it as an advantage to possibly have their values checked more often than they would if they did not participate in the study, which may indicate that the benefit is greater than the harm to the individual participant.

With the study hypothesis of increasing PA and improving several health outcomes, the intent is to do good for the participants, i.e., "the principal of beneficence". Furthermore, the research interest should also be taken in account. Possible benefits of study I include the possibility to gain new knowledge about PA and the risk of MI and stroke that could be implemented in clinical guidelines. This benefits the study participants, as well as populations, at a national and international level. The public interest is likely to be large, as the cost of T2D, stroke, and MI is high and the patient suffering great. Moreover, the results of a mHealth intervention may directly be implemented in healthcare through new digital solutions as a supplement to healthcare. In this way, resources can be made available for patients in need of increased PA, not only for persons with T2D, but also for other patient groups.

All studies were approved by the Regional Ethical Review Board, Karolinska Institutet, Stockholm, Sweden:

Study I: Dnr: 2017/796-31; 97-205

Study II-IV: Dnr: 2016/2041-31/2; 2016/99-32; 2017/1406-32; 2018/286-32.

4 Results

4.1 Study I

Among the 31,581 participants from the SNMC, 66% were women. The participants in the highest tertile of TPA were more likely to be younger, have a lower education level, and have a lower BMI and waist circumference than those with lower TPA. Women in the study tended to have more MET-h in activities with a MET value of 1.5-2, while men tended to have more MET-h in activities with higher intensity level (MET ranging from 3-8). During the 17.9 years of mean follow-up, 1,621 incident cases of MI and 1,879 of stroke were detected.

Total physical activity and MI

We found a statistically significant inverse association between level of TPA and risk of MI in women. There was a 22% lower risk of MI in the highest tertile (HR: 0.78; 95% CI: 0.63–0.97; p for trend=0.02) compared with the lowest after adjusting for potential confounders. Moreover, we found a 1% lower risk of MI with each 1 METh/d increase (95% CI: 0.98–0.99). No association was observed between TPA and MI among all participants, nor among men when analyzed separately.

Total physical activity and stroke

We did not find any association between TPA and stroke, neither in women or men, nor when we analyzed hemorrhagic and ischemic stroke separately.

Leisure time physical activity and MI

The HR and corresponding 95% CIs in the highest tertile compared to the lowest of the association between LPA and risk of MI among all participants was 0.79 (95% CI: 0.66–0.94; p for trend= <0.01) in the multivariable-adjusted model (table 2). When analyzing men and women separately, we only found a statistically significant protective effect of LPA on risk of MI in men with a reduced risk of 22% (HR: 0.78; 95% CI: 0.62–0.98; p for trend=0.03). On the contrary, when the exposure was studied as a continuous variable the effect was only significant in women.

Leisure time physical activity and stroke

When investigating the association between LPA and stroke, an 22% lower risk was found in men in the third tertile versus the first (HR: 0.78; 95% CI: 0.61–0.99; p for

trend=0.04) in the multivariable-adjusted models (table 2). This was not seen when studying hemorrhagic and ischemic stroke separately.

No significant association was observed among all participants for total stroke, nor for ischemic and hemorrhagic stroke separately in the multivariable-adjusted models, when using LPA categorized into tertiles. However, among the total population, each 1 METh/day increase in LPA was associated with a 7% (95% CI: 0.86–0.99) lower risk of hemorrhagic stroke. No significant association was found among women when analyzed separately.

Table 2. Hazard ratios of myocardial infarction and stroke for leisure time physical activity (LPA).

Sex-specific tertiles of LPA (METh/day)	Low	Medium	High	*P* trend
Male	0-1.6	>1.6-3.6	>3.6-16.3	
Female	0-1.5	>1.5-3.1	>3.1-16.3	
Total				
Myocardial infarction				
Number of events	428	404	250	
Person-years	148,444	145,680	147,299	
Event rate per 100,000 person-years[a]	288.3	277.3	169.7	
HR (95% CI)[a]	1.00 (reference)	0.88 (0.77-1.01)	0.75 (0.64-0.87)	0.00
HR (95% CI)[b]	1.00 (reference)	0.92 (0.79-1.06)	0.81 (0.68-0.95)	0.01
HR (95% CI)[c]	1.00 (reference)	0.89 (0.76-1.03)	0.79 (0.66-0.94)	0.01
Stroke (ischemic and hemorrhagic)				
Number of events	490	461	307	
Person-years	148,334	145,194	147,037	
Event rate per 100,000 person-years[a]	330.3	317.5	208.8	
HR (95% CI)[a]	1.00 (reference)	0.88 (0.77-1.00)	0.79 (0.69-0.91)	0.01
HR (95% CI)[b]	1.00 (reference)	0.92 (0.80-1.05)	0.83 (0.71-0.97)	0.02
HR (95% CI)[c]	1.00 (reference)	0.93 (0.81-1.07)	0.86 (0.73-1.00)	0.06
Male				
Myocardial infarction				
Number of events	234	239	143	
Person-years	47,753	46,096	47,342	
Event rate per 100,000 person-years[a]	490.0	518.5	302.1	
HR (95% CI)[a]	1.00 (reference)	0.92 (0.77-1.11)	0.76 (0.61-0.93)	0.01
HR (95% CI)[b]	1.00 (reference)	0.96 (0.79-1.17)	0.80 (0.64-1.00)	0.04
HR (95% CI)[c]	1.00 (reference)	0.96 (0.78-1.17)	0.78 (0.62-0.98)	0.03
Stroke (ischemic and hemorrhagic)				
Number of events	203	221	127	
Person-years	48,129	46,193	47,516	
Event rate per 100,000 person-years[a]	421.8	478.4	267.3	
HR (95% CI)[a]	1.00 (reference)	0.96 (0.79-1.16)	0.75 (0.60-0.94)	0.01
HR (95% CI)[b]	1.00 (reference)	0.95 (0.77-1.16)	0.78 (0.61-0.98)	0.03
HR (95% CI)[c]	1.00 (reference)	0.94 (0.76-1.16)	0.78 (0.61-0.99)	0.04
Female				
Myocardial infarction				
Number of events	194	165	107	
Person-years	100,691	99,584	99,957	
Event rate per 100,000 person-years[a]	192.7	165.7	107.0	
HR (95% CI)[a]	1.00 (reference)	0.83 (0.67-1.02)	0.74 (0.58-0.93)	0.01
HR (95% CI)[b]	1.00 (reference)	0.86 (0.68-1.07)	0.82 (0.64-1.06)	0.13
HR (95% CI)[c]	1.00 (reference)	0.80 (0.63-1.01)	0.80 (0.61-1.04)	0.10
Stroke (ischemic and hemorrhagic)				
Number of events	287	240	180	
Person-years	100,205	99,001	99,522	
Event rate per 100,000 person-years[a]	286.4	242.4	180.9	
HR (95% CI)[a]	1.00 (reference)	0.82 (0.69-0.97)	0.82 (0.68-0.99)	0.05
HR (95% CI)[b]	1.00 (reference)	0.89 (0.74-1.07)	0.88 (0.72-1.07)	0.23
HR (95% CI)[c]	1.00 (reference)	0.92 (0.76-1.11)	0.91 (0.74-1.13)	0.43

HR Hazard ratio, *CI* Confidence interval

[a] Adjusted for age and sex at enrollment

[b] Adjusted for age, cigarette smoking, alcohol consumption, level of education, and body mass index

[c] Adjusted for age, cigarette smoking, alcohol consumption, level of education, body mass index, hypertension, diabetes, and lipid disturbance

Additional analyses and sensitivity analyses

Most of the sensitivity analyses did not significantly affect our results. First, when excluding MI and stroke that occurred during the first two years of follow up, the effect of LPA on the risk of stroke was no longer statistically significant among men. The other findings remained similar. Secondly, by limiting the follow-up time to 10 years, our results were not affected by this sensitivity analysis. Thirdly, when testing the effect of extremely high versus extremely low PA among all participants, we found a similar inverse association for LPA and the risk of MI, and between LPA and stroke, and similarly no association was found between TPA and MI or stroke. Lastly, after adjusting our main models for waist circumference due to the high missing values as well as when using imputed missing data, our results remained similar.

When investigating the role of potential effect modifiers, we found that sex was an effect modifier between TPA and MI. We did not find effect modification by sex in any other model, nor for age, BMI, smoking, and alcohol consumption at baseline.

4.2 Study II

In the DiaCert-study, a total of 181 participants with T2D were included. Of these, 93 and 88 participants were randomized to the intervention and control group, respectively. The mean age at baseline was 60.0 years, the mean BMI was 30.4 kg/m2, the mean HbA1c was 53.6 mmol/mol, and 65.8% were men. At baseline, 156 participants had valid data on accelerometer measured PA, of which 137 (87.8%) also had valid data on the primary outcome at the follow-up at 3 months.

There was a statistically significant difference between the study groups in accelerometer measured MVPA at baseline. The intervention group had a higher MVPA of 38.3 min/day compared to 29.8 min/day in the control group ($p = 0.04$). After using the imputed data for the intervention group, MVPA was estimated to be lower (32.3 min/day), and there was no statistically significant difference between the groups ($p = 0.62$). In addition, when analysing the self-reported PA at baseline, there was no statistically significant difference between the groups ($p = 0.20$ for time spent exercising and $p = 0.20$ for total leisure time activity).

We found no statistically significant differences between the study groups regarding other baseline characteristics (age, sex, BMI, waist circumference, BP,

HbA1c, total cholesterol, LDL, HDL, triglycerides, smoking, time since diabetes diagnosis, education level, and care center).

Intervention effect

When analyzing the difference in min/day of MVPA between the groups after 3 months, we found a statistically significant predicted mean difference of 10.05 minutes (95% CI: 1.66- 18.44), with a higher MVPA in the intervention group than in the control group. No difference in MVPA between the intervention and control group was seen at the 6-month follow up (5.02, 95% CI: -3.72 to 13.75). The mean change in min/day of MVPA in the intervention and control group, respectively, is graphically illustrated from baseline to follow-ups in figure 8.

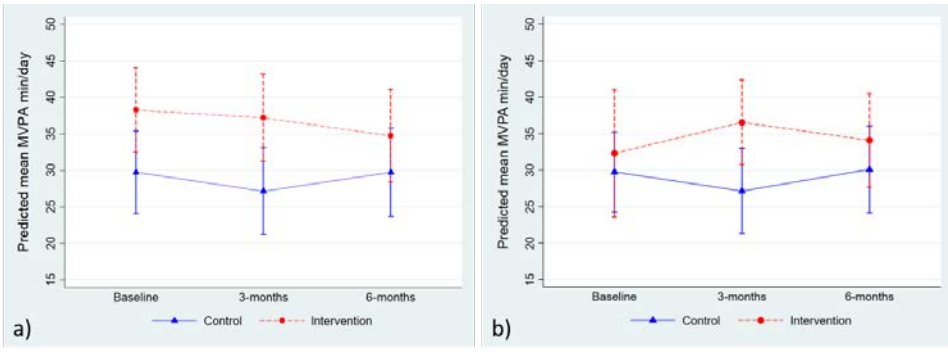


Figure 8. Changes over time in moderate-to-vigorous physical activity (MVPA, min/day) in the intervention and control group in a) main analysis and b) sensitivity analysis using imputed data for MVPA at baseline.

When analyzing the intervention effect, i.e., the difference in change in MVPA from baseline to follow-ups between the groups, we found no statistically significant effect on MVPA at the 3- and 6-month follow up, respectively, nor when we used the imputed baseline data. See table 3.

Table 3. The intervention effect on daily minutes of MVPA at 3- and 6-months of follow up

	Group by Time interaction[a]	
	β	95% CI
3-months	1.51	(-5.53 to 8.55)
3-months, using imputed data	6.86	(-4.05 to 17.78)
6-months	-3.53	(-10.97 to 3.92)
6-months, using imputed data	1.44	(-9.87 to 11.76)

[a] Results from linear mixed models

We found no statistically significant differences in any of the secondary outcomes after the 3-month long intervention. At the 6-month follow-up, there was a statistically significant intervention effect of BMI (group by time interaction: 0.52, 95% CI: 0.20 to 0.84), while no difference was seen in mean BMI between the groups (predicted difference in mean: 0.11, 95% CI: -1.47 to 1.67). Moreover, participants in the control group had a somewhat higher mean BMI at baseline with 30.6 kg/m^2 compared to 30.2 kg/m^2 in the intervention group, although this difference was not statistically significant (p=0.61). We found no statistically significant differences in intervention effect in any of the other secondary outcomes at the 6-month follow- up.

4.3 Study III

Of the 181 participants included in the DiaCert-study, 166 participants were included in the analysis of study III. In total, 15 participants had missing data on RAND-36 at baseline and were thus excluded. The majority were men (65%), and the mean age among all participants were 60.2 years. A significant lower score for the health concept score energy/fatigue was seen in the intervention group compared to the control group (58.4 versus 64.9, p = 0.04) at baseline. There were no statistically significant differences between the groups regarding the other health concept scores, nor the other baseline characteristics (sex, age, BMI, waist circumference, educational level, or smoking status).

Intervention effect and sensitivity analysis

Within-group analyses showed a significantly higher HRQoL in three of the health concept scores within the intervention group at the 3-month follow-up. Those were: emotional well- being (p = 0.02), energy/fatigue (p = 0.02), and health change (p = 0.02). In the control group, a significantly lower score for role limitations caused by physical health problems was seen (p = 0.02) at the 3-month follow-up.

Between-group analyses presented a statistically significant difference in means in the health concept role limitations caused by physical health problems (-14.8, 95% CI -26.5 to -3.1) at the follow-up after 3 months, with higher scores in the intervention group.

The difference in change in HRQoL from baseline to follow-ups between the groups, i.e., the intervention effect, is shown in table 4. We found a statistically

significant effect on the health concept scores; role limitations caused by physical health problems (-16.9; 95% CI -28.5 to -5.4), role limitations caused by emotional problems (-13.9; 95% CI -25.8 to -2.1), and emotional wellbeing (-5.7; 95% CI -10.4 to -1.0), at the 3-month follow-up with improved scores in the intervention group. This was no longer seen after 6 months. Nevertheless, the overall trend was significant in the intervention group for role limitations caused by physical health problems (p = 0.01). In sensitivity analyses where we included only complete cases (126 participants), results remained similar at follow-ups, but only the intervention effect of role limitations caused by physical health problems remained statistically significant.

Table 4. The intervention effect on HRQoL at 3- and 6-months of follow up.

RAND-36 health concepts scores	3 months[a]		6 months[a]		
	Intervention effect	(95% CI)	Intervention effect	(95% CI)	*p* for trend[a]
Physical functioning	-3.1	(-8.7 to 2.5)	1.6	(-4.3 to 7.4)	0.28
Social functioning	-5.9	(-12.8 to 1.0)	-5.3	(-12.6 to 1.9)	0.19
Role functioning/physical	-16.9	(-28.5 to -5.4)	-3.9	(-16.0 to 8.2)	0.01
Role functioning/emotional	-13.9	(-25.8 to -2.1)	-10.8	(-23.2 to 1.5)	0.05
Emotional well-being	-5.7	(-10.4 to -1.0)	-3.4	(-8.3 to 1.6)	0.06
Energy/Fatigue	-3.4	(-8.2 to 1.5)	-1.5	(-6.6 to 3.6)	0.40
Pain	-0.2	(-7.4 to 7.1)	-1.6	(-9.2 to 6.0)	0.90
General health	1.0	(-3.3 to 5.3)	-0.8	(-5.3 to 3.7)	0.74
Health change	-5.0	(-12.5 to 2.5)	0.9	(-6.9 to 8.8)	0.28

[a] Calculated using generalized estimating equation

Role limitations caused by physical health problems and role limitations caused by emotional problems measure problems with work or other regular daily activities during the past 4 weeks due to physical and emotional problems, respectively. Emotional well-being measures symptoms of depression and nervousness/anxiety during the past 4 weeks. A 5-point difference is seen as clinically relevant, which was shown for all three of the health concepts that showed an improvement in our study after 3 months (99).

4.4 Study IV

In study IV, 180 participants with data on manual BP were included. Participants mean age and BMI were 60.1 (SD 11.4) years and 30.4 (SD 5.4) kg/m2, respectively. The mean BP for all participants with the manual monitor was 138 (SD 15.5) / 83

(SD 9.7) mmHg. Descriptive characteristics of the participants with low BP versus high BP did not differ significantly regarding age, gender, or smoking status, however, we found a statistically significant higher BMI (p = 0.02) and a statistically significant greater waist circumference (p = 0.04) for men in the group with high BP compared to the group with low BP.

Validity

The mean difference between each automatic BP monitor and the manual BP monitor for SBP and DBP, respectively, are shown in table 5.

Table 5. The mean difference in systolic and diastolic blood pressure between Beurer BM 85 and the manual monitor and Andersson Lifesense BDR and the manual monitor, respectively.

	Mean difference (SD)	
	Systolic blood pressure (mmHg)	Diastolic blood pressure (mmHg)
Beurer BM 85	11.1 (11.2)	8.0 (8.1)
Andersson Lifesense BDR	3.2 (10.8)	4.2 (7.2)

We found that 49.1% (83/169) of all measurements by Beurer BM 85 differed by 10mmHg or less in SBP and 30.8% (52/169) by 5mmHg or less for DBP. For Andersson Lifesense BDR 2.0, the corresponding percentages were 69.7% (108/155) for SBP and 49.0% (76/155) for DBP (fig. 9).

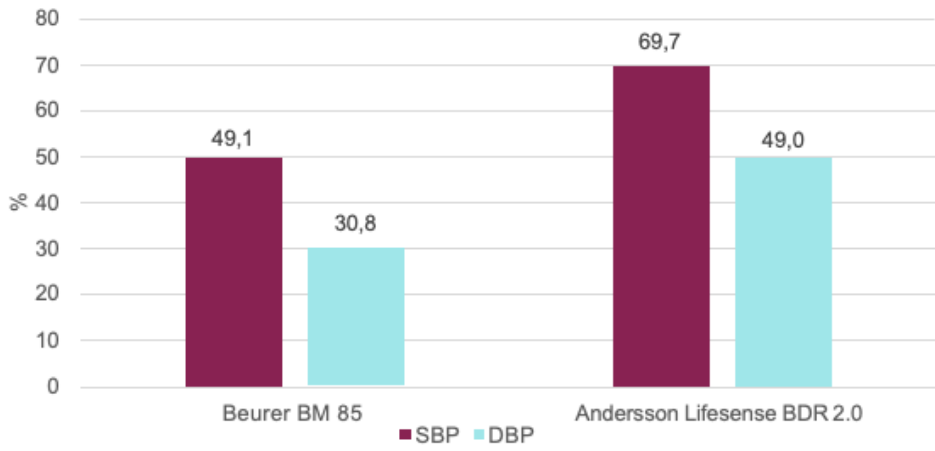


Figure 9. The percentage of measurements differing by 10mmHg or less in systolic blood pressure (SBP) and by 5mmHg or less in diastolic blood pressure (DBP) between each automatic BP monitor and the manual BP monitor.

The Spearman rank correlation coefficient for Beurer BM 85 was r=0.78 for SBP and r=0.69 for DBP, and for Andersson Lifesense BDR 2.0; r=0.78 for SBP and r=0.71 for DBP, with a significant correlation between all automatic BP measurements and the manual measurements. The Bland-Altman plots in figures 10 and 11 show that the data points in all of the plots are located around the means of the y-axis with the accuracy not being impacted by high or low BP. However, the intervals were wide and there were some outliers, although most of the data point fell within the limits of agreement (±2SD).

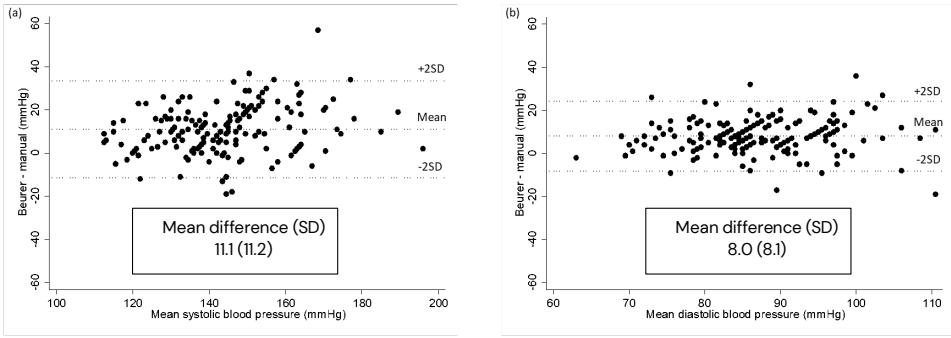


Figure 10. Bland-Altman plots of the difference between the Beurer BM 85 measurements and the manual measurements for a) systolic blood pressure and b) diastolic blood pressure.

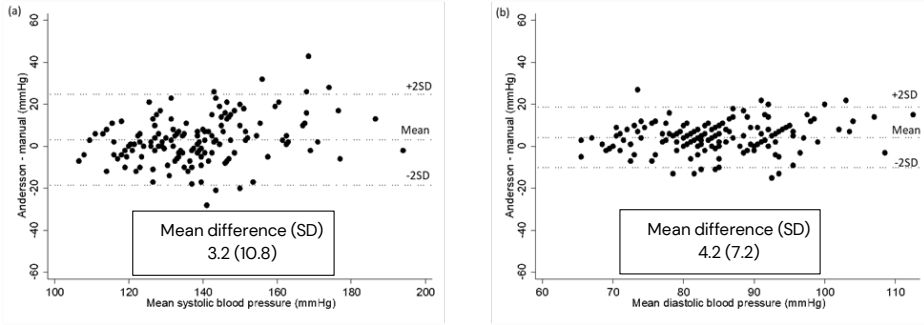


Figure 11. Bland-Altman plots of the difference between the Andersson Lifesense BDR measurements and the manual measurements for a) systolic blood pressure and b) diastolic blood pressure.

Sensitivity analysis

The findings for Beurer BM 85 remained similar when we only included the participants that we also had BP data on using Andersson Lifesense BDR 2.0.

5 Discussion

The overall aim of this thesis was to extend previous knowledge about the association between PA, cardiovascular events, and T2D that will be useful for preventing MI and stroke and improving health status in persons with T2D while using mHealth. In this chapter, the interpretations of the main findings for the studies included in this thesis are presented and discussed, followed by some methodological considerations.

5.1 Discussion of the main findings

The association between total physical activity and leisure time physical activity on the risk of MI and stroke

Our findings provide evidence that a higher level of TPA is associated with a lower risk of MI among women, while a higher level of LPA is associated with a lower risk of MI and stroke among men. Our findings are in line with results reported from previous studies with a higher LPA being associated with a lower risk of CVD (125-128). This inverse association was in a Finnish study confined to men (129), which was confirmed by our study. However, few previous studies have assessed TPA. Our findings of no effect between TPA and stroke is consistent with a previous study. The same study also found an inverse association between TPA and MI (124). In our study, this was only seen in women.

Our results showing different associations between women and men suggests that different types of PA could have diverse physiological effects, e.g., on estrogen in women that is known to have a protective effect on the cardiovascular system. Furthermore, this may also be due to the "physical activity paradox", i.e., that occupational PA (included in TPA) impact the risk of CVD negatively, with more men having physically strenuous jobs with heavy lifting etc. (55).

Nevertheless, the SNMC includes more women than men, and our sample of men may be too small to detect a statistically significant association between TPA and CVD in men. Moreover, the prevalence of MI and stroke increases at an older age in women compared to men. A longer follow-up time may have found more cases of CVD among women, with a potential association seen between TPA and the risk of stroke and between LPA and the risk of MI and stroke in women. Overall, our results support previous findings that PA is inversely associated with the risk of MI and stroke, and it further highlights potential differences regarding LPA and TPA on the risk of CVD between the sexes.

The effect of an app-based step intervention

Our results add to the conflicting evidence on the effect on smartphone app interventions on MVPA, clinical markers, and HRQoL in persons with T2D (83, 85, 86, 88, 89, 130, 131).

There are apps targeting lifestyle behaviors among persons with T2D that have been shown to be successful (82-86). However, contrary to our DiaCert-app, most of the apps studied include multiple functions. Few studies have primarily targeted PA in smartphone app interventions among persons with T2D. Our results of no increase in accelerometer measured MVPA after 3- and 6-months of follow up compared to routine care is supported by a study on an app-based intervention with interval walking that did not find an effect on MVPA after 52 weeks in persons with T2D (86). However, in another eHealth/mHealth intervention targeting PA among people with T2D, an increasement in PA was found in the intervention group compared to the control group (85).

There is convincing evidence that PA contributes to a lower risk of CVD with a curvilinear dose- response relationship, i.e., with greatest gain for those who increase their activity from being inactive (75). An increase of only 5 minutes of MVPA per day for people at a low PA level has shown to give a decrease in risk of all-cause mortality of nearly 40% (75). We hypothesized that our participants would have a low activity level at baseline, given their T2D (132, 133), and with a clinically significant difference between groups after the 3-month long intervention of 8 minutes/day in MVPA. An improvement of 8 minutes per day would give 56 minutes per week. Almost one extra hour MVPA per week could make people on a low activity level to reach recommendations and thereby achieve health benefits.

The participants in the DiaCert-study already met the level of recommendations at baseline according to the accelerometer measurements (more than 30 minutes/day on average). This may have contributed to the result of no effect on the primary outcome since a high activity level at baseline makes improvement more difficult. The health benefits gained are greatest for those who start from being inactive or with a low activity level, according to the curvilinear dose-response relationship between PA and health. Hence, the participants in the DiaCert-study were not on a low activity level at start of the study as assumed.

Further, at the baseline meeting, the participants were informed about their group allocation. The accelerometer measurements were performed after the baseline meeting, that is, prior to the intervention group was given access to the DiaCert-app and the intervention started. Not being blinded to their group allocation may have influenced their PA level during the days of accelerometer measuring. This is a clear limitation of the study.

Although we found no effect on any clinical variables studied at the 3- and 6-months follow-up in the DiaCert-study, results from other studies indicate that mHealth targeting lifestyle in persons with T2D can have a positive effect on cardiometabolic markers were HbA1c-levels are most often studied (83, 84, 130, 134). However, unlike the DiaCert-study, most app interventions showing an effect on HbA1c include monitoring of blood glucose, which could be one possible explanation for the unchanged HbA1c in our study. Moreover, it is known that aerobic PA combined with muscle-strengthening PA has the greatest effect on HbA1c (5, 135, 136). Support for muscle-strengthening PA was not included as an intervention component in the DiaCert-study.

As mentioned above, the majority of apps previously evaluated for self-management of T2D vary in the functions they provide. PA is seldom the primarily target, and the effect on HRQoL is even more seldom studied. The existing evidence on the effect of app interventions on HRQoL is conflicting (86, 88, 89). In an app intervention targeting interval walking in persons with T2D with the primary outcome MVPA, HRQoL was also studied. Similarly with the results from the DiaCert-study, physical HRQoL was improved, although MVPA was not, implying that this improvement was driven by something else than change in PA (86).

Behavior change techniques as user-friendly design, goal-setting, feedback, and self-monitoring in apps have been shown to improve effectiveness in attaining health behavior change (82, 87). Even though we did not see an effect on the primary outcome of MVPA at 3 months, the included app features mentioned above may have contributed to the improvement of HRQoL. Continuity of care has been found to improve HRQoL in persons with T2D (137), hence, the active support from the app between regular health care visits might affect the HRQoL. Moreover, the improvement in HRQoL was not maintained at the 6-month follow up, which may imply that daily support from the app is needed for persistent change. However, the DiaCert-app did not include reminders or the possibility to

share data with other study participants, which also have shown to be effective (138).

The RAND-36 has previously been used by persons with T2D (101-103) and the Swedish translated questionnaire has been shown to be valid, reliable, responsive and sensitive (139, 140). By choosing a questionnaire that measures several aspects of HRQoL, we aimed at measuring HRQoL from various perspectives.

The psychometric properties of RAND-36 have not been studied specifically in a diabetic population. However, SF-36 has shown satisfactory reliability and validity when studied among persons with T2D. Nonetheless, when comparing a diabetes-specific instrument with the generic SF-36, the two instrument were superior to one another in different psychometric properties, suggesting a combined use of a generic and disease-specific instrument for HRQoL measurement would be desirable. It has also been shown that the HRQoL measured by SF-36 is affected by non-diabetic comorbidity in T2D. However, in our RCT where we studied an intervention effect among a randomized study population, we found no statistically significant differences between the study groups regarding baseline characteristics as sex, age, or educational level etc. Due to the nature of the study, there should most likely be no differences regarding non-diabetic comorbidity among the two randomized study arms, even though this was not studied. It has been suggested by earlier studies that SF-36/RAND-36 may underestimate the effect of diabetes on HRQoL. Though, the use of a diabetes-specific HRQoL-instrument, in addition to RAND-36, may have shown an intervention effect in more disease-specific measurements of HRQoL (141-143).

In a study by Ohlsson-Nevo et al. (140) validating the Swedish RAND-36, population-based norm-data was also presented allowing for comparison with the general population. A sampling weight was used with the same age and gender distribution as the Swedish population in 2015. Population norms has also been presented for the Swedish SF-36 (144). Obtained in the 1990s, they have been frequently used to compare populations. At baseline in our study, the participants scored lower HRQoL in all health concepts compared to the norm-data for SF-36, and in all health concepts except two compared to the norm-data for RAND-36. This is in line with other studies that shows an impaired HRQoL in persons with T2D, compared to the general population. It is known that HRQoL is lower if diabetes complications are present than if not (100, 102). This might reflect the scores at baseline in our study with two of the health concepts having a marginally

higher HRQoL among our study sample compared to the norm-data for RAND-36. Hence, our study population was younger with a mean age of 60 years compared to 68 years among the general patient with T2D in Sweden, and diabetes complications are known to be more common with longer diabetes duration and older age.

Furthermore, as a group, our study participants were already adequately physically active in accordance with the recommended level, which may have affected their HRQoL at baseline since it is known that PA improves HRQoL. A high baseline HRQoL makes less room for improvement. Importantly, when comparing with population-based norm-data, we should not forget that the general population includes both the healthy population and those with chronic and acute illness.

The validation of automatic BP monitors

When validating automatic BP monitors, a difference in SBP of 10mmHg and DBP of 5mmHg would be clinically acceptable according to Masding et al. (145). In our study, Andersson Lifesense BDR 2.0 met this requirement. However, the predefined ranges presented by Masding et al. (145) can be argued to be wide. For example, a large meta-analysis showed that a decrease in only 2mmHg SBP resulted in a risk reduction of 7% for MI and 10% for stroke (146). Furthermore, with today's narrow recommendation targets for BP, there is a need for monitors that measure sufficiently accurate.

5.2 Methodological considerations

When we study the association between an exposure and outcome, we need to be aware of the risk of biases and confounding, called systematic errors, which can lead to wrong conclusions on the association (147). If there are systematic errors, the internal validity of the study is affected. Internal validity means that the conclusions that can be drawn from the study are valid within the study population. The internal validity, in turn, affects the external validity. The latter refers to the generalizability of the study results to the population target, external to the study population. Errors in epidemiological studies can be systematic or random, where the latter due to chance may not represent the true population even though the study population is selected randomly and thereby affect precision of the study results. We have made efforts to minimize both sources of

errors, while considering the methodological aspects that are summarized in this section.

Random errors

A p-value, or a confidence interval, tells us how random errors affects the precision of the results. In our studies, we used the commonly used significance level of a p-value below 0.05 that tells us that we can reject the null hypothesis (that there is no difference between the groups) with a 5% risk that it is false positive. We also used confidence intervals and set the level of confidence at the commonly used 95%, which means that the interval should include the correct value in 95% of future measurements.

A large sample size provides a greater precision and reduces random errors related to sampling. In order to ensure sufficient power to detect a significant difference in the outcome in an intervention study, but also to not recruit more participants than needed, a power calculation a priori is important to get an estimate of sample size.

Selection bias

Selection bias arises when there are systematic differences in selecting the study groups. It occurs when the association between exposure and outcome is different in the population studied compared to the whole population who were eligible for the study. This can happen either in the sampling phase of the study (e.g., self-selection bias as volunteer bias) or if there is a differential loss of subjects during follow-up (e.g., loss to follow-up and competing risk). Selection bias may affect the internal validity and can contribute to an underestimation or overestimation of the association under study. For example, volunteer bias is when the study population for some reason is more likely to participate than others in the target population, which in the end may reduce the generalizability of the results. The aim of the National March event was to raise funds including time, "an hour for research", for cancer research. This might have attracted more people with cancer in the family, including some with an increased risk of cancer later in life due to genetics or lifestyle, and may thereby bias the findings. Similarly, there may also be a healthy volunteer bias since more health-conscious people might be included. In fact, participants in the cohort did smoke less than the general adult population in Sweden by that time, but had a slightly higher BMI (107, 148). Moreover, the SNMC includes more than 40,000 participants, has a low

proportion of missing data, and has a long follow-up time with few losses to follow-up since linked to National registers (107). The latter limits selection bias caused by loss to follow-up.

In a prospective cohort study, we are interested in the event and the time to the event. However, at the end of the follow-up not all participants will have experienced a MI or stroke, and for those, the time to the event remains unknown. An unknown survival time is called censoring and will underestimate the true time to event. One additional type of selection bias in a cohort study is competing risk. A competing event would be death from other causes than those studied, here, MI and stroke. Hence, the death of a participant is a competing event that prevent us from observing a MI or stroke in that participant.

In an RCT, the goal with randomization is to remove the influence from known and unknown confounders as well as bias of selection by creating an equal distribution among the study groups. For example, selection bias occurs if there are differences between the groups in baseline characteristics despite randomization, hence, the intervention effect cannot solely be attributed to the intervention. However, selection bias is also possible in the analysis stage if only complete data is analyzed, and not data missing at random. For that reason, the analyses in the DiaCert-study were made according to the intention-to-treat approach, i.e., all participants with baseline data were included in the analysis according to their group allocation, regardless of if they used the smartphone app or not, or dropped out etc., and thereby the randomization was preserved.

Information bias

Information bias refers to misclassification of exposure or outcome. In study I, the outcomes studied where obtained from the Swedish National Inpatient & Outpatient Register and the Cause of Death register, and the misclassification of outcome is considered very small, even though an underestimation of the outcome as cause of death is possible e.g., wrong diagnose due to medical history, no autopsy etc. Even if a diagnosis is listed in 99% of all hospital discharges, Ludvigsson et al. (111) found, in a review validating the diagnoses in the National Inpatient & Outpatient Register, that the sensitivity and positive predictive value (PPV) of diagnoses varied among different diagnoses. In most studies included, validation was made by comparing the ICD codes in the National Inpatient & Outpatient Register with the diagnoses in medical records. The PPV for MI varied

between 98-100% and for stroke 68.5%-98.6%. The sensitivity varied between 77.0-91.5% and 84.2-95% for MI and stroke, respectively (111).

Misclassification can be either differential, that is, when the misclassification differs between the study groups or non-differential, i.e., the misclassification is equal among the study groups. Differential misclassification can be due to recall bias, e.g., when the study participant's reporting of exposure is affected by the outcome. This is not thought to be an issue in the SNMC-study since the exposures were assessed before the outcomes. However, PA is self- reported in the SNMC-study. Although the questionnaire used has been previously validated (112), PA has been shown to often be overestimated, while sedentary time is often underestimated (149). Differential misclassification can either over- or underestimate the effect. If the misclassification is non-differential, that is, the likelihood of misclassification is equal among the groups studied, the estimates of the association will generally tend to be underestimated. Due to the prospective design in the SNMC-study, any misclassification related to PA was likely non-differential.

Ideally, participants and study personnel in an RCT should be blinded to which group the participants are assigned to. However, due to the intervention in the DiaCert-study with the use of a smartphone app, neither participants, nor study personnel were unaware of the group allocation. Possibly, just being randomized to the intervention might have impacted the baseline daily steps even before starting to use the app. Furthermore, knowing that you are in the intervention group may also arise expectations that have an impact on the intervention outcome rather than the intervention itself. This includes potential differential misclassification in HRQoL with respect to group allocation. Outcomes as blood samples and objectively measured PA with accelerometers are likely not biased due to study personnel not being blinded. Although the DiaCert-study was an RCT, the repeated study measurements in all participants may have had an impact on motivation towards a healthy lifestyle in both groups, affecting the internal validity.

Confounding and effect modification

Confounding occurs when a third factor is associated with both the exposure and the outcome (independent of the exposure) and is not in the casual pathway between the exposure and the outcome. This leads to a risk of a false association between the exposure and outcome, even though no causal effect exists.

The risk of confounding bias can be limited by the study design, e.g., an RCT as the DiaCert- study, but can also be taken into account when analyzing the data by controlling for known confounders in statistical models. A strength of the SNMC-study is the information on numerous possible confounders that the 36-page questionnaire provided us, and adjusted for in the analyses. Known risk factors for MI and stroke were carefully selected as potential confounders. In addition, we used DAGs where each variable was suggested to be a confounder (see fig. 4). However, waist circumference was a potential confounder to adjust for, but given the high number of missing values we decided to adjust for this factor in a sensitivity analysis. Naturally, residual confounding may still be present. Another potential residual confounder is heredity. A participant with family history of MI or stroke may be more prone to a healthy lifestyle, including being more physically active, to reduce the risk of CVD. We did not have any information on family history of CVD among our participants.

Additionally, we tried to further investigate if the effect of TPA/LPA on MI/stroke was modified by the following covariates: sex, age, BMI, smoking, and alcohol consumption. We found that sex was an effect modifier between TPA and MI. However, some categories of interest may have been simplified, and thereby may have hidden a potential effect. For example, smoking was categorized into never, former, and current smoking, and we did for this analysis not consider number of packages smoked per day or years since quitting.

Reverse causality

We also tested for reverse causation by excluding MI and stroke cases during the first two years after enrollment. Participants with a MI or stroke in the beginning of the follow-up might e.g., have had undiagnosed conditions or symptoms which could have affected their PA level at baseline. After excluding cases, the effect of LPA on the risk of stroke was no longer statistically significant among men, but the other findings were not affected. Nonetheless, there is no exact timeframe to tell us when reverse causality is avoided. If potential reverse causation remains even after excluding cases during the first two years, the association will most likely be overestimated.

Generalizability

When we conducted studies among adult persons with T2D, our findings may not be generalizable to other population groups. We recruited from six heath care

clinics located in areas in and around Stockholm with diverse population and levels of socioeconomic status. This, together with the proportion of men and women and similar levels of BMI and HbA1c as the average person with T2D in Sweden, show generalizability to the general population of T2D. Nevertheless, patients that choose to participate in a PA intervention most probably want to change their PA level. Additionally, our participants were more physically active at baseline than we had expected given their diagnosis of T2D. They were also slightly younger compared to the average person with T2D. Since knowledge of Swedish was an inclusion criterion of the study, non-Swedish speaking patients were not offered to participate. Taken together, our sample may be underrepresented by the most vulnerable persons with T2D. Therefore, our results may not be generalizable to these patients.

The possibility to include a large number of participants is an advantage of a cohort study compared to an intervention study, which increases generalizability of results. Nevertheless, limits include that a long follow up time is often needed. The self-selection in the SNMC may affect the generalizability, but at the same time gives an advantage since the individuals choosing to participate probably were motivated to fill out the baseline questionnaire with low missing data as a result.

Validity of a method

The validity of a method is how well it is able to measure what is supposed to measure. When studying an association between an exposure and outcome, it is of importance to use validated measurements for both exposure and outcome. Moreover, validated measurements are needed in health care for reliable results. In the studies included in this thesis, we used validated questionnaires for the assessment of physical activity and HRQoL, respectively (112, 114, 139, 140). Moreover, we validated two automatic BP monitors by comparing the measurements with the measurement of the reference method of manual BP monitoring.

6 Conclusions

Study I: In the SNMC-study, a higher baseline total physical activity was related to a lower risk of myocardial infarction among women, whereas no association was found between total physical activity and myocardial infarction among men or between total physical activity and stroke among both sexes. Further, the relationship between leisure time physical activity and cardiovascular events showed a lower risk of MI and stroke among men, whereas no association was seen among women.

Study II: No evidence was found for an effect of the mHealth-intervention DiaCert promoting daily steps on moderate-to-vigorous intensity physical activity (MVPA) at 3 or 6 months in persons with type 2 diabetes. No effect was seen on the secondary outcomes body mass index, waist circumference, blood pressure, HbA1c, and blood lipids.

Study III: Improvement in HRQoL was found for the step promoting DiaCert-app intervention on role limitations caused by physical health problems, role limitations caused by emotional problems, and emotional wellbeing in persons with type 2 diabetes after 3 months. This effect had disappeared after 6 months.

Study IV: The two automatic blood pressure monitors validated showed a mean difference compared to the manual monitor of 11.1mmHg for systolic blood pressure and 8.0mmHg for diastolic blood pressure (Beurer BM 85) and of 3.2mmHg for systolic blood pressure and 4.2mmHg for diastolic blood pressure (Andersson Lifesense BDR 2.0), respectively, with the latter more often differing within what would be acceptable in clinical practice.

7 Points of perspective

Physical activity is a modifiable lifestyle factor that plays a central role in prevention of chronic diseases. This includes primary prevention of CVD in the general population, as well as secondary prevention among persons with T2D, investigated in this doctoral thesis. The role of PA in relation to CVD has been broadly investigated previously. However, our results in study I may indicate different optimal type of PA for women and men in terms of prevention of cardiovascular events. Additional large-scale studies are necessary to verify our findings.

Taken together, study II and III brought additional evidence that an mHealth app intervention may improve some aspects of both physical and emotional HRQoL in people with T2D, but future research is needed to conclude what type of mHealth solution that would be effective in supporting PA and improve cardiometabolic factors in this patient group. Future intervention studies should make sure to reveal group allocation to participants after completing all the baseline measurements.

Our results in study IV show that the two monitors validated differ in accuracy. This suggests that validation of automatic BP monitors for home BP management is of importance to ensure the quality of the care, before implementing those in mHealth solutions.

With the population getting older and with an increasing prevalence of lifestyle diseases, primary and secondary prevention is crucial. It is known that those that are physically inactive or on a low activity level are those who gain the most health benefits when they increase their PA. However, the most vulnerable patients, including those less active, may be those that are more difficult to reach. Future research needs to focus on this group for the possibility to give optimal support.

The technology is continuously developing, so is the research field within self-management and mHealth. Early on, mHealth consisted of websites and mobile phones with short text message service. Today, apps are common and new digital solutions like smart watches, tools with the ability to transfer data, and artificial intelligence are arising. More patients are calling for digital tools. Therefore, evaluated mHealth solutions that health care professionals are comfortable recommending to patients are needed. Moreover, self-care is an essential supplement to healthcare, so time and resources can reach more patients. With

increasing implementation of digital solutions in health care, future research will need to focus on this.

8 Acknowledgements

I would like to express my sincere gratitude to all those who have contributed to this thesis. There are many people that in one way or another have inspired, encouraged, guided, and supported me throughout this PhD journey. In particular, I would like to thank the following:

Ylva Trolle Lagerros – My main supervisor, for believing in me already as a medical student. Thank you for introducing me to the world of research in general and the field of clinical epidemiology in particular. Thank you for giving me the possibility of doing this PhD. Thank you for your enthusiasm for doing research, your infinite energy (I still wonder how many hours you have per day?), and your contagious laughter.

Stephanie Bonn – My co-supervisor of co-supervisors, thank you for always making time for me. Thank you for all the valuable discussions, your support, and guidance (not least with STATA). I couldn't ask for a better co-supervisor.

Rino Bellocco – My co-supervisor. For the opportunity to attend Summer school in Italy and for letting me come for a study visit to the Department of Statistics and Quantitative Methods, University of Milano-Bicocca, to work with your research group, I am utterly thankful.

Marie Löf - My co-supervisor. Thank you for agreeing to be part of my team, and for contributing with your important knowledge.

In addition to my supervisors, thanks to all co-authors that I have collaborated with: **Hans-Olov Adami, Weimin Ye, Essi Hantikainen, Christina Alexandrou, Giulia Peveri, and Helén Eke.** Thank you for your collaboration, comments, and reviews!

All **study participants** across the papers of this thesis – Thank you for your participation and for your contribution to research. Without you, my work would never been possible.

All current and former PhD-students in our research group, especially; **Helén Eke, Linnea Sjöblom, Liisa Tolvanen, Mari Hult, Francesca Ghilotti, Elin Roos, Charlotte Goodrose Flores, Daniel Söderberg, Wafa Kamal, and Oskar Swartling** – Thank you for your support and good luck with your future projects! A special thank you to **Essi Hantikainen** for the team work and your guidance while working on study I.

Gustavsbergs Vårdcentral – It's a privilege to work at an "University Primary care center" were clinic meets research in Family medicine. Thank you for making it possible for me to combine this PhD-project with my clinical work. I'm grateful for working with so many inspiring colleagues.

Ann Söderlund & Björn Eriksson – Thank you for inspiring me as an intern (AT) at Råslätts Vårdcentral and (ST) at Gustavsbergs Vårdcentral, respectively, to pursue to become the best medical doctor in Family medicine as possible. With your knowledge, compassion, efficiency, and responsiveness towards the patients I could not ask for more inspiring clinical supervisors.

Lars & Ann-Marie Hellström – My teachers, thank you for believing in me as a high school student and for making science even more interesting.

Anna, Caroline, Susanne & Beatrice – My besties. Wherever we are, scattered around the globe or just around the corner, I know we will always have each other. I love you. **Anna**, for being the perfect mix of fun and support through life. **Caroline**, for having the most honest answers and thoughtful solutions. **Susanne**, for your sisterly love. **Beatrice**, for your way of living and your endless optimism. I value you for that, and for everything else that are you.

Sara - My forever favorite colleague and one of my nearest, and dearest friends. I value your honesty, loyalty, and thoughtfulness more than I think you know.

"The Nässjö-girls"; **Emma, Emma, Lina, Lina, Kristin, Josefine & Caroline** – We're having each other's back since 1st grade. Life would be boring without you. Thank you **Caroline** for your illustration on the cover page of this thesis - it means a lot to me.

"The KI-girls"; **Caroline, Benedicte, Amanda, Karin & Anna** – Thank you for your supportive conversations about work, family, and life in general, and for fun times since Medical school at Karolinska Institutet.

Nelly & Rickard, Tove & Carl, Karin & Johan among many – When your better half already have found the best of friends – lucky me!

My big family – I could not imagine how life would be without a big, sprawling, and sparkling family. I love you all.

My mother Margareta – The strongest woman I know. For your unconditional love, encouragement, and support I will forever be grateful. You are not only the best mother one could ask for, but also a best friend, and the one I always turn to for advice and support (almost daily by phone). You have made me who I am today, and I don't know who I would be without you.

My brother Carl – August's and Henning's godparent. Please guide them through life (but you might not need to teach them everything you know).

My grandfather Herbert – Thank you for making me feel special every day, and for showing me how proud you were crying happy tears when I presented to you my very first grades. I miss you greatly.

Most of all, to my little family.

My husband Mikael – The Love of my life. The rock of the family. My strength. Thank you for loving me, for making sure that I always know you are by my side, for helping without me asking, and for your endless optimism (that sometimes drives me crazy). Thank you for doing life with me and our boys. Forever Team M&M.

My sons August & Henning - While giving birth to August, the anesthesiologist asked me "What do you want to be in the future?". As a colleague I know he referred to my profession, but I answered, "A good mother". My boys, you will forever be my number one priority. I love you more than I could ever put into words.

9 References

1. Ryan AS. Insulin resistance with aging: effects of diet and exercise. Sports Med. 2000;30(5):327-46.

2. Perry IJ. Healthy diet and lifestyle clustering and glucose intolerance. Proc Nutr Soc. 2002;61(4):543-51.

3. Alberti KG, Zimmet P, Shaw J. International Diabetes Federation: a consensus on Type 2 diabetes prevention. Diabet Med. 2007;24(5):451-63.

4. Lee IM, Shiroma EJ, Lobelo F, Puska P, Blair SN, Katzmarzyk PT, et al. Effect of physical inactivity on major non-communicable diseases worldwide: an analysis of burden of disease and life expectancy. Lancet. 2012;380(9838):219-29.

5. Cosentino F, Grant PJ, Aboyans V, Bailey CJ, Ceriello A, Delgado V, et al. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. Eur Heart J. 2019.

6. Finer S, Robb P, Cowan K, Daly A, Robertson E, Farmer A. Top ten research priorities for type 2 diabetes: results from the Diabetes UK-James Lind Alliance Priority Setting Partnership. Lancet Diabetes Endocrinol. 2017;5(12):935-6.

7. Poretsky L. Principles of diabetes mellitus. 2nd ed. New York: Springer; 2009.

8. Sun H, Saeedi P, Karuranga S, Pinkepank M, Ogurtsova K, Duncan BB, et al. IDF Diabetes Atlas: Global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. Diabetes Res Clin Pract. 2022;183:109119.

9. Nationella Diabetesregistret, årsrapport 2018. 2018. Available from: https://www.ndr.nu/pdfs/Arsrapport_NDR_2018.pdf.

10. Federation ID. The IDF Diabetes Atlas 8th edition. Sweden country report 2017.

11. Nasykhova YA, Barbitoff YA, Serebryakova EA, Katserov DS, Glotov AS. Recent advances and perspectives in next generation sequencing application to the genetic research of type 2 diabetes. World J Diabetes. 2019;10(7):376-95.

12. Langenberg C, Lotta LA. Genomic insights into the causes of type 2 diabetes. Lancet. 2018;391(10138):2463-74.

13. Gerich JE. Is insulin resistance the principal cause of type 2 diabetes? Diabetes Obes Metab. 1999;1(5):257-63.

14. Boden G. Pathogenesis of type 2 diabetes. Insulin resistance. Endocrinol Metab Clin North Am. 2001;30(4):801-15, v.

15. Eeg-Olofsson K, Åkesson K, Nåtman J, Almskog I, Hermansson Carter V, Linder E, et al. Årsrapport 2022. Nationella Diabetesregistret. Available from: https://www.ndr.nu/pdfs/Arsrapport_NDR_2022.pdf.

16. Tancredi M, Rosengren A, Svensson AM, Kosiborod M, Pivodic A, Gudbjornsdottir S, et al. Excess Mortality among Persons with Type 2 Diabetes. N Engl J Med. 2015;373(18):1720-32.

17. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice. Rev Esp Cardiol (Engl Ed). 2016;69(10):939.

18. Sattar N, Rawshani A, Franzén S, Svensson AM, Rosengren A, McGuire DK, et al. Age at Diagnosis of Type 2 Diabetes Mellitus and Associations With Cardiovascular and Mortality Risks. Circulation. 2019;139(19):2228-37.

19. Pantalone KM, Hobbs TM, Wells BJ, Kong SX, Kattan MW, Bouchard J, et al. Clinical characteristics, complications, comorbidities and treatment patterns among patients with type 2 diabetes mellitus in a large integrated health system. BMJ Open Diabetes Res Care. 2015;3(1):e000093.

20. Roy T, Lloyd CE. Epidemiology of depression and diabetes: a systematic review. J Affect Disord. 2012;142 Suppl:S8-21.

21. Anderson RJ, Freedland KE, Clouse RE, Lustman PJ. The prevalence of comorbid depression in adults with diabetes: a meta-analysis. Diabetes Care. 2001;24(6):1069-78.

22. Rubin RR, Peyrot M. Quality of life and diabetes. Diabetes Metab Res Rev. 1999;15(3):205-18.

23. Goldstein DE, Little RR, Lorenz RA, Malone JI, Nathan D, Peterson CM, et al. Tests of glycemia in diabetes. Diabetes Care. 2004;27(7):1761-73.

24. World Health Organization (WHO). Use of Glycated Haemoglobin (HbA1c) in the Diagnosis of Diabetes Mellitus. Abbreviated Report of a WHO Consultation. Geneva; 2011.

25. Bartoli E, Fra GP, Carnevale Schianca GP. The oral glucose tolerance test (OGTT) revisited. Eur J Intern Med. 2011;22(1):8-12.

26. Laakso M, Kuusisto J. Understanding patient needs Diabetology for cardiologists. Eur Heart J Supplements. 2003.

27. Davies MJ, Aroda VR, Collins BS, Gabbay RA, Green J, Maruthur NM, et al. Management of hyperglycaemia in type 2 diabetes, 2022. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia. 2022;65(12):1925-66.

28. World Health Organization (WHO). Fact Sheets. Cardiovascular diseases (CVDs). Available from: https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases- (cvds).

29. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, et al. Third universal definition of myocardial infarction. Circulation. 2012;126(16):2020-35.

30. Sacco RL, Kasner SE, Broderick JP, Caplan LR, Connors JJ, Culebras A, et al. An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2013;44(7):2064- 89.

31. National Board of Health and Welfare. Socialstyrelsen. Nationella riktlinjer för vård vid hjärtsjukvård: Socialstyrelsen; 2018. Available from: https://www.socialstyrelsen.se/globalassets/sharepoint-dokument/artikelkatalog/nationella-riktlinjer/2018-3-11.pdf.

32. National Board of Health and Welfare. Socialstyrelsen. Nationella riktlinjer för vård vid stroke: Socialstyrelsen; 2018. 2018. Available from: https://www.socialstyrelsen.se/globalassets/sharepoint-dokument/artikelkatalog/nationella-riktlinjer/2018-6-28.pdf.

33. American Diabetes Association. 9. Cardiovascular Disease and Risk Management. Diabetes Care. 2017;40(Suppl 1):S75-s87.

34. Sarwar N, Gao P, Seshasai SR, Gobin R, Kaptoge S, Di Angelantonio E, et al. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. Lancet. 2010;375(9733):2215-22.

35. Roper NA, Bilous RW, Kelly WF, Unwin NC, Connolly VM. Excess mortality in a population with diabetes and the impact of material deprivation: longitudinal, population based study. Bmj. 2001;322(7299):1389-93.

36. Di Angelantonio E, Kaptoge S, Wormser D, Willeit P, Butterworth AS, Bansal N, et al. Association of Cardiometabolic Multimorbidity With Mortality. JAMA. 2015;314(1):52-60.

37. Johansen OE, Birkeland KI, Brustad E, Aaser E, Lindahl AK, Midha R, et al. Undiagnosed dysglycaemia and inflammation in cardiovascular disease. Eur J Clin Invest. 2006;36(8):544-51.

38. Norhammar A, Tenerz A, Nilsson G, Hamsten A, Efendíc S, Rydén L, et al. Glucose metabolism in patients with acute myocardial infarction and no previous diagnosis of diabetes mellitus: a prospective study. Lancet. 2002;359(9324):2140-4.

39. Hu DY, Pan CY, Yu JM. The relationship between coronary artery disease and abnormal glucose regulation in China: the China Heart Survey. Eur Heart J. 2006;27(21):2573-9.

40. Rawshani A, Franzen S, Sattar N, Eliasson B, Svensson AM, Zethelius B, et al. Risk Factors, Mortality, and Cardiovascular Outcomes in Patients with Type 2 Diabetes. N Engl J Med. 2018;379(7):633-44.

41. Nyström F, Malmström O, Karlberg BE, Ohman KP. Twenty-four hour ambulatory blood pressure in the population. J Intern Med. 1996;240(5):279-84.

42. Edmonds D, Foerster E, Groth H, Greminger P, Siegenthaler W, Vetter W. Does self-measurement of blood pressure improve patient compliance in hypertension? J Hypertens Suppl. 1985;3(1):S31-4.

43. Eguchi K, Ishikawa J, Hoshide S, Pickering TG, Shimada K, Kario K. Masked hypertension in diabetes mellitus: a potential risk. J Clin Hypertens (Greenwich). 2007;9(8):601-7.

44. Caspersen CJ, Powell KE, Christenson GM. Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research. Public Health Rep. 1985;100(2):126-31.

45. Ainsworth BE, Haskell WL, Leon AS, Jacobs DR, Montoye HJ, Sallis JF, et al. Compendium of physical activities: classification of energy costs of human physical activities. Med Sci Sports Exerc. 1993;25(1):71-80.

46. Ainsworth BE, Haskell WL, Whitt MC, Irwin ML, Swartz AM, Strath SJ, et al. Compendium of physical activities: an update of activity codes and MET intensities. Med Sci Sports Exerc. 2000;32(9 Suppl):S498-504.

47. Migueles JH, Cadenas-Sanchez C, Ekelund U, Delisle Nyström C, Mora-Gonzalez J, Löf M, et al. Accelerometer Data Collection and Processing Criteria to Assess Physical Activity and Other Outcomes: A Systematic Review and Practical Considerations. Sports Med. 2017;47(9):1821-45.

48. World Health Organization (WHO). Physical inactivity. Available from: https://www.who.int/data/gho/indicator-metadata-registry/imr-details/3416.

49. Lim SS, Vos T, Flaxman AD, Danaei G, Shibuya K, Adair-Rohani H, et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380(9859):2224-60.

50. Socialstyrelsen. Nationella riktlinjer för sjukdomsförebyggande metoder. Stockholm2011.

51. Ekblom-Bak E, Olsson G, Ekblom O, Ekblom B, Bergstrom G, Borjesson M. The Daily Movement Pattern and Fulfilment of Physical Activity Recommendations in Swedish Middle-Aged Adults: The SCAPIS Pilot Study. PLoS One. 2015;10(5):e0126336.

52. Posadzki P, Pieper D, Bajpai R, Makaruk H, Könsgen N, Neuhaus AL, et al. Exercise/physical activity and health outcomes: an overview of Cochrane systematic reviews. BMC Public Health. 2020;20(1):1724.

53. Lacombe J, Armstrong MEG, Wright FL, Foster C. The impact of physical activity and an additional behavioural risk factor on cardiovascular disease, cancer and all- cause mortality: a systematic review. BMC Public Health. 2019;19(1):900.

54. Wahid A, Manek N, Nichols M, Kelly P, Foster C, Webster P, et al. Quantifying the Association Between Physical Activity and Cardiovascular Disease and Diabetes: A Systematic Review and Meta-Analysis. J Am Heart Assoc. 2016;5(9).

55. Li J, Loerbroks A, Angerer P. Physical activity and risk of cardiovascular disease: what does the new epidemiological evidence show? Curr Opin Cardiol. 2013;28(5):575-83.

56. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet. 2004;364(9438):937-52.

57. O'Donnell MJ, Xavier D, Liu L, Zhang H, Chin SL, Rao-Melacini P, et al. Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study. Lancet. 2010;376(9735):112-23.

58. Börjesson M, Onerup A, Lundqvist S, Dahlöf B. Physical activity and exercise lower blood pressure in individuals with hypertension: narrative review of 27 RCTs. Br J Sports Med. 2016;50(6):356-61.

59. Snowling NJ, Hopkins WG. Effects of different modes of exercise training on glucose control and risk factors for complications in type 2 diabetic patients: a meta-analysis. Diabetes Care. 2006;29(11):2518-27.

60. Umpierre D, Ribeiro PA, Kramer CK, Leitão CB, Zucatti AT, Azevedo MJ, et al. Physical activity advice only or structured exercise training and association with HbA1c levels in type 2 diabetes: a systematic review and meta-analysis. JAMA. 2011;305(17):1790- 9.

61. Zierath JR. Invited review: Exercise training-induced changes in insulin signaling in skeletal muscle. J Appl Physiol (1985). 2002;93(2):773-81.

62. Hawley JA, Lessard SJ. Exercise training-induced improvements in insulin action. Acta Physiol (Oxf). 2008;192(1):127-35.

63. Yrkesföreningar för Fysisk Aktivitet (YFA). Dohrn I, Jansson E, Börjesson M, Hagströmer M. Fysisk aktivitet i sjukdomsprevention och sjukdomsbehandling, FYSS 2021. Stockholm: Läkartidningen Förlag AB; 2021.

64. Blomster JI, Chow CK, Zoungas S, Woodward M, Patel A, Poulter NR, et al. The influence of physical activity on vascular complications and mortality in patients with type 2 diabetes mellitus. Diabetes Obes Metab. 2013;15(11):1008-12.

65. Zethelius B, Gudbjörnsdottir S, Eliasson B, Eeg-Olofsson K, Cederholm J, Register SND. Level of physical activity associated with risk of cardiovascular diseases and mortality in patients with type-2 diabetes: report from the Swedish National Diabetes Register. Eur J Prev Cardiol. 2014;21(2):244-51.

66. Thiel DM, Sayah FA, Vallance J, Johnson ST, Johnson JA. Physical Activity and Health-Related Quality of Life in Adults With Type 2 Diabetes: Results From a Prospective Cohort Study. J Phys Act Health. 2017;14(5):368-74.

67. Nicolucci A, Balducci S, Cardelli P, Cavallo S, Fallucca S, Bazuro A, et al. Relationship of exercise volume to improvements of quality of life with supervised exercise training in patients with type 2 diabetes in a randomised controlled trial: the Italian Diabetes and Exercise Study (IDES). Diabetologia. 2012;55(3):579-88.

68. Ausili D, Bulgheroni M, Ballatore P, Specchia C, Ajdini A, Bezze S, et al. Self- care, quality of life and clinical outcomes of type 2 diabetes patients: an observational cross- sectional study. Acta Diabetol. 2017;54(11):1001-8.

69. Sazlina SG, Browning CJ, Yasin S. Effectiveness of Personalized Feedback Alone or Combined with Peer Support to Improve Physical Activity in Sedentary Older Malays with Type 2 Diabetes: A Randomized Controlled Trial. Front Public Health. 2015;3:178.

70. Chau JY, Grunseit AC, Chey T, Stamatakis E, Brown WJ, Matthews CE, et al. Daily sitting time and all-cause mortality: a meta-analysis. PLoS One. 2013;8(11):e80000.

71. Patterson R, McNamara E, Tainio M, de Sa TH, Smith AD, Sharp SJ, et al. Sedentary behaviour and risk of all-cause, cardiovascular and cancer mortality, and incident type 2 diabetes: a systematic review and dose response meta-analysis. Eur J Epidemiol. 2018;33(9):811-29.

72. World Health Organization (WHO). Physical activity. Fact Sheet No 385. Updated February 2018.

73. Hultquist CN, Albright C, Thompson DL. Comparison of walking recommendations in previously inactive women. Med Sci Sports Exerc. 2005;37(4):676-83.

74. Tudor-Locke C, Craig CL, Brown WJ, Clemes SA, De Cocker K, Giles-Corti B, et al. How many steps/day are enough? For adults. Int J Behav Nutr Phys Act. 2011;8:79.

75. Ekelund U, Tarp J, Steene-Johannessen J, Hansen BH, Jefferis B, Fagerland MW, et al. Dose-response associations between accelerometry measured physical activity and sedentary time and all cause mortality: systematic review and harmonised meta-analysis. Bmj. 2019;366:l4570.

76. Sattelmair J, Pertman J, Ding EL, Kohl HW, 3rd, Haskell W, Lee IM. Dose response between physical activity and risk of coronary heart disease: a meta-analysis. Circulation. 2011;124(7):789-95.

77. Samitz G, Egger M, Zwahlen M. Domains of physical activity and all-cause mortality: systematic review and dose-response meta-analysis of cohort studies. Int J Epidemiol. 2011;40(5):1382-400.

78. Holtermann A, Krause N, van der Beek AJ, Straker L. The physical activity paradox: six reasons why occupational physical activity (OPA) does not confer the cardiovascular health benefits that leisure time physical activity does. Br J Sports Med. 52. England2018. p. 149-50.

79. World Health Organization (WHO). mHealth: New horizons for health through mobile technologies: second global survey on eHealth. Available from: https://www.who.int/goe/publications/goe_mhealth_web.pdf.

80. Internetstiftelsen. The Swedes and the Internet 2019. [In Swedish: Svenskarna och internet 2019]. Internetstiftelsen i Sverige.; 2019. Available from: https://svenskarnaochinternet.se/app/uploads/2019/10/svenskarna-och-internet-2019-a4.pdf.

81. Internetstiftelsen. The Swedes and the Internet 2023. [In Swedish: Svenskarna och internet 2023]. Available from: https://svenskarnaochinternet.se/rapporter/svenskarna-och-internet-2023/english/#chapter2.

82. Schoeppe S, Alley S, Van Lippevelde W, Bray NA, Williams SL, Duncan MJ, et al. Efficacy of interventions that use apps to improve diet, physical activity and sedentary behaviour: a systematic review. Int J Behav Nutr Phys Act. 2016;13(1):127.

83. Lee JJN, Abdul Aziz A, Chan ST, Raja Abdul Sahrizan R, Ooi AYY, Teh YT, et al. Effects of mobile health interventions on health-related outcomes in older adults with type 2 diabetes: A systematic review and meta-analysis. J Diabetes. 2023;15(1):47-57.

84. Moschonis G, Siopis G, Jung J, Eweka E, Willems R, Kwasnicka D, et al. Effectiveness, reach, uptake, and feasibility of digital health interventions for adults with type 2 diabetes: a systematic review and meta-analysis of randomised controlled trials. Lancet Digit Health. 2023;5(3):e125-e43.

85. Poppe L, De Bourdeaudhuij I, Verloigne M, Shadid S, Van Cauwenberg J, Compernolle S, et al. Efficacy of a Self-Regulation-Based Electronic and Mobile Health Intervention Targeting an Active Lifestyle in Adults Having Type 2 Diabetes and in Adults Aged 50 Years or Older: Two Randomized Controlled Trials. J Med Internet Res. 2019;21(8):e13363.

86. Thorsen IK, Yang Y, Valentiner LS, Glümer C, Karstoft K, Brønd JC, et al. The Effects of a Lifestyle Intervention Supported by the InterWalk Smartphone App on Increasing Physical Activity Among Persons With Type 2 Diabetes: Parallel-Group, Randomized Trial. JMIR Mhealth Uhealth. 2022;10(9):e30602.

87. Zhao J, Freeman B, Li M. Can Mobile Phone Apps Influence People's Health Behavior Change? An Evidence Review. J Med Internet Res. 2016;18(11):e287.

88. Veazie S, Winchell K, Gilbert J, Paynter R, Ivlev I, Eden KB, et al. Rapid Evidence Review of Mobile Applications for Self-management of Diabetes. J Gen Intern Med. 2018;33(7):1167-76.

89. Bonoto BC, de Araújo VE, Godói IP, de Lemos LL, Godman B, Bennie M, et al. Efficacy of Mobile Apps to Support the Care of Patients With Diabetes Mellitus: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. JMIR Mhealth Uhealth. 2017;5(3):e4.

90. Kanaley JA, Colberg SR, Corcoran MH, Malin SK, Rodriguez NR, Crespo CJ, et al. Exercise/Physical Activity in Individuals with Type 2 Diabetes: A Consensus Statement from the American College of Sports Medicine. Med Sci Sports Exerc. 2022;54(2):353-68.

91. Ried-Larsen M, MacDonald CS, Johansen MY, Hansen KB, Christensen R, Almdal TP, et al. Why prescribe exercise as therapy in type 2 diabetes? We have a pill for that! Diabetes Metab Res Rev. 2018;34(5):e2999.

92. Moghetti P, Balducci S, Guidetti L, Mazzuca P, Rossi E, Schena F. Walking for subjects with type 2 diabetes: A systematic review and joint AMD/SID/SISMES evidence- based practical guideline. Nutr Metab Cardiovasc Dis. 2020;30(11):1882-98.

93. World Health Organization (WHO). Measuring quality of life. Introducing WHOQOL instruments 2012.

94. Karimi M, Brazier J. Health, Health-Related Quality of Life, and Quality of Life: What is the Difference? Pharmacoeconomics. 2016;34(7):645-9.

95. Wändell PE. Quality of life of patients with diabetes mellitus. An overview of research in primary health care in the Nordic countries. Scand J Prim Health Care. 2005;23(2):68-74.

96. Poljicanin T, Ajduković D, Sekerija M, Pibernik-Okanović M, Metelko Z, Vuletić Mavrinac G. Diabetes mellitus and hypertension have comparable adverse effects on health-related quality of life. BMC Public Health. 2010;10:12.

97. Wändell PE, Brorsson B, Aberg H. Quality of life among diabetic patients in Swedish primary health care and in the general population: comparison between 1992 and 1995. Qual Life Res. 1998;7(8):751-60.

98. Hays RD, Sherbourne CD, Mazel RM. The RAND 36-Item Health Survey 1.0. Health Econ. 1993;2(3):217-27.

99. Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36).

I. Conceptual framework and item selection. Med Care. 1992;30(6):473-83.

100. Schmid AA, Atler KE, Malcolm MP, Grimm LA, Klinedinst TC, Marchant DR, et al. Yoga improves quality of life and fall risk-factors in a sample of people with chronic pain and Type 2 Diabetes. Complement Ther Clin Pract. 2018;31:369-73.

101. de Visser CL, Bilo HJ, Groenier KH, de Visser W, Jong Meyboom-de B. The influence of cardiovascular disease on quality of life in type 2 diabetics. Qual Life Res. 2002;11(3):249-61.

102. Landman GW, van Hateren KJ, Kleefstra N, Groenier KH, Gans RO, Bilo HJ. Health-related quality of life and mortality in a general and elderly population of patients with type 2 diabetes (ZODIAC-18). Diabetes Care. 2010;33(11):2378-82.

103. Slagter SN, van Vliet-Ostaptchouk JV, van Beek AP, Keers JC, Lutgers HL, van der Klauw MM, et al. Health-Related Quality of Life in Relation to Obesity Grade, Type 2 Diabetes, Metabolic Syndrome and Inflammation. PLoS One. 2015;10(10):e0140599.

104. MacMahon BP, TF. Epidemiology: principles and methods. Boston, Little, Brown1970.

105. UCI Libraries. Evidence-Based Medicine Subject Guide: EBM Pyramid. Available from: https://guides.lib.uci.edu/ebm/pyramid.

106. Bonn SE, Alexandrou C, Hjörleifsdottir Steiner K, Wiklander K, Östenson CG, Löf M, et al. App-technology to increase physical activity among patients with diabetes type 2- the DiaCert-study, a randomized controlled trial. BMC Public Health. 2018;18(1):119.

107. Trolle Lagerros Y, Hantikainen E, Mariosa D, Ye W, Adami HO, Grotta A, et al. Cohort Profile: The Swedish National March Cohort. Int J Epidemiol. 2017;46(3):795-e.

108. Ludvigsson JF, Almqvist C, Bonamy AK, Ljung R, Michaëlsson K, Neovius M, et al. Registers of the Swedish total population and their use in medical research. Eur J Epidemiol. 2016;31(2):125-36.

109. National Board of Health and Welfare. Inpatient Register. 2019. Available from: https://www.socialstyrelsen.se/statistik-och-data/register/alla-register/patientregistret/.

110. National Board of Health and Welfare. Cause of Death Register. 2018. Available from: https://www.socialstyrelsen.se/statistik-och-data/register/alla-register/dodsorsaksregistret/.

111. Ludvigsson JF, Andersson E, Ekbom A, Feychting M, Kim JL, Reuterwall C, et al. External review and validation of the Swedish national inpatient register. BMC Public Health. 2011;11:450.

112. Lagerros YT, Mucci LA, Bellocco R, Nyrén O, Bälter O, Bälter KA. Validity and reliability of self-reported total energy expenditure using a novel instrument. Eur J Epidemiol. 2006;21(3):227-36.

113. Bonn SE, Alexandrou C, Trolle Lagerros Y. A Digital Platform and Smartphone App to Increase Physical Activity in Patients With Type 2 Diabetes: Overview Of a Technical Solution. JMIR Form Res. 2023;7:e40285.

114. Olsson SJ, Ekblom Ö, Andersson E, Börjesson M, Kallings LV. Categorical answer modes provide superior validity to open answers when asking for level of physical activity: A cross-sectional study. Scand J Public Health. 2016;44(1):70-6.

115. Twisk J, Bosman L, Hoekstra T, Rijnhart J, Welten, Heymans M. Different ways to estimate treatment effects in randomised controlled trials. Contemp Clin Trials Commun. 2018;10:80-5.

116. Azur MJ, Stuart EA, Frangakis C, Leaf PJ. Multiple imputation by chained equations: what is it and how does it work? Int J Methods Psychiatr Res. 2011;20(1):40-9.

117. VanderZee KI, Sanderman R, Heyink JW, de Haes H. Psychometric qualities of the RAND 36-Item Health Survey 1.0: a multidimensional measure of general health status. Int J Behav Med. 1996;3(2):104-22.

118. Hays RD, Morales LS. The RAND-36 measure of health-related quality of life. Ann Med. 2001;33(5):350-7.

119. The RAND Corporation. 36-Item Short Form Survey (SF-36) Scoring Instructions. Available from: https://www.rand.org/health-care/surveys_tools/mos/36-item-short- form/scoring.html.

120. Registercentrum sydost and Uppsala Clinical Research Center. Manual for the Swedish RAND-36 (In Swedish: Manual svenska RAND-36). 2016.

121. The RAND Corporation. 36-Item Short Form Survey (SF-36) Scoring Instructions. Available from: https://www.rand.org/health-care/surveys_tools/mos/36-item-short- form/scoring.html.

122. Taft C, Karlsson J, Sullivan M. Do SF-36 summary component scores accurately summarize subscale scores? Qual Life Res. 2001;10(5):395-404.

123. World Medical Association (WMA). Declaration of Helsinki – Ethical principles for medical reserach involving human subjects.

124. Lear SA, Hu W, Rangarajan S, Gasevic D, Leong D, Iqbal R, et al. The effect of physical activity on mortality and cardiovascular disease in 130 000 people from 17 high- income, middle-income, and low-income countries: the PURE study. Lancet. 2017;390(10113):2643-54.

125. Gunnell AS, Knuiman MW, Divitini ML, Cormie P. Leisure time physical activity and long-term cardiovascular and cancer outcomes: the Busselton Health Study. Eur J Epidemiol. 2014;29(11):851-7.

126. Oliveira A, Barros H, Azevedo A, Bastos J, Lopes C. Impact of risk factors for non-fatal acute myocardial infarction. Eur J Epidemiol. 2009;24(8):425-32.

127. Hu G, Sarti C, Jousilahti P, Silventoinen K, Barengo NC, Tuomilehto J. Leisure time, occupational, and commuting physical activity and the risk of stroke. Stroke. 2005;36(9):1994-9.

128. Gulsvik AK, Thelle DS, Samuelsen SO, Myrstad M, Mowe M, Wyller TB. Ageing, physical activity and mortality--a 42-year follow-up study. Int J Epidemiol. 2012;41(2):521-30.

129. Haapanen N, Miilunpalo S, Vuori I, Oja P, Pasanen M. Association of leisure time physical activity with the risk of coronary heart disease, hypertension and diabetes in middle-aged men and women. Int J Epidemiol. 1997;26(4):739-47.

130. Wu X, Guo X, Zhang Z. The Efficacy of Mobile Phone Apps for Lifestyle Modification in Diabetes: Systematic Review and Meta-Analysis. JMIR Mhealth Uhealth. 2019;7(1):e12297.

131. Kim JE, Park TS, Kim KJ. The Clinical Effects of Type 2 Diabetes Patient Management Using Digital Healthcare Technology: A Systematic Review and Meta-Analysis. Healthcare (Basel). 2022;10(3).

132. Fagour C, Gonzalez C, Pezzino S, Florenty S, Rosette-Narece M, Gin H, et al. Low physical activity in patients with type 2 diabetes: the role of obesity. Diabetes Metab. 2013;39(1):85-7.

133. Ozdirenç M, Biberoğlu S, Ozcan A. Evaluation of physical fitness in patients with Type 2 diabetes mellitus. Diabetes Res Clin Pract. 2003;60(3):171-6.

134. Jimenez G, Lum E, Car J. Examining Diabetes Management Apps Recommended From a Google Search: Content Analysis. JMIR Mhealth Uhealth. 2019;7(1):e11848.

135. Schwingshackl L, Missbach B, Dias S, König J, Hoffmann G. Impact of different training modalities on glycaemic control and blood lipids in patients with type 2 diabetes: a systematic review and network meta-analysis. Diabetologia. 2014;57(9):1789-97.

136. Pan B, Ge L, Xun YQ, Chen YJ, Gao CY, Han X, et al. Exercise training modalities in patients with type 2 diabetes mellitus: a systematic review and network meta-analysis. Int J Behav Nutr Phys Act. 2018;15(1):72.

137. Hänninen J, Takala J, Keinänen-Kiukaanniemi S. Good continuity of care may improve quality of life in Type 2 diabetes. Diabetes Res Clin Pract. 2001;51(1):21-7.

138. Sporrel K, Nibbeling N, Wang S, Ettema D, Simons M. Unraveling Mobile Health Exercise Interventions for Adults: Scoping Review on the Implementations and Designs of Persuasive Strategies. JMIR Mhealth Uhealth. 2021;9(1):e16282.

139. Orwelius L, Nilsson M, Nilsson E, Wenemark M, Walfridsson U, Lundstrom M, et al. The Swedish RAND-36 Health Survey - reliability and responsiveness assessed in patient populations using Svensson's method for paired ordinal data. J Patient Rep Outcomes. 2017;2(1):4.

140. Ohlsson-Nevo E, Hiyoshi A, Norén P, Möller M, Karlsson J. The Swedish RAND-36: psychometric characteristics and reference data from the Mid-Swed Health Survey. J Patient Rep Outcomes. 2021;5(1):66.

141. Jacobson AM, de Groot M, Samson JA. The evaluation of two measures of quality of life in patients with type I and type II diabetes. Diabetes Care. 1994;17(4):267-74.

142. Woodcock AJ, Julious SA, Kinmonth AL, Campbell MJ. Problems with the performance of the SF-36 among people with type 2 diabetes in general practice. Qual Life Res. 2001;10(8):661-70.

143. Huang IC, Hwang CC, Wu MY, Lin W, Leite W, Wu AW. Diabetes-specific or generic measures for health-related quality of life? Evidence from psychometric validation of the D-39 and SF-36. Value Health. 2008;11(3):450-61.

144. Sullivan M, Karlsson J, Ware JE, Jr. The Swedish SF-36 Health Survey--I. Evaluation of data quality, scaling assumptions, reliability and construct validity across general populations in Sweden. Soc Sci Med. 1995;41(10):1349-58.

145. Masding MG, Jones JR, Bartley E, Sandeman DD. Assessment of blood pressure in patients with Type 2 diabetes: comparison between home blood pressure monitoring, clinic blood pressure measurement and 24-h ambulatory blood pressure monitoring. Diabet Med. 2001;18(6):431-7.

146. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet. 2002;360(9349):1903-13.

147. Rothman KJ. Epidemiology: an introduction . Oxford university press.; 2012.

148. Statistics Sweden. Living Conditions 1980-2016 - selected indicators Statistics Sweden: Social Welfare Statistics Unit; 2018.

149. Prince SA, Adamo KB, Hamel ME, Hardt J, Connor Gorber S, Tremblay M. A comparison of direct versus self-report measures for assessing physical activity in adults: a systematic review. Int J Behav Nutr Phys Act. 2008;5:56.