Promoting physical activity and lifestyle changes in primary health care. Interviews, randomised controlled trial and cohort studies examining lifestyle factors and venous thromboembolism.

Nymberg, Peter

2021

[Link to publication](#)

Total number of authors:
1

Promoting physical activity and lifestyle changes in primary health care

Interviews, randomised controlled trial and cohort studies examining lifestyle factors and venous thromboembolism

Peter Nymberg

LUND
UNIVERSITY

DOCTORAL DISSERTATION

by due permission of the Faculty of Medicine, Lund University, Sweden.
To be defended at Agardhsalen, Clinical Research Centre, Malmö.
Date 17th of September 2021 at 09.00 am.

Faculty opponent
Professor Carl Johan Östgren
Linköping University

Organization LUND UNIVERSITY	Document name **Doctoral Dissertation**
	Date of issue 17 September 2021
Author: Peter Nymberg	Sponsoring organization

Title; Promoting physical activity and lifestyle changes in primary health care
Subtitle; Interviews, randomised controlled trial and cohort studies examining lifestyle factors and venous thromboembolism

Background: Unhealthy lifestyle habits, low socioeconomic status, and low self-rated health (SRH) increase the risk of non-communicable diseases, such as cardiovascular disease. There are shared risk factors between arterial and venous thrombosis (VTE), and they predispose for one another. Targeted health dialogues have proven to be an effective method for finding those at risk. The Swedish healthcare system uses physical activity on prescription (PAP) to motivate increased physical activity. Mindfulness seems to facilitate lifestyle changes through increased motivation. The Swedish PAP has a suggested effectiveness of 60% but the effect is not sustainable over time, and the best effect is seen among the already physically active. Therefore, it is important to study methods to increase physical activity among inactive individuals. But also, whether there is a connection between factors affected by physical activity (SRH and mitochondrial DNA copy number (mtDNA-CN)), and whether these factors, that predict the risk of arterial blood clots also can predict blood clots in venous vessels.
Aim: The overall aim of the thesis was to study lifestyle changes among primary care patients, both in terms of their perception of lifestyle changes and the effect of a physical activity intervention. The thesis also investigated if poor SRH, lifestyle, and low mtDNA-CN were associated with an increased risk of VTE. **Methods:** Focus group interviews (paper I) with 14 patients after visiting a nurse-led lifestyle clinic, analysed with content analysis. A pilot-study with 88 participants (paper II & III) with 3 groups containing mindfulness training, PAP, or a combination. Feasibility was assessed by recruitment rate, dropouts, and adherence to mindfulness intervention. Activity was measured with accelerometers and self-rated. Cox regression (paper IV) to examine the association between SRH and incident VTE in a cohort containing 6917 women between 50-64 years. Finally, the association between mtDNA-CN and incident VTE (paper V) in a cohort containing 2521 women between 50-64 years. **Results:** Paper I revealed both unfulfilled expectations and the sense of security among the interviewed patients. Paper II described the design of the three-armed randomised intervention study and paper III showed a high recruitment rate, a low number of dropouts, but low adherence to the mindfulness intervention. Highest increase of physical activity was found in the combination group. Paper IV confirmed already well-known risk factors of VTE and showed a non-significant small increase of risk when self-rated health was considered as poor. Paper V showed no significant association between mtDNA-CN and VTE. **Conclusion:** Prevention in primary health care through nurse-led lifestyle clinics requires frequent recurrent training in Motivational Interviewing. Visits to lifestyle clinics should be preceded by screening forms, and blood sampling, fulfilled before the appointment and include the assessment of both the risk for arterial cardiovascular diseases and VTE as they predispose for each other and share many risk factors. There should be follow-ups among those who are in need of changing a lifestyle habit and require help with the modification.The pilot-study seems possible to conduct after adjustments to the mindfulness intervention. The web-based training should be shorter than in the pilot-study, as a suggestion with SMS reminders each day, and maybe web-based group meetings.There may be an additional effect on PAP with regular mindfulness training. This may also affect SRH rating more than both only PAP or only mindfulness. Neither poor SRH nor low mtDNA-CN seem to be useful predictors of incident VTE.

Keywords Primary health care, Physical activity, mindfulness, venous thromboembolism, Self-rated health, mitochondria-DNA copy-number, accelerometers, randomised trial, pilot-study.

Classification system and/or index terms (if any)
Lund University, Faculty of Medicine Doctoral Dissertation Series 2021:39

Supplementary bibliographical information		**Language** English
ISSN and key title 1652-8220		**ISBN** 978-91-8021-045-4
Recipient's notes	**Number of pages** 92	Price
	Security classification	

Promoting physical activity and lifestyle changes in primary health care

Interviews, randomised controlled trial and cohort studies examining lifestyle factors and venous thromboembolism

Peter Nymberg

Department of Clinical Sciences, Malmö, Lund University

LUND UNIVERSITY

"Those who think they have no time for bodily exercise will sooner or later have to find time for illness"

Edward Stanley (1826-1893)

Table of Contents

Abstract

Background: Unhealthy lifestyle habits, low socioeconomic status, and low self-rated health (SRH) increase the risk of non-communicable diseases, such as cardiovascular disease. There are shared risk factors between arterial and venous thrombosis (VTE), and they predispose for one another. Targeted health dialogues have proven to be an effective method for finding those at risk. The Swedish healthcare system uses physical activity on prescription (PAP) to motivate increased physical activity. Mindfulness seems to facilitate lifestyle changes through increased motivation. The Swedish PAP has a suggested effectiveness of 60% but the effect is not sustainable over time, and the best effect is seen among the already physically active. Therefore, it is important to study methods to increase physical activity among inactive individuals. But also, whether there is a connection between factors affected by physical activity (SRH and mitochondrial DNA copy number (mtDNA-CN)), and whether these factors, that predict the risk of arterial blood clots, also can predict blood clots in venous vessels. **Aim:** The overall aim of the thesis was to study lifestyle changes among primary care patients, both in terms of their perception of lifestyle changes and the effect of a physical activity intervention. The thesis also investigated if poor SRH, lifestyle, and low mtDNA-CN were associated with an increased risk of VTE. **Methods:** Focus group interviews (paper I) with 14 patients after visiting a nurse-led lifestyle clinic, analysed with content analysis. A pilot-study with 88 participants (paper II & III) with 3 groups containing mindfulness training, PAP, or a combination. Feasibility was assessed by recruitment rate, dropouts, and adherence to mindfulness intervention. Activity was measured with accelerometers and self-rated. Cox regression (paper IV) to examine the association between SRH and incident VTE in a cohort containing 6917 women between 50-64 years. Finally, the association between mtDNA-CN and incident VTE (paper V) in a cohort containing 2521women between 50-64 years. **Results:** Paper I revealed both unfulfilled expectations and the sense of security among the interviewed patients. Paper II described the design of the three-armed randomised intervention study and paper III showed a high recruitment rate, a low number of dropouts, but low adherence to the mindfulness intervention. Highest increase of physical activity was found in the combination group. Paper IV confirmed already well-known risk factors of VTE and showed a non-significant small increase of risk when self-rated health was considered as poor. Paper V showed no significant association between mtDNA-CN and VTE. **Conclusion:** Prevention in primary health care through nurse-led lifestyle clinics requires frequent recurrent training in

Motivational Interviewing. Visits to lifestyle clinics should be preceded by screening forms, and blood sampling, fulfilled before the appointment and include the assessment of both the risk for arterial cardiovascular diseases and VTE as they predispose for each other and share many risk factors. There should be follow-ups among those who are in need of changing a lifestyle habit and require help with the modification. The pilot-study seems possible to conduct after adjustments of the mindfulness intervention. The web-based training should be shorter than in the pilot-study, as a suggestion with SMS reminders each day, and maybe web-based group meetings. There may be an additional effect on PAP with regular mindfulness training. This may also affect SRH rating more than both only PAP, or only mindfulness. Neither poor SRH nor low mtDNA-CN seem to be useful predictors of incident VTE.

List of papers

I.   **Nymberg, P**., & Drevenhorn, E. (2016). Patients' experience of a nurse-led lifestyle clinic at a Swedish health centre. *Scandinavian Journal of Caring Sciences,* 30(2), 349-355. https://doi.org/10.1111/scs.12254

II.   **Nymberg, P**., Ekvall Hansson, E., Stenman, E., Calling, S., Sundquist, K., Sundquist, J., & Zoller, B. (2018). Pilot study on increased adherence to physical activity on prescription (PAP) through mindfulness: study protocol. *Trials,* 19(1), 563. https://doi.org/10.1186/s13063-018-2932-9

III.   **Nymberg, P**., Calling,S., Stenman,E., Palmér,K., Ekvall Hansson,E., Sundquist,K., Sundquist,J., Zöller,B. (2021), Effect of mindfulness on physical activity in primary healthcare patients: a randomised controlled trial pilot study. *Pilot and Feasibility Studies*, 7(1), 70. https://doi.org/10.1186/s40814-021-00810-6

IV.   **Nymberg, P**., Stenman, E., Calling, S., Sundquist, J., Sundquist, K., & Zöller, B. (2020). Self-rated health and venous thromboembolism among middle-aged women: a population-based cohort study. *J Thromb Thrombolysis*, 49(3), 344-351. https://doi.org/10.1007/s11239-019-01995-7

V.   **Nymberg, P**., Memon,A.A., Sundquist,J., Sundquist,K., Zöller,B. (2021). Mitochondria-DNA copy-number and incident venous thromboembolism among middle-aged women: a population-based cohort study. J Thromb Thrombolysis. https://doi.org/10.1007/s11239-021-02446-y. April 15 Online ahead of print

List of abbreviations

ATP — Adenosine triphosphate
BMI — Body mass index
CI — Confidence interval
CVD — Cardiovascular disease
DBP — Diastolic blood pressure
ddPCR — Optimized droplet digital PCR
DVT — Deep vein thrombosis
FFMQ — Five Facets of Mindfulness Questionnaire
FH — Family history
HR — Hazard ratio
ISI — Insomnia Severity Index
LIPA — Light physical activity
MBCT — Mindfulness Based Cognitive Therapy
MBSR — Mindfulness Based Stress Reduction
MI — Motivational interviewing
mtDNA-CN — Mitochondrial DNA copy number
MVPA — Moderate to vigorous physical activity
PAP — Swedish model of Physical Activity on Prescription
PCR — Polymerase chain reaction
PE — Pulmonary embolism
PHN — Primary healthcare nurse
RCT — Randomised controlled trial
SBP — Systolic blood pressure
SMS — Short message service
SRH — Self-rated health
VTE — Venous thromboembolism
WHILA — Women´s Health In the Lund Area study
WHO — World Health Organization

Introduction

Lifestyle and disease

Cambridge dictionary (2021) defines lifestyle as a concept describing a person's way of living and habits. Unhealthy but changeable lifestyle habits such as insufficient physical activity, use of tobacco, or bad dietary habits (such as low amounts of fruit, vegetables, and whole grains) are common risk factors for many non-communicable diseases (I. M. Lee et al., 2012; McTiernan et al., 2019; Yusuf et al., 2004). Besides lifestyle habits, low education seems to be associated with increased risk of diabetes, hypertension, heart/circulation problems, and depression (McNamara et al., 2017). Thus, socioeconomic status seems to affect the risk of non-communicable diseases as well (McNamara et al., 2017). Research shows that a healthy lifestyle can prevent diabetes, cardiovascular diseases (CVD), and cancer (I. M. Lee et al., 2012; McTiernan et al., 2019; World Health Organization, 2011; World Health Organization, 2020).

About 23 percent of the adult population in the world is insufficiently physically active (World Health Organization, 2011). Insufficient amount of physical activity accounts, worldwide, for about 1.6 million of all deaths each year (Forouzanfar et al., 2015). The global goal for the United Nations (2015) towards a sustainable development until 2030 is to decrease the amount of people dying of non-communicable diseases by preventive actions and treatment (goal 3.4) (United Nations, 2015).

The World Health Organization (2017) has identified several preventive lifestyle changes that have the potential to decrease the number of premature deaths, and at the same time decrease the costs for healthcare and medication. The "best buy" of promoting physical activity is broad campaigns in mass media to arouse public awareness, but also community-based public education. Other recommended cost-effective preventive actions in primary health care are to offer counselling and referrals to increase physical activity levels (World Health Organization, 2017). This type of targeted health dialogues with physical examinations among citizens seem to effectively find people at risk of noncommunicable diseases and may reduce premature mortality (Blomstedt et al., 2015; Lingfors et al., 2003; Lingfors & Persson, 2019; Lingfors et al., 2009).

Venous thromboembolism

Venous thromboembolism (VTE) is the third most common cardiovascular disease and affects 100 cases per 100,000 person-years (Wilbur & Shian, 2012). The recurrence rate within 10 years is about 30% after first VTE diagnosis (Crous-Bou et al., 2016). VTE can briefly be described as a blood clot in any arm or leg, i.e., deep vein thrombosis (DVT) or if a blood clot can get stuck in blood vessels around the lungs, pulmonary embolism (PE) (Crous-Bou et al., 2016). In about 40% of patients with DVT, a PE is also found and about 70% of those first diagnosed with PE also appear to be affected by DVT (Wilbur & Shian, 2012). The risk factors that contribute to the development of VTE consist both of strong heredity and environmental factors, thus VTE is a complex medical disorder. Between 40 to 60% of the variance in VTE incidence is associated with genetic effects (Crous-Bou et al., 2016; Zöller et al., 2015; Zöller et al., 2013; Zöller et al., 2014). Such hypercoagulable conditions involve either alterations in the vessel wall, the blood flow, and/or the composition of the blood (Virchow's triad) (Zöller et al., 2020). The environmental factors can be divided into two groups: provoking factors (e.g., surgery, fracture, cancer, immobilization, pregnancy, etc.) and non-provoking factors (e.g., age, sex, obesity, diet, physical inactivity, etc.) (Crous-Bou et al., 2016). However, the importance of lifestyle related non-provoking factors such as diet and physical activity are not so well established as other factors for VTE. Nevertheless, slow blood flow may be caused by prolonged sitting and physical inactivity and might contribute to the increased VTE incidence in modern society (Dexter, 1973).

Shared risk factors

VTE and arterial CVD have previously been regarded as two different diseases with their own aetiologies. Although they share some common features, such as hypercoagulability and inflammation that support the production of thrombi in both arterial and venous vessels, risk factors for these two diseases are only partially shared (Ageno et al., 2008; Lijfering et al., 2011). In addition to the partially shared risk, VTE and arterial CVD predispose for each other, i.e., patients with VTE have an increased risk of arterial CVDs and vice versa (Franchini & Mannucci, 2008; Prandoni, 2017).

Obesity, oestrogens (Lowe, 2008), and obstructive sleep-apnea syndrome (Lippi et al., 2015; Somers et al., 2008) are some of the shared risk factors with equal risk elevation for VTE and CVD. Smoking (Ageno et al., 2008; Deflandre et al., 2016) is a risk factor that strongly predicts arterial CVD but has weaker evidence regarding VTE. The same pattern is revealed for dietary habits; a high consumption of fruit, vegetables (Steffen et al., 2007), fish (Hansen-Krone et al., 2014; Steffen et al., 2007), and whole grains (Varraso et al., 2012) may decrease the risk of VTE, but

have well-documented associations with decreased risk of arterial CVD. On the contrary, high consumption of red meat leads to an increased risk of any kind of thrombosis (Steffen et al., 2007; Varraso et al., 2012).

The preventive effect of physical activity on the risk of arterial CVD is well known (Armstrong et al., 2015; Carlsson et al., 2013; Chiuve et al., 2014; Warburton & Bredin, 2017; Warburton et al., 2006; Yusuf et al., 2004), but regarding VTE it has been debated whether the risk increases (Glynn & Rosner, 2005; van Stralen et al., 2008) or decreases (Olson et al., 2015; Wattanakit et al., 2012) with physical activity. A systematic review with meta-analysis revealed a significantly decreased risk of incident VTE if being physically active compared with those who had a sedentary or less active lifestyle (Kunutsor et al., 2020). These results were neither confounded nor mediated by body mass index (BMI), or differed by geographical location, sex, age, duration of follow-up, degree of adjustment, or by methodological quality of studies.

Self-rated health

Physical and mental health

The association between physical as well as mental health and self-rated health (SRH) is strong, with similar results from 19 European countries (Baćak & Ólafsdóttir, 2017). Despite the finding of a link between cardiovascular disease and SRH in Europe as a whole, it is not possible to compare SRH between different countries due to the cultural differences (Emmelin et al., 2006; Jylha, 2009). There may also be variations between different age groups and over time (Johansson et al., 2015). Strong validity for predicting illnesses, but not for mortality, has been shown among women (Baćak & Ólafsdóttir, 2017). Self-rated health has shown to be an independent risk factor of mortality, even when adjusted for confounding health status indicators or other covariates associated with mortality (Fylkesnes & Forde, 1991; Idler & Benyamini, 1997; Sundquist & Johansson, 1997; van der Linde et al., 2013). A dose-response relationship has been revealed between SRH worse than very good and arterial CVD. However, it has not been examined whether SRH contributes with any additional predictive value for arterial CVD together with well-known risk factors (Waller et al., 2015). Whether SRH is associated with VTE remains to be determined.

Assessment of Self-rated health

The assessment of SRH is commonly made with a single question about the individual's subjective perceived general health. The answer is performed on a

Likert scale, graded with either 5 or 7 steps from very poor to very good and has been shown to include all the individual dimensions physical, mental, and social health (Jylha, 2009). Measuring SRH using the single question is comparable, regarding prediction of death or need for medical care, to more extensive questionnaires (Medical Outcomes Study Short Form (SF-36), and Seattle index of comorbidity (SIC)) (DeSalvo et al., 2005).

Mitochondrial DNA

Mitochondrial DNA and epigenetics

The first descriptions of different structures within the cell arrived around 1850 (Scheffler, 2008). During the late 1890s the structures, which we now refer to as mitochondria, were proposed to be autonomous, elemental living units, forming bacteria-like colonies in the cytoplasm of the cell (Scheffler, 2008). Mitochondria have a central place in the metabolism by producing adenosine triphosphate (ATP), which is the energy giving substance that is included in most of the intra-cellular processes (Sand et al., 2007). The number of mitochondria differ between different types of cells, from a few per cell up to hundreds in cells with high metabolism, for example muscle cells (Sand et al., 2007). During the past decade it has been recognized that the mitochondria are much more than the "powerhouse of the cell". Mitochondria are involved in the function, life, and death of a cell, and can set off factors/proteins that initiate the process of apoptosis (Scheffler, 2008). Although the structure of the mitochondria was discovered in the late 1800s, it was not until 1963 that it was revealed that mitochondria were carriers of hereditary information, by the identification of mitochondrial DNA (Nass & Nass, 1963). Epigenetics is the science about how heritable phenotypes change without alterations in the DNA sequence (Goldberg et al., 2007). Epigenetics are suggested to be affected by our chosen lifestyle, where the nutritional intake, use of tobacco, stress, high intake of alcohol and amount of physical activity can affect the DNA-methylation, and the gene expression (Alegría-Torres et al., 2011; Sharma et al., 2019). The condition of the cell in this respect can lead to the genes being reprogrammed and therefore expressed differently than the DNA-signals. In other words, the epigenome's signals can override the DNA inherited from the parents (Hallgrímsson & Hall 2011). Epigenetics is also important in the regulation of mitochondrial DNA and involves DNA methylation, non-coding RNAs, and post-translational modifications of nucleoid proteins (Sharma et al., 2019).

Lifestyle and disease

Ineffective energy production due to mitochondrial dysfunction is a hallmark of many chronic diseases and aging (Castellani et al., 2020). Mitochondrial DNA copy number (mtDNA-CN) is a biomarker and proxy for mitochondrial dysfunction (Casellano et al., 2020). Low mtDNA-CN in circulating blood is a suggested risk indicator for arterial CVDs according to a systematic review with a meta-analysis of the result from five articles with 8252 cases and 20904 controls (Yue et al., 2018). Individuals with high BMI and metabolic syndrome have in studies shown a low mtDNA-CN compared with healthy individuals (Huang et al., 2011; Lee et al., 2014). MtDNA-CN is also suggested to be a biomarker for aging where those with age-related diseases have lower mtDNA-CN (Maximov et al., 2019). It has been suggested that damage to mitochondrial DNA and loss of mitochondrial genome integrity even could play a direct role in the development of chronic age-related diseases (Sharma et al., 2019). Lifestyle may also affect the levels of mtDNA-CN, where current smoking is associated with a lower mtDNA-CN (Vyas et al., 2020) and some studies have suggested that high alcohol consumption may lower the mtDNA-CN as well (Cakir et al., 2007; von Wurmb-Schwark et al., 2008). In addition, poor SRH has also been associated with lower mtDNA-CN (Takahashi et al., 2018). In contrast, a healthy lifestyle with recommended amount of regular physical activity is associated with higher mtDNA-CN (Chang et al., 2016; Eluamai & Brooks, 2013), and better SRH (Han et al., 2009; Jepsen et al., 2014; Kerr et al., 2012; Smiley et al., 2020; Södergren et al., 2008). Neither mtDNA-CN nor SRH have been investigated in relation to venous thromboembolism (VTE), even though there are several shared factors with arterial CVDs, affecting both mtDNA-CN, and SRH.

Physical activity

Physical activity can briefly be described as any movement produced of skeletal muscles that results in energy expenditure (Caspersen et al., 1985). Physical activity has also been defined as all activity and not just exercise, which is planned, repetitive, and strives to maintain or improve a certain physical ability (Caspersen et al., 1985; Cech & Martin, 2012; Pate et al., 1995).

Recommendations

The previous recommendation from the WHO was a physical activity level of at least 150 minutes per week at moderate intensity, or 75 minutes per week at vigorous intensity (World Health Organization, 2011). It was recommended to do exercise that strengthens the muscles involving the major muscle groups twice a

week (World Health Organization, 2011). The amount of time in aerobic physical activity could be doubled for additional health benefits (Bull et al., 2020). The new WHO recommendations from November 2020 are 150 to 300 minutes per week with an increase of the pulse, instead of a minimum of 150 minutes/week. Another change is the clarification that it is better with a little activity than none. The muscle strengthening activity is still included in the recommendations (World Health Organization, 2020). The recommendations were compiled due to the fact that insufficient levels of physical activity are one of the leading risk factors for death worldwide (World Health Organization, 2011; World Health Organization, 2009; World Health Organization, 2020). Although people in northern Europe are physically active (Gerovasili et al., 2015), they report more sedentary time than their southern European counterparts (Loyen et al., 2016). In Sweden, the national public health survey showed that 66% of the citizens, when self-assessing their physical activity, reached the goal of the previously recommended 150 activity minutes per week (Public Health Agency of Sweden, 2020). However, research using accelerometers measuring the amount of time in physical activity has shown that a very low proportion (7.1%) of Swedish people aged 50 to 64-year, fulfil the WHO physical activity recommendation (Ekblom-Bak et al., 2015). There has been criticism of the guidelines regarding the lack of recommendations for sedentary time (Bouchard et al., 2015). However, the new guidelines of physical activity, include recommendations of decreasing the sedentary time (World Health Organization, 2020). The definition of sedentary behaviour is taken from the latest version from the WHO regarding physical activity.

> "For adults, sedentary behaviour is defined as time spent sitting or lying with low energy expenditure, while awake, in the context of occupational, educational, home and community settings, and transportation" (World Health Organization, 2020)

Previous review articles show a lack of threshold for when physical activity starts to generate health benefits. It is claimed that the greatest benefits arise when a sedentary person starts from zero physical activity to being physically active, even if they do not meet the WHO guidelines (Füzéki et al., 2017; Powell et al., 2011; Warburton & Bredin, 2017). Small increases in physical activity among physically inactive persons might have a greater impact on public health than interventions to promote increased activity levels among those with a fairly healthy lifestyle that includes physical activity (Rose, 2001).

Disease prevention with physical activity

It is well-known that prolonged sitting increases the risk for incident non-communicable diseases such as obesity, diabetes type 2, breast, and colon cancer, VTE and arterial CVD (Bouchard et al., 2015; Edwardson et al., 2012; Francesconi et al., 2019; Johansson et al., 2019; Knowler et al., 2002; Kubota et al., 2018;

Kunutsor et al., 2020; I. M. Lee et al., 2012; Pan et al., 1997; Veerman et al., 2012; World Health Organization, 2020; Yusuf et al., 2004). While prolonged sitting increases the risk for illnesses, physical activity prevents illness and leads to improved health status (Ancellin, 2019; Darren & Shannon, 2019; Kruk, 2007; Pasanen et al., 2017; Warburton et al., 2006). Besides the preventive effect on physical illnesses, certain types of physical activity also seem to strengthen the psychological fitness and protect against anxiety and depression (Malm et al., 2019; Mammen & Faulkner, 2013; Schuch et al., 2018). Research has pointed out some specific activities, such as popular team sports, cycling, aerobics, and gym activities, which provide protection against mental illness (Chekroud et al., 2018; Choi et al., 2019; McDowell et al., 2019). The effect seems to be bidirectional, where depression and anxiety also predispose for lower levels of physical activity (Roshanaei-Moghaddam et al., 2009). This can be an explanation as to why the level of physical activity among those with depression or anxiety syndrome is generally low and the sedentary time is dominant (Helgadottir et al., 2015; Schuch et al., 2017). However, excessive physical activity can also, in some individuals, be associated with impaired mental health related to disturbances like "excessive exercise" and "overtraining syndrome" (Peluso & Guerra de Andrade, 2005). In addition to the preventive effect of physical activity for many non-communicable diseases, there is a positive correlation between increased physical activity and total energy expenditure. However, those already physically active seem not to increase their total energy expenditure, i.e., weight loss, by further increasing the level of physical activity (Pontzer et al., 2016). Physical activity seems to give a wider health span among humans both with and without multimorbidity, where there has been shown an inverse association between the amount of physical activity and mortality (Chudasama et al., 2019).

Physical activity and self-rated health

Physical activity seems to influence both the physical and the psychological health, and this is a possible explanation as to why physically active individuals rate their SRH better than those who are less physically active (Han et al., 2009; Jepsen et al., 2014; Smiley et al., 2020). Previous research, which was performed in Sweden, revealed that exercise on a regular basis with 6 hours/week or more of physical activity generated a higher odds of considering the self-rated health to be good (Södergren et al., 2008). There is a proposed additional effect of better physical and mental health if performing physical activity outdoors, but there is not sufficient evidence regarding this suggestion (Lahart et al., 2019). Among older adults, there was no evidence of different effect on SRH between outdoors and indoors physical activity (Kerr et al., 2012). Thus, it may be the physical activity itself that affects SRH in a positive direction.

Measurement of physical activity

The golden standard for measuring energy expenditure (i.e., physical activity) in a free-living population is the doubly labelled water technique (Schoeller et al., 1995). This method is an isotope-based technique that assesses the energy expenditure based on the difference between the turnover rates of the hydrogen and oxygen of body water as a function of carbon dioxide production. The results of accelerometers correlate reasonably well with doubly labelled water (Plasqui & Westerterp, 2007) and require no isotope intake or analysis of body fluids. This makes accelerometers an often-preferable method.

Nevertheless, there is a limitation with most accelerometer devices, which is the tendency to underestimate the amount of noticeably light and high intensity activities (Aparicio-Ugarriza et al., 2015). Due to the inability of accelerometers to capture all types of activities (i.e., swimming, weightlifting etc), there can be a need for self-assessment depending on the aim with the investigation conducted. In addition, self-assessment is cheaper and easier to carry out than measures with accelerometers or doubly labelled water (Ara et al., 2015). However, a problem with self-assessment of physical activity is related to the risk of overestimating the time spent doing it (Dyrstad et al., 2014; Forsen et al., 2010; Prince et al., 2008; Troiano et al., 2008).

The most common way to examine the effect of the Swedish model with physical activity on prescription (PAP) (in Swedish FaR) has been by self-reported measurements, and in some of the studies with a complement using pedometers (Onerup et al., 2018). Only one previous study has used accelerometers to evaluate if PAP increased the time in moderate to vigorous physical activity among patients who suffered from transient ischemic attack (Moren et al., 2016). However, the study did not find any significantly increased level of physical activity, which may have been due to an already high baseline level of physical activity and a small sample size (n=88).

Physical activity interventions

According to Healthcare regulations, primary healthcare has the responsibility to prevent diseases among the Swedish population (Hälso- och sjukvårdslag [HSL], 2017). Several intervention studies have been conducted during the past years with the aim to decrease the incidence of non-communicable diseases via a changed lifestyle. The interventions have shown improvements with a lower incidence rate of diabetes (Knowler et al., 2002; Pan et al., 1997; Sakane et al., 2014; Tuomilehto et al., 2001), hypertension (Eriksson et al., 2006; Hinderliter et al., 2014; Svetkey et al., 2009), and decreased weight (Barnes et al., 2020; Fitzpatrick et al., 2015; Goodpaster et al., 2010; McDoniel et al., 2010). High qualitative counselling is important when working at a healthcare centre that focuses on lifestyle habits

(Noordman et al., 2013). Research upon patients' experience of lifestyle counselling by general practitioners showed an expectation to be promoted, motivated, and that their everyday life should be considered, when receiving advice regarding behavioural changes (Walseth et al., 2011). Both patients in the United States and in Sweden have high expectations of lifestyle counselling from their general practitioner and, if they need help with behavioural changes, more than 80% of the patients wished for support from primary healthcare (Jerdén et al., 2018). Lifestyle counselling by registered nurses have identified several health risks and resulted in guidance to help lead a healthier life (Duaso & Cheung, 2002). When counselling regarding lifestyle changes it is important to use methods that promote the conversation about changing the unhealthy behaviour in order to achieve a successful result (Poskiparta et al., 2006). This approach is in-line with what patients express as important to achieve a fruitful meeting (Persson & Friberg, 2009). However, patients' previous experiences with counselling influence the impact on lifestyle changes (Kärner et al., 2005). In addition, registered nurses express higher work satisfaction when using a patient-centred way in lifestyle counselling (Drevenhorn et al., 2014).

Modelling motivation to physical activity

In Sweden, the healthcare services recommend the use of PAP as a complementary treatment to motivate patients to increase their physical activity level (Swedish National Institute of Public Health, 2010). The treatment addresses both primary and secondary prevention of disease. PAP strives towards the recommendations for physical activity both in health promotion and in prevention for high-risk individuals (Kallings, 2011). The written prescription in the PAP model can be a proposal for an activity or an extensive solution with a supportive structure depending on the patient's needs and level of motivation. When prescribing PAP, the dialogue should be based on motivational interviewing (MI), to improve the patient's intrinsic motivation to practise physical activity (Forsberg et al., 2009; Holm Ivarsson, 2013; Miller & Rollnick, 2013). The written prescription has an activity diary on the backside, which functions as an external motivator. The PAP model has been associated with up to 60% increased activity levels, but the effect has not shown sustainability over time, (Leijon et al., 2009; Onerup et al., 2018). The individuals who increase their physical activity are often those who are already active and not the sedentary ones (Morgan, 2005). An explanation might be that already active individuals have more positive thoughts about physical activity, which increases the satisfaction with physical activity (Baldwin et al., 2013). The satisfaction can be due to an increased induction of endogenous opioids if spending more time conducting physical activity (Boecker & Dishman, 2013). With positive thoughts about physical activity there may already be a manifested intrinsic

motivation, which may have come through earlier satisfaction of being physically active (W. Lee et al., 2012).

Number of individuals needed to treat

It is a challenging task trying to help individuals with an inadequate amount of physical activity to change their behaviour. Systematic reviews have estimated that one must treat 12 sedentary adults with a physical activity promotion intervention to make one of them achieve the recommended physical activity level at one-year follow-up (Orrow et al., 2012; Williams et al., 2014). However, physical activity interventions seem to be quite effective when compared to other interventions for a changed behaviour. For example, in smoke cessation, the number needed to treat with nicotine replacement therapy is 29 for one person to quit smoking (Barry & Finke, 2020).

Motivation

The origin of the word "motivation" is from the Latin *moveo* which can be translated as "to move". Motivation can generally be defined as the force, process or action that influences someone to perform something (McCoach & Flake, 2018). It is claimed that motivation plays a crucial role in achieving success in any part of life. Motivation functions as a catalyst for success in any area. The absence of motivation suppresses the ability of achievement (Deckers, 2005) and prohibits a successful end of any action. Both extrinsic and intrinsic motivation can affect the result of a behavioural change (McCoach & Flake, 2018). Extrinsic motivation can be described as an outer motivator i.e., winning a reward or evading a penalty (Tranquillo & Stecker, 2016). The opposite—intrinsic motivation—is to do something because the behaviour in itself is rewarding i.e., gives satisfaction (W. Lee et al., 2012). Research has demonstrated that satisfaction with a new behaviour plays a crucial role when changing behaviour e.g., from less to more physically active (Baldwin et al., 2013), smoking cessation (Baldwin et al., 2006) or weight loss (Baldwin et al., 2009). If an action provides immediate rewards in the anterior cortex (satisfaction) by, for example, endogenous opioids (Boecker & Dishman, 2013), the action can become an automatic behaviour, much like an instinct, where the reaction will be delivered automatically without any thought of how or whether to respond on a trigger (Brewer et al., 2014). The capability of taking autonomous decisions, without influence of automatic behaviours, are decisive for how successful a behavioural change will be (Ludwig et al., 2020).

Mindfulness

Mindfulness can be described as an attitude of conscious presence, which is about living in greater awareness of oneself here and now, without valuing thoughts and feelings. Kabat-Zinn initiated 1979 in the University of Massachusetts Medical School a meditative secular approach used all over the world to treat pain and depression (Kabat-Zinn, 2013) defined mindfulness as;

> "the awareness that arises from paying attention, on purpose, in the present moment and non-judgmentally" (Kabat-Zinn, 2003 p. 145)

This approach makes the individual perceive the outside world as it is without being affected by previous experiences, preconceived notions, or feelings, which in turn possibly strengthens the ability to make decisions in an objective way (Epstein, 1999). The practice of mindfulness might give the individual an increased curiosity, openness, and acceptance because of the orientation toward one's experiences in the present moment (Bishop et al., 2004). Mindfulness cannot be taught explicitly, instead it needs to be experienced and explored by the individual themselves with the help of mentors (Epstein, 1999; Ludwig & Kabat-Zinn, 2008). People have varying capacities to attend to, and to be aware of the present moment. This is called dispositional mindfulness, and it is an intrinsic but a modifiable trait (Brown & Ryan, 2003). The ability of mindfulness training to evoke attention has been developed using various meditation techniques derived from Buddhist spiritual methods (Bishop et al., 2004). The training can be described as a process which leads to an increased quality of attention to moment-by-moment experience (Kabat-Zinn, 2013), and can be exerted as sitting meditation but also as an approach to everyday life (Kabat-Zinn, 1994).

Mindfulness and motivation

There is an association between the risk of CVD and the ability to be consciously present, where individuals with good cardiovascular health have better ability to be consciously present (Loucks, Britton, et al., 2015). Mindfulness can be a helpful tool when changing a behaviour, e.g., in obese individuals, when changing their behaviour and relation to food, especially regarding negative behaviours like binge eating, consolation eating, and eating between the main meals (Dalen et al., 2010; O'Reilly et al., 2014; Sojcher et al., 2012). The connection could be due to improved attention control, emotion regulation, and self-awareness (Loucks, Schuman-Olivier, et al., 2015). For example, those who can maintain their physical activity might have a better ability for acceptance and to be in conscious presence, than those who interrupt (Ulmer et al., 2010). However, it is not clear whether maintaining the

physically active lifestyle over time is due to conscious presence or whether the physical activity strengthens the ability of conscious presence (Mothes et al., 2014).

To experience increased satisfaction with a behaviour e.g., physical activity, awareness of the present is crucial and may be facilitated by practising mindfulness (K.-E. Tsafou et al., 2016; K. E. Tsafou et al., 2016). This might explain why mindfulness seems to mediate the relationship between intrinsic motivation and the physical activity level (Ruffault et al., 2016). A systematic review indicated that mindfulness interventions operate better when implementing physical activity behaviour if they target satisfaction, motivation, self-efficacy, acceptance, and other psychological factors. More than half of the 40 reviewed articles showed positive physical activity outcomes (Schneider et al., 2019). Besides mindfulness's supposed effect on physical activity behaviour, practising mindfulness seems to increase pain tolerance (Mohammed et al., 2018; Zeidan et al., 2019). The increased pain tolerance seems to be due to mindfulness practice independent of endogenous opioids (Zeidan et al., 2016). An additional effect of mindfulness besides increased awareness, and conscious presence, is that it seems to increase the experience of satisfaction and moderate the inconvenience related to physical activity. The mitigated discomfort may explain why mindfulness practising individuals, compared with a control group, did not decrease the amount of physical activity due to seasonal changes (Meyer et al., 2018).

Although increased exercise, motivation, and self-reported daily activity can be predicted by high dispositional mindfulness at baseline, the effect is also mediated by lower negative emotions and feelings of shame (Kang et al., 2017). Mindfulness and satisfaction are suggested to be consecutive mediators for the path between possessing a dispositional tendency to be mindful and physically activity (K. E. Tsafou et al., 2016). With awareness in a specific positive situation and reduction of negative thoughts, combined with perceived progress to set goals, the satisfaction with a specific behaviour, e.g., about physical activity, can be increased (Baldwin et al., 2013).

The mechanism by which mindfulness induces behavioural changes may be the increased awareness of, or the effect of, an undesirable behaviour that is incompatible with the individual's long-term goals (Ludwig et al., 2020). Based on the Self-determination theory, practising mindfulness could create a gap between an individual's automatic behaviour and their long-term goals (Ryan & Deci, 2000). This gap of awareness gives the individual an opportunity to think and reflect on a behaviour before automatically acting on a trigger.

Aims of the thesis

Main aim

The overall aim of the thesis was to study lifestyle changes among primary care patients, both in terms of perception of and with an intervention for increased physical activity. This thesis also investigated if poor SRH, lifestyle, and low mtDNA-CN have an association with an increased risk of VTE.

Specific aims

Paper I

The purpose was to explore patients' experiences of visiting a nurse-led lifestyle clinic.

Paper II

A study protocol for a randomised controlled trial (RCT) pilot study with the aim to test feasibility in preparation for a full-scale study. The results are presented in paper III.

Paper III

The aim was to examine the feasibility of the study design as a preparation for a full-scale study. The intervention outcome was differences of change in physical activity level over time between three groups: PAP, mindfulness, and a combination containing both PAP and mindfulness, in a population with insufficient self-reported level of physical activity.

Paper IV

The main aim of this cohort study was to examine the association between baseline SRH in middle-aged women (50-64 years) and incident VTE. The second aim was to analyse the association between lifestyle habits, i.e., physical activity, diet, smoking, alcohol consumption, and VTE.

Paper V
The main aim of this cohort study was to examine the association between baseline mtDNA-CN in middle-aged women (50-64 years) and incident VTE.

Methods

An overview of the studies is presented in Table 1.

Table 1
Overview of the papers

Paper	I	II & III	IV	V
Design	Qualitative	RCT[1], Study protocol, Pilot- and feasibility study, Intervention with mindfulness and physical activity	Cohort	Cohort
Outcome	Patients' experience	Recruitment rate, dropout, adherence to intervention. Difference in change of, time in PA[3], SRH[4], FFMQ[5]	Time to VTE[6]	Time to VTE[6]
Participants	13 women, 1 man of 137 potential participants, age 40-84	88 of 136 eligible inactive primary health care patients 64 women, 24 men age 40-65	5626 women aged 50-60	2117 women aged 50-60
Data Collection	Focus group interviews	Accelerometers, blood samples, questionnaires, anthropometric measurements	Questionnaires, anthropometric measurements, blood samples, Swedish registers	Questionnaires, anthropometric measurements, blood samples, Swedish registers
Data collection period	2011-2012	2016-2018	1995-2000	1995-2000
Data analyses	Qualitative content analysis	Linear mixed-effects model.	Chi^2-test, Student´s t-test, Cox-regression	Chi^2-test, Student´s t-test, Wilcoxon rank sum test, Cox-regression

[1]**RCT**-Randomised controlled trial, [3]**PA**-physical activity, [4]**SRH**-self-rated health,[5]**FFMQ**- five facets of mindfulness, [6]**VTE**- venous thromboembolism

Study design

Paper I was a qualitative study using focus groups to collect the material. The results were analysed with qualitative content analysis.

Paper II was a study protocol for a randomised controlled trail (RCT) pilot- and feasibility study, result of the pilot-study is presented in paper III.

Paper III was an RCT, pilot- and feasibility study where three different groups were compared at three different time points regarding change. Analysis was done with a linear mixed-effects model.

Paper IV was a cohort study examining the association between SRH and risk of VTE by Cox´s proportional hazards-regression. Comparisons of baseline variables between those who were affected with incident VTE and those who were not were made with Chi^2 test, and Student´s t-test.

Paper V was a cohort study using Cox´s proportional hazards-regression studying the associations between mtDNA-CN and VTE. Baseline categorical variables were examined by Chi^2-test and Wilcoxon rank sum test for not normally distributed variables. Student´s t-test was used for continuous variables.

Study populations

Paper I

Patients aged 40, 50, or 60 years, and listed at a health care centre were invited to the newly started lifestyle clinic at a primary health care center. Patients of any other age could also make an appointment but were not actively invited. An invitation to participate in a focus-group interview was sent out by letter to every fifth patient consecutively among the 137 patients who had visited the lifestyle clinic. As many patients declined participation, invitations were sent out to all the 137 patients. Fourteen patients agreed to participate (13 women and 1 man). Of these, 10 had been invited, and four had visited the lifestyle clinic on their own initiative. The interviewed patients had a median age of 50.5 (range 40–84) years. Time between visiting the lifestyle clinic and focus-group interviews differed between one to eight months.

Paper II & III

Three health care centres volunteered to participate in the pilot- and feasibility study. The recruitment of patients between 40-65 years old with a physical activity level below WHO´s recommendations (150 minutes per week) started in September 2016, and the study ended in December 2018. The patients needed to be fluent in Swedish, without dementia, severe mental disorder, unstable untreated angina pectoris or myocardial infarction within six weeks before entering the study. A total of 136 patients were informed about the study and invited to participate. 88 patients accepted (64.7 participation rate) to be included, 64 women and 24 men with an

average age of 53.9. Among those 29 women and 19 men who declined participation, there was a slightly higher average age of 56 years.

Paper IV

The Women´s Health In the Lund Area study (WHILA study) (Samsioe et al., 2010), 10,766 women, aged between 50 and 60 years old, were invited and 6917 agreed to participate. Of these, 6916 had complete datasets. The cohort was identified through a population registry that comprises all inhabitants. Information concerning medication and diseases later in life were obtained from the Swedish Hospital Discharge Register, the Hospital Outpatient Register and the Swedish Cancer Register 1990-2011 and linked self-reported data from the WHILA study baseline. In the present study, we excluded patients with stroke, arterial CVD or VTE before baseline. Women living in nursing homes, medicated with anticoagulants were also excluded. A total of 5626 women remained after exclusion.

Paper V

An adjustment of the study was made halfway through the WHILA study, and blood samples began to be collected for DNA analysis. Therefore, blood samples were only available for 3062 women. Out of these blood samples there were 541 with poor quality of DNA as observed during droplet digital PCR analysis of a reference gene. 2521 women with sufficient quality of DNA remained after exclusion of those with poor quality DNA. After further exclusions, i.e., the same as in paper IV, 2117 women remained in the cohort and were included for analysis in the current study.

Procedure

Paper 1

The interviews were done in focus groups where the moderator guided the conversation within the aim of the study (Kvale & Brinkmann, 2009; Parahoo, 2006). A total of 14 respondents were interviewed in four different sessions (4, 3, 3 and 4 respondents at each interview). Each interview started with an open question: "Tell me about your experience of visiting the nurse-led lifestyle clinic", and then follow-up questions when needed to keep up the conversation (Côté-Arsenault & Morrison-Beedy, 1999).

Paper II & III

A pilot study is not just a small study, it contains several measures of feasibility besides the intervention measures (Browne, 1995). To test the feasibility in this pilot-study there were measures for recruitment rate, dropout rate, and attendance rate to mindfulness courses as well as the web-based mindfulness practice. The sample size was calculated for a full-scale study and reduced according to the budget, and by a rule of thumb, pointing out that you need approximately 30 participants to test a variable (Browne, 1995; Leon et al., 2011). The possibility to implement the intervention in routine care was also investigated.

Interventions

The pilot-study comprised three groups: PAP, mindfulness, and a combination of PAP and mindfulness. Measurements and questionnaires were performed at baseline, three months, and six months (Figure 1, flowchart describing the study design). To obtain equal groups, the randomisation was done by a minimisation method with a random element (Pocock & Simon, 1975). The minimisation variables were age and sex. The randomisation was done using STATA version 15 (Stata corp, College Station, Texas). All patients answered the same questionnaires, and the same type of blood samples were drawn, regardless of which group they were randomised to.

PAP

The participants in this group got a counselling based on MI and PAP according to their preferences and motivation. As an early follow-up, they were offered an appointment by telephone or by a visit at the reception after three weeks. The same procedures as at baseline were repeated at both three and six months. The patients were also offered an adjustment of the PAP if needed.

Mindfulness

Patients who were randomised to the mindfulness group underwent, besides the same measurements, questionnaires, and blood sampling at the same time points as the PAP group, an eight-week mindfulness course. The mindfulness course was held once a week after working hours at the primary health care centre. They also got admission to web based instructions for 20 minutes long daily exercises. The mindfulness programme "Here and Now" (in Swedish: Här och Nu from Mindfulnesscenter AB Sweden) was designed by the general practitioner Ola Schenström, who is also a Swedish expert in mindfulness. The programme was based on both Mindfulness Based Stress Reduction (MBSR) and Mindfulness Based Cognitive Therapy (MBCT), with meditative exercises included in the programme (Sundquist et al., 2015). The courses were led by teachers trained by Ola Schenström. The course was free of charge for the participants.

Combination

The third group was a mix of the other two interventions and with the same measurements, questionnaires, and blood sampling as the other two groups. In the combination group, the participants got counselling with MI to promote increased levels of physical activity. In addition, they attended the same mindfulness intervention for eight weeks as the mindfulness group.

Figure 1. Flowchart describing the study design


```
All patients, aged between 40- 65 years old, who visit the health care centre will be asked about their PA
level. If low PA level they will be asked to participate in the study. Informed consent.
                                           ↓
                          Blood sampling, surveys and
                          accelerometers one week. Randomisation
                                           ↓
                  Follow-up visit with blood pressure, BMI, feedback on blood
                  samples and surveys. PAP to those who have been randomised into
                  a group with PAP.
          ↓                              ↓                              ↓
    Mindfulness                    Mindfulness + PAP                   PAP
          ↓                              ↓                              ↓
   Mindfulness course 8         Mindfulness course 8 weeks and    PA according to PAP
   weeks                        PA according to PAP
          ↓                              ↓                              ↓
   3 months follow-up for all groups, with blood sampling, surveys, blood pressure, BMI. PAP to those who
   have been randomised into any group with PAP.
                                           ↓
   6 months follow-up with blood sampling, surveys, blood pressure and BMI
                                           ↓
   In full length study follow-up in 12 months with blood sampling, surveys, blood pressure, BMI
```

PA-Physical Activity, BMI-Body mass index. PAP- Physical Activity on Prescription (Nymberg et al, 2018).

Measurements

The primary outcome of the intervention was difference between groups in change of time in physical activity. The physical activity was measured both with ACTi Graph GT1X activity monitors and by the National Board of Health and Welfare validated questionnaires. The accelerometers should be worn by the hip in an elastic

31

band during waking hours for seven consecutive days before randomisation, and before the, three-, and six-month follow-ups (Fig 2).

The accelerometer data was analysed using the same definitions and methods as used in previously published research of physical activity (Ekblom-Bak et al., 2015; Moren et al., 2016). Activity monitor data were divided into sedentary, light physical activity and moderate to vigorous physical activity. Wear time was defined by subtracting non-wear time from 24 hours. Non-wear time was defined as at least 60 consecutive minutes with no movement (0 counts 125 per minute), with allowance for maximum two minutes of counts between 0-100 (Ekblom-Bak et al., 2015; Troiano et al., 2008). We considered ≥ 600 minutes wear time per day for at least four days to be valid compliance (Ekblom-Bak et al., 2015; Moren et al., 2016). Due to the sample size, there was no demand for consecutive wear days with valid wear time, and no difference was made between weekdays and weekends. Average was expressed as total counts divided by wear time in minutes per day (counts per minute) and averaged over worn days. Registrations below 100 counts per minute were determined as being sedentary (Ekblom-Bak et al., 2015; Matthews et al., 2008; Moren et al., 2016). 100 – 2019 counts per minute were considered as light physical activity and > 2020 counts per minute as moderate to vigorous physical activity (Ekblom-Bak et al., 2015; Moren et al., 2016). The results are presented as percentage sedentary, light physical activity or moderate to vigorous physical activity per valid day and averaged over the number of valid days (Moren et al., 2016). Self-reported daily activity (e.g., gardening, slow walks, biking etc.) was measured by an eight-step scale (0 = 0 min/ week, 7 ≥300 min/week). Self-reported leisure time activity (e.g., running, football etc) was measured by a seven-step scale (0 = 0 min/week, 6 ≥ 200 min/week).

Secondary outcome

Self-rated health was assessed by a 5-graded Likert scale from very poor to very good (Johansson et al., 2015; Södergren et al., 2008).

Mindfulness was assessed by the Five Facets of Mindfulness Questionnaire (FFMQ) which contains 29 questions in the Swedish version (Baer et al., 2006; Baer et al., 2008). The five facets of mindfulness are: observing (7 items), describing (6 items), acting with awareness (5 items), non-judging of inner experience (5 items), and non-reactivity to inner experience (6 items).

Blood pressure was measured in mmHg on the right arm, after 5 minutes of resting in a sitting position with both feet on the floor.

Perceived sleep disorders were assessed by the Insomnia Severity Index (ISI) (Bastien et al., 2001; Dragioti et al.). ISI contains seven questions with Likert scales (0-5) for assessment of the sleep quality, quantity, and how it affects the person's daily living.

Figure 2. SPIRIT Figure: Schedule of forms and procedures per study time point

TIMEPOINT**	Enrolment	Week 0	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	3 months follow-up	6 months follow-up
ENROLMENT:												
Eligibility screen	X											
Informed consent	X											
Baseline assessment	X										X	X
Follow up visit with feedback		X									X	X
Allocation	X											
INTERVENTIONS:												
PAP			●————————————————————●								X	X
Mindfulness+ PAP			●————————————————●								X	X
Mindfulness			●————————————————●								X	X
ASSESSMENTS:												
Accelerometer Data	X										X	X
FFMQ	X										X	X
ISI	X										X	X
Self Rated Health	X										X	X
Lifestyle Habits Questionnaire	X										X	X
Blood Pressure	X										X	X
BMI	X										X	X
Blood Samples	X										X	X

FFMQ- Five Facets Mindfulness Questionnaire. ISI- Insomnia Severity Index. Self-rated Health scale with five options from very poor to very good. Lifestyle habits questionnaire, short questions about physical activity level, food, smoking, alcohol consumption. BMI-Body Mass Index. Blood samples- high density-lipoprotein cholesterol, blood sugar, biomarkers, gene and protein expression (Nymberg et al., 2018).

Paper IV & V

The baseline measures were collected via a routine physical exam and a postal questionnaire with 104 questions concerning education, household, working status, perimenopausal status, medical history, drug treatment, personal and family history of diabetes, or CVD (myocardial infarction, stroke, deep venous thrombosis, or hypertension in parents or siblings with an event before the age of 60 years). It also contained questions about habits like smoking, alcohol consumption, physical activity, general dietary habits, quality of life, as well as subjective physical, and mental symptoms. This questionnaire was a composite of several pre-existing and validated questionnaires. SRH was assessed only at baseline from a single question, in which the participants were asked to rate their perceived health in a 7-graded Likert scale from "Very poor" to "Excellent, could not be better" (1=very poor, 7=Excellent) (Samsioe et al., 2010). In this study, we classified alternatives 1–4 as poor SRH and 5–7 as good SRH, as in other studies where the middle value has

been classified as poor health in dichotomization (Leão et al., 2009). Weight and height were rounded off to the nearest 0.1 kg and 0.5 cm. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared (kg/m^2). Subjects were categorized as current smokers, former smokers, or non-smokers. Low physical activity, i.e., less than 30 minutes moderate activity 5 days a week (Organization, 2011) was defined as the lower tertial among the answering alternatives. If high intake of sugar or fat or low intake of dietary fibre or fruit were reported, the diet was considered as less healthy. If low intake of sugar and fat and high intake of fruit and dietary fibre was reported, the diet was considered to be healthy. Education was categorised into three classes: comprehensive school (9 years), upper secondary school (12 years), and university degree. Since waist circumference is a valid predictor for VTE, waist circumference was used instead of BMI (Borch et al., 2010) in the analysis.

Laboratory measurement of mtDNA-CN

The mtDNA-CN was determined by a droplet digital PCR (ddPCR) based method for quantification of absolute copy number of mtDNA in whole blood, as described in detail (Memon et al., 2017). Compared to real time PCR, ddPCR has a greater precision and improved reproducibility and provides ultrasensitive and absolute nucleic acid quantification (Hindson et al., 2013). The used ddPCR method for mtDNA-CN determination has been well optimised with intra- and inter-assay coefficient variances as 3.1% and 4.2% respectively (Memon et al., 2017).

Qualitative analysis

Paper 1

In Paper I the focus group interviews were recorded, and after each interview transcribed verbatim including laughter, sighs, and pauses. Each focus group interview lasted between 30 to 60 minutes. The analysis of the material started after all interviews were transcribed and was done using qualitative content analysis (Graneheim & Lundman, 2004). Interviews and field notes were read through several times to get to know the material. Both similarities and differences in the informants' stories were displayed. All text relating to the purpose of the study was extracted and brought together and divided into meaning units. A meaning unit could be a single word, parts of paragraphs, or sentences. These meaning units were then condensed. The condensed meaning units were abstracted and coded. Codes were sub-classified to obtain broad categories that explained the content and responded to the purpose. Authors discussed differences and similarities in sub-categories and categories during the sub-classification of codes and when gathering them into categories.

Statistical Analysis

Statistical analyses were all performed using STATA software (Stata Corp, Texas, USA). In Paper III Stata version 15.1, Paper IV Stata version 14.1, and Paper V Stata version 16.1. Power calculations were done by www.openepi.com version 3.01 updated 2013/04/06. All statistical analysis were done by the author of the thesis with statistical support of the Center of Primary Health Care Research statistician Karolina Palmér.

Paper III

Pilot and feasibility measures were set according to similar research; a recruitment rate more than 30% (King et al., 1991), a dropout rate of less than 30%, compliance to the mindfulness course: ≥ 70% of those randomised to any of the groups containing mindfulness and they should participate in at least 75% of the mindfulness meetings (Sundquist et al., 2015), and web-based practice for at least 20 minutes five days per week (800 minutes) by 70% of patients randomised to any group containing mindfulness (Gluck & Maercker, 2011).

The intervention effect on changes in outcome measures was examined by analysing average group differences (PAP, Combination, Mindfulness) in baseline score and change in each outcome between baseline and three- and six-months follow-up using a linear mixed-effects model. Each model included the time variable and group as indicator variables, and an interaction analysis between time and group to estimate treatment differences in change over time, adjusted for baseline measures and taking the correlation between repeated measurements into account. We did not adjust for the minimisation variables in the analysis.

Paper IV

To examine differences and similarities between those who were affected by VTE and those who were not, all variables related to arterial CVD, were compared between the groups. All continuous variables were examined using two-sided Student´s t-test, and with chi^2-test for the dichotomous variables to calculate p-values. P-values <0.05 were considered significant. For the analysis of the relationship between SRH and time to VTE, Cox´s proportional hazards regression was used. Hazard ratios (HR) with 95% confidence intervals (CI) were calculated (Juul & Frydenberg, 2014; Kirkwood & Sterne, 2003). A censoring was done of women diagnosed after baseline with hypertension, varicose veins as well as those who were affected by stroke, arterial CVD, or cancer diagnosis before the VTE during the follow-up time. At first, a univariate model was carried out and, further on, multivariate models were tested with the confounding variables showing a

significantly increased incident -VTE risk in the univariate test. The first model was adjusted for age, the second model with an addition of physical activity, smoking, and waist circumference. The third model included varicose veins, and hypertension besides the variables in model one and two. In both Paper IV and Paper V, the material was compared between responders and partial responders (those who only responded partially to the questionnaire). A non-significant slightly increased risk of VTE was seen for the partial responders (those who only responded partially to the questionnaire) in a Cox regression model adjusted for age. Among the partial responders there was a bigger proportion of smokers, and low education. More of the partial responders rated their SRH in the lower part of the scale and reported a greater proportion of sedentary behaviour. Partial responders were not excluded since this should only influence the results to a minor extent, as there was less than 5% partial responders.

The material was investigated in different ways, at first without exclusion of those who were diagnosed with VTE, arterial CVD, stroke, or cancer before baseline. At a second analysis for test of the robustness, no women were excluded; neither those with prevalent disease (VTE, arterial CVD, stroke, or cancer), nor those with incident disease (arterial CVD, stroke, or cancer) were censored before VTE. However, irrespective of different exclusions, similar results appeared with small differences in HRs and level of significances. To test if the ratio of hazards was constant over time between any two individuals, Schoenfeld residuals were used (Juul & Frydenberg, 2014; Kirkwood & Sterne, 2003). The effect was constant over time in both the second and third model and not significant when testing the proportional hazard assumption. The proportional hazard assumption test was only significant in the first model thus meaning the effect was not constant and changed over the follow-up time. The material was investigated by breaking it up into shorter time span of 5 years (0–5, 5–10, 10–15, 15–20). The hazard ratios differed between the timespans; however, the confidence intervals were overlapped when comparing between the different time spans.

Paper V

The same analyses were used as in Paper IV with addition for Wilcoxon rank sum test for not normally distributed variables. It was a smaller sample due to exclusions of those not being blood sampled for DNA analysis. MtDNA-CN were used both as a dichotomised variable according to the median and as a continuous variable. A power analysis showed that a risk ratio of 1.8 could be detected at a significance level of 5% (two-sided) with a power of 82% in the studied population when using mtDNA-CN as a dichotomous predictor variable. Robustness was tested as in Paper IV with no major differences regardless of exclusions.

Ethical considerations

All studies were done according to the principles of the 1964 Helsinki Declaration.

Paper I

The study was approved by the Health Sciences Ethics Committee (VEN 30-11). The informants provided written informed consent including the voluntariness of participation in the study before each interview, and confidentiality was assured. The interviews were collected by using a digital recorder and made anonymous before transcription and the result was presented in a way that kept the informants anonymous.

Paper II & III

The study was approved by the Regional Ethical Review Board in Lund (registration number 2016/404). The study was also registered at ClinicalTrials.gov, registration number NCT02869854. Written informed consent was obtained from all patients entering the study.

Paper IV & V

The WHILA study was approved by the Regional Ethics Committee at Lund University (LU 174-95, 2011/494 and 2015/6) and the Data Registry Inspection in Stockholm. All participants were given full information, and informed consent was obtained from all participants.

Results

Paper I

The analysis resulted in two categories with 3 subcategories each (Table 2).

Tabel 2. Categories and subcategories

Sense of security	Unfulfilled expectations
Seen as being on an equal level	Disappointment
Control of health	Missing being seen as an individual
The importance of the responsible authority	Physical examination

(Nymberg & Drevenhorn., 2016)

The category *Sense of security* included the subcategories *Seen as being on an equal level, Control of health, The importance of the responsible authority*. Some patients felt safe when being able to identify themselves with the primary health care nurse (PHN) that they met, regarding age and sex. Other patients pronounced that the competence and communication skills were determinant for a positive experience of the counselling. The patients visited the lifestyle clinic due to an uncertainty of being healthy, even if they considered themselves having a healthy lifestyle. There was a wish from the patients to be followed by primary health care for recurrent monitoring of their health status. They thought of primary care as a reliable service that stands for high quality in contrast to their beliefs about occupational health care.

Regarding the category *Unfulfilled expectations* with the subcategories *Disappointment, Missing being seen as an individual* and *Physical examination*, there was brought up a lack of information in the invitation to the lifestyle clinic regarding structure and what they could expect from the visit. There was also disappointment about the absence of psychological aspects that could affect health. The patients expected the PHN to be updated about their previous health care history when visiting the lifestyle clinic, which affected the experience negatively. Since there were no planned follow-up visits, the amount of time discussing their health felt short, even if they had a healthy lifestyle and no problems to solve. The patients felt that they should have been better prepared before the visit, by having filled out questionnaires beforehand instead of doing it during the visit, due to an expectation
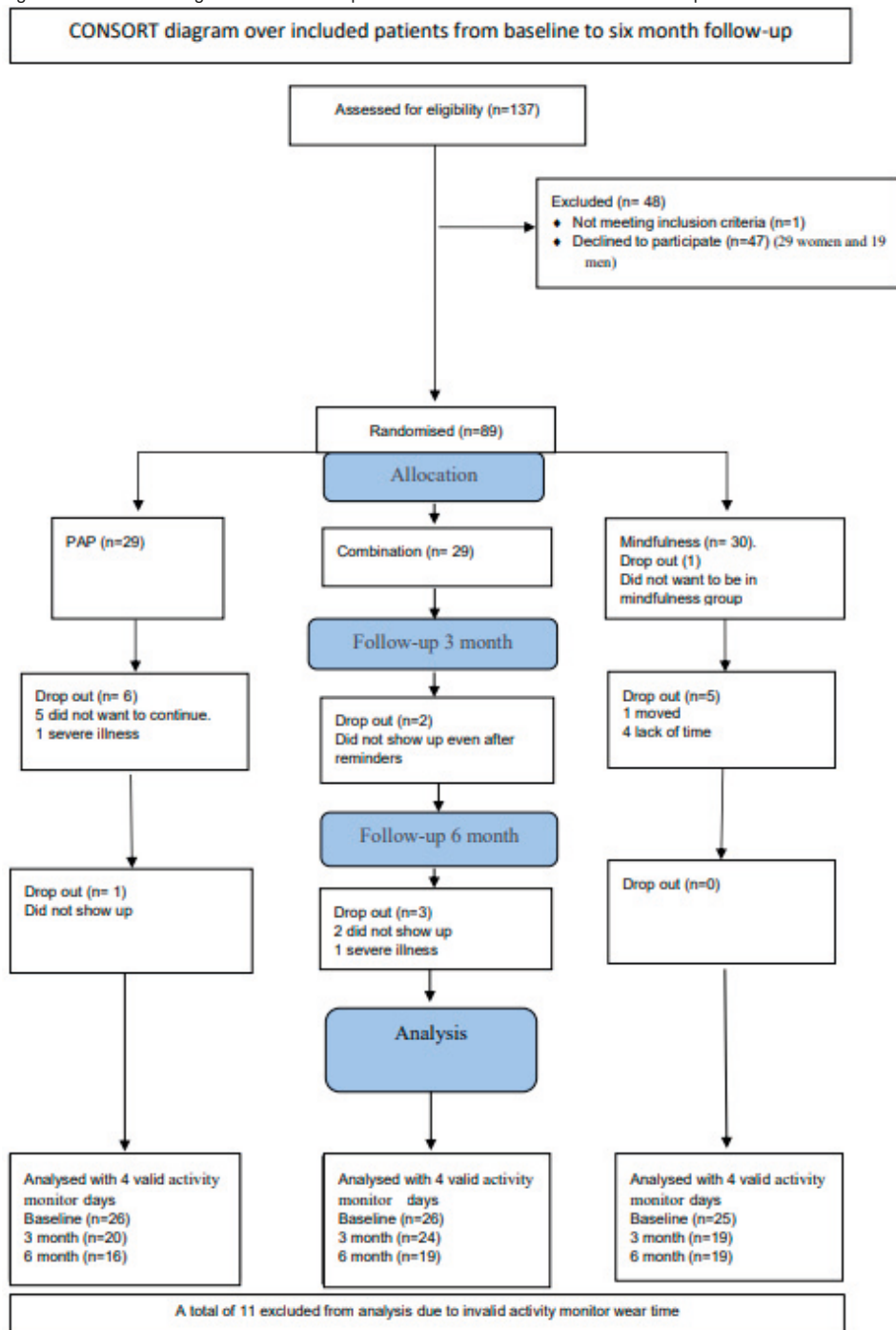
of getting more time for help if needed. They expressed disappointment for not having an overall picture of their lifestyle and were stimulated to find out what to change and get motivated to make the change. They expressed feelings of being treated unprofessionally when the PHN compared her own experiences in life with the patient's problems. It was mentioned that even if there was a good intention, sarcasm should not belong in the counselling, since it could mistakenly be perceived as concrete advice. Some patients expressed an expectation of being examined with a big set of blood samples, or at least fatty acids in blood.

Paper II & III

Feasibility

From the 1st of September 2016 to the last of December 2018, 88 patients from a total of 136 eligible patients were included (Figure 3). This gave a recruitment rate of 64.7%, which is higher than the 30% we accepted for a successful recruitment. The dropout rate was about 20.4%, which is lower than the set limit with a maximum dropout rate of 30%. An expected attendance rate of $\geq 70\%$ of those randomised to any intervention containing a mindfulness course should attend at least 75% of the mindfulness sessions. The result ended at 52% (n=15 in the mindfulness group, n=16 in the combination) who attended at least six out of eight times. For a successful intervention 70% of patients randomised to any group containing mindfulness should use the web-based application for a total of 800 minutes or more during the mindfulness course. However, only eight percent (seven persons) managed to reach 800 minutes or more. Thus, the result of the feasibility study shows a need for the mindfulness intervention to be remoulded in order to achieve a better compliance to the intervention in a full-scale study.

Figure 3. CONSORT diagram over included patients from baseline to six-month follow-up


CONSORT diagram over included patients from baseline to six month follow-up

Assessed for eligibility (n=137)

Excluded (n= 48)
- Not meeting inclusion criteria (n=1)
- Declined to participate (n=47) (29 women and 19 men)

Randomised (n=89)

Allocation

PAP (n=29)

Combination (n= 29)

Mindfulness (n= 30).
Drop out (1)
Did not want to be in mindfulness group

Follow-up 3 month

Drop out (n= 6)
5 did not want to continue.
1 severe illness

Drop out (n=2)
Did not show up even after reminders

Drop out (n=5)
1 moved
4 lack of time

Follow-up 6 month

Drop out (n= 1)
Did not show up

Drop out (n=3)
2 did not show up
1 severe illness

Drop out (n=0)

Analysis

Analysed with 4 valid activity monitor days
Baseline (n=26)
3 month (n=20)
6 month (n=16)

Analysed with 4 valid activity monitor days
Baseline (n=26)
3 month (n=24)
6 month (n=19)

Analysed with 4 valid activity monitor days
Baseline (n=25)
3 month (n=19)
6 month (n=19)

A total of 11 excluded from analysis due to invalid activity monitor wear time

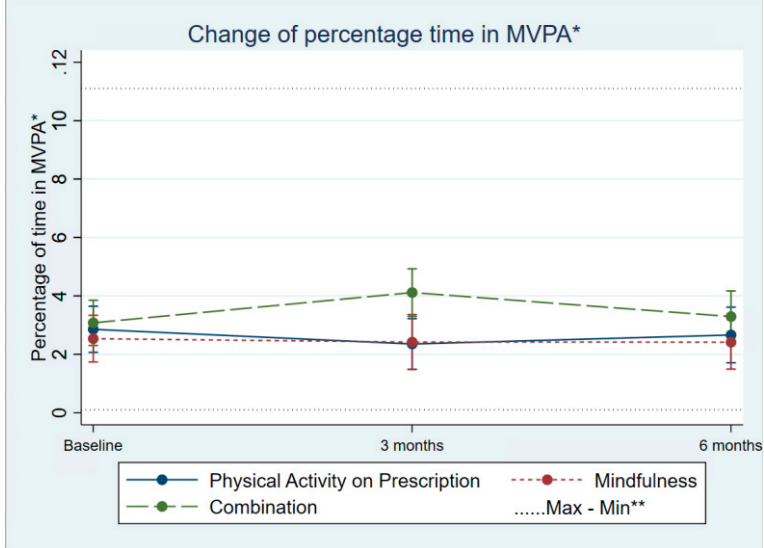(Nymberg[1] et.al., 2021)

40

Primary intervention outcome

Neither light physical activity (Figure 4) nor moderate to vigorous physical activity (Figure 5) showed any significant differences between the three groups in change over time (Table 4). The same absence of significant differences appeared between the three groups in both self-reported daily activity (Figure 6) and leisure time activity (Figure 7) (Table 4).

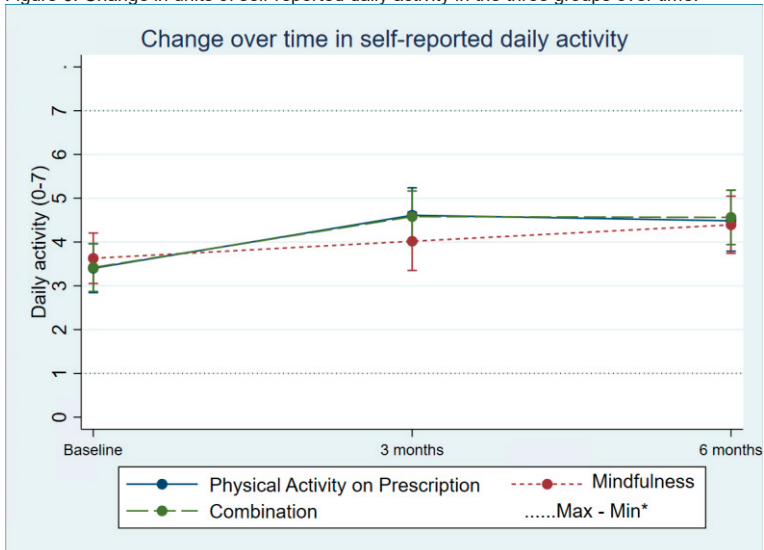Figure 4. Change in percentage light physical activity (LIPA), in the three groups over time.
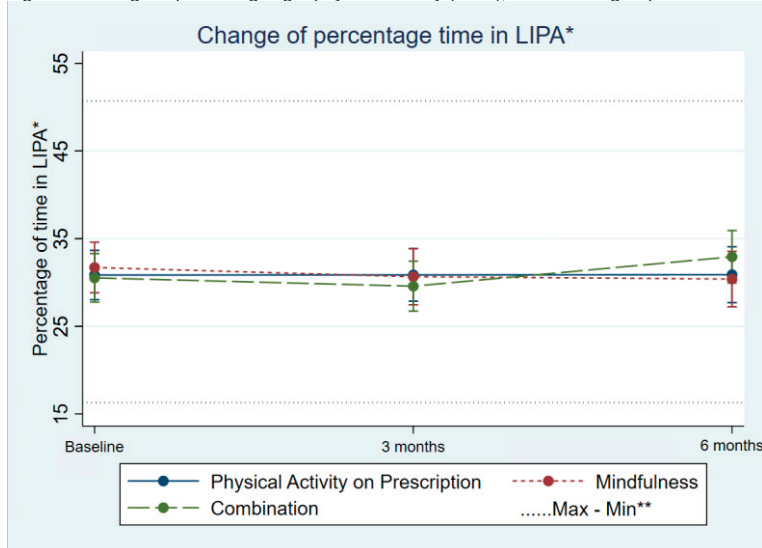
Differences between the groups are estimated by a mixed effect model. *Light physical activity **Maximum and minimum value of all observations. (Nymberg[1] et.al., 2021)

Figure 5. Change in percentage moderate to vigorous physical activity MVPA, in the three groups over time.
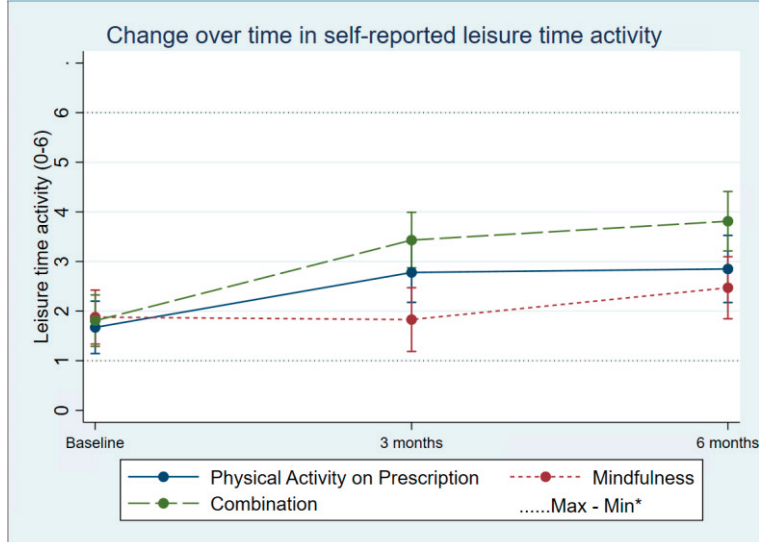

Differences between the groups are estimated by a mixed effect model. * Moderate to vigorous physical activity
**Maximum and minimum value of all observations. (Nymberg[1] et.al., 2021)

Figure 6. Change in units of self-reported daily activity in the three groups over time.

Differences between the groups are estimated by a mixed effect model. *Maximum and minimum value of all
observations. (Nymberg[1] et.al., 2021)

Figure 7. Change in units of self-reported leisure time activity in the three groups over time.
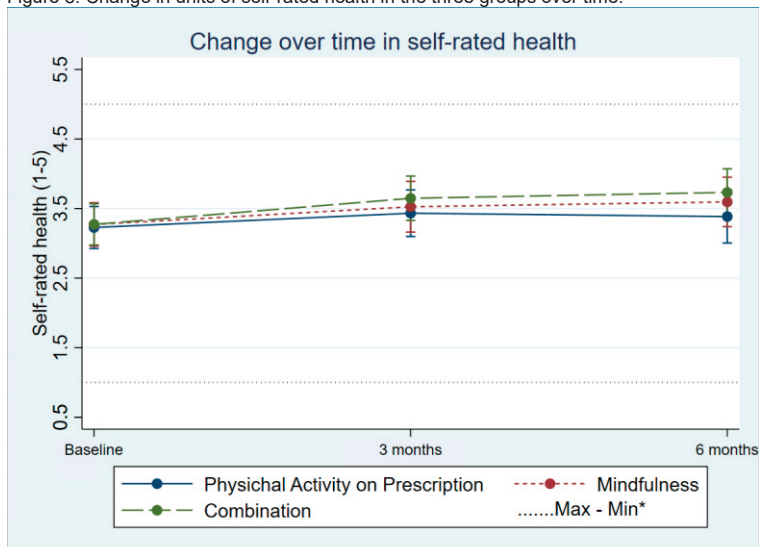

Differences between the groups are estimated by a mixed effect model. **Maximum and minimum value of all observations. (Nymberg[1] et.al., 2021)

Secondary intervention outcome

There were no significant differences in change over time between the three groups regarding SRH (Fig 8), ISI, FFMQ, blood pressure, weight, BMI, nor in lipids (Table 3).

Figure 8. Change in units of self-rated health in the three groups over time.

Differences between the groups are estimated by a mixed effect model. *Maximum and minimum value of all observations. (Nymberg[1] et.al., 2021)

Table 3. Intercept (adjusted baseline value) and changes from baseline to 3 and 6 months in the three groups using mixed effect models. Individuals with at least 4 valid days (600 minutes activity monitor wear time/day).

Outcome	Adjusted baseline value	3 months change	6 months change	Mean difference between groups over time (95% CI)
BMI * (kg/m²)				
PAP	31.7	-0.7	-1.5	0.21 (-0.06 ; 0.49)
Combination	29.0	-0.2	-0.5	
Mindfulness	30.0	-0.1	-0.3	
Total cholesterol (mmol/L)				
PAP	5.23	-0.14	-0.06	-0.08 (-0.24 ; 0.07)
Combination	5.54	-0.43	-0.31	
Mindfulness	5.70	-0.51	-0.27	
LDL ** (mmol/L)**				
PAP	3.47	-0.15	-0.02	-0.01 (-0.15 ; 0.13)
Combination	3.79	-0.25	-0.06	
Mindfulness	3.87	-0.52	-0.24	
HDL(mmol/L)				
PAP	1.57	-0.03	0.02	-0.3 (-0.06 ; 0.00)
Combination	1.51	-0.08	-0.14	
Mindfulness	1.49	-0.002	0.04	
Triglycerides (mmol/L)				
PAP	1.41	-0.01	0.07	-0.06 (-0.17 ; 0.06)
Combination	1.67	-0.08	-0.17	
Mindfulness	1.70	0.11	-0.06	
Systolic Blood pressure (mmHg)				
PAP	128.0	-5.4	-5.2	1.88 (-0.51 ; 4.27)
Combination	125.1	-2.7	3.0	
Mindfulness	120.1	0.3	4.7	
Diastolic blood pressure (mmHg)				
PAP	79.5	-1.9	0.2	0.72 (-0.99 ; 2,43)
Combination	76.3	-1.7	3.3	
Mindfulness	77.6	-0.9	2.3	
ISI^				
PAP	9.2	0.2	-1.2	-0.27 (-1.12 ; 0,58)
Combination	10.7	-1.4	-2.0	
Mindfulness	11.3	-1.3	-0.2	
FFMQ^^				
PAP	105.1	1.7	1.8	0.50 (-0.76 ; 1.75)
Combination	100.6	3.5	3.3	
Mindfulness	105.9	1.3	-1.3	

*Body mass index, ** low-density-lipoprotein cholesterol, *** high density-lipoprotein cholesterol ^Insomnia severity index, ^^ Five Facets of mindfulness questionnaire. (Nymberg[1] et.al., 2021)

Table 4. Intercept (adjusted baseline value) and changes from baseline to 3 and 6 months in the three groups using mixed effect models. Individuals with at least 4 valid days (600 minutes activity monitor wear time/day).

Outcome	Adjusted baseline value	Change from baseline to 3 months.	Change from baseline to 6 months.	Mean difference between groups over time. (95% CI)
Sedentary * (percentage)				-0.75 (-1.74 ; 0.22)
PAP	66.3	0.5	0.2	
Mindfulness	65.8	1.1	1.4	
Combination	66.4	-0.2	-2.8	
LIPA * (percentage)				0.56 (-0.35 ; 1.47)
PAP	30.9	0.01	0.03	
Mindfulness	31.7	-1.1	-1.3	
Combination	30.5	-0.9	2.4	
MVPA* (percentage)				0.15 (-0.19 ; 0.48)
PAP	2.9	-0.5	-0.2	
Mindfulness	2.5	-0.1	-0.1	
Combination	3.1	1.0	0.2	
Leisure time activity (0-6) **				0.23 (-0.03 ; 0.49)
PAP	1.67	1.11	1.18	
Mindfulness	1.88	-0.05	0.59	
Combination	1.81	1.62	2.00	
Daily activity (0-7) **				1.93 (-0.22 ; 0.26)
PAP	3.40	1.21	1.09	
Mindfulness	3.63	0.39	0.77	
Combination	3.42	1.16	1.14	
Weight (kg)				0.18 (-0.32 ; 0.68)
PAP	90.9	-1.8	-2.4	
Mindfulness	85.3	-0. 13	-0.6	
Combination	84.8	-0.74	-1.6	
SRH^ (1-5)				0.8 (-0.06 ; 0.21)
PAP	3.2	0.2	0.2	
Mindfulness	3.3	0.3	0.3	
Combination	3.3	0.4	0.5	

* Percentage of mean time measured by activity monitor. LIPA= Light physical activity, MVPA= Moderate to vigorous physical activity.**Self-reported measurements: leisure time activity on a scale from 0 = 0 minutes per week, 6 ≥ 120 min/week. Daily activity on a scale 0 = 0 minutes per week, 7 ≥ 300 min per week. ^ Self-Rated Health (Nymberg[1] et.al., 2021)

Paper IV

During a follow-up time of 20.4 years, a total of 220 women were affected by VTE. The sum of the follow-up time was 85,645.836 years corresponding to a VTE incidence rate of 3.9 (95% CI 2.26–2.94) per 1000 person-years.

Those women with incident VTE were, on average, both heavier and taller with a greater waist-hip ratio than those who were not affected. They tended to be less physically active, and a higher percentage were smokers. The women with incident VTE had a poorer diet overall and a higher proportion had varicose veins compared with their counterparts. Regarding SRH, there was a significant difference between the groups, with a higher percentage reporting poor SRH among those with incident VTE.

VTE risk was investigated with an unadjusted Cox´s regression showing significantly increased risk by age (HR 1.05, 95% CI 1.00–1.10, p=0.033). When SHR was dichotomised into poor/good, poor SRH showed a significantly increased risk for VTE (HR 1.51, CI 1.13–2.03, p=0.005). Low self-reported physical activity was associated with a significant risk for incident VTE (HR 1.70, CI 1.07–2.74, p=0.026). Reported smoking at baseline was associated with a significantly increased risk of incident VTE (HR 1.43, CI 1.04–1.96, p=0.028). Former smokers showed a non-significant decreased risk for incident VTE (0.92, 0.65–1.32, p=656). A significantly increased risk for incident VTE was also seen in waist circumference (HR 1.03, CI 1.02–1.04, p=0.000) and varicose veins (HR 2.70, CI 2.47–4.95, p=0.001). There were neither any significant associations between unhealthy diet, nor hypertension and incident VTE.

When adjusting for age and SRH in the Cox´s regression (table 5), there was a 51% higher risk to be affected with VTE if dichotomised SRH was rated as poor (HR 1.51, CI 1.12-2.02 p=0.006).

When adjustment was made for lifestyle related variables (physical activity, smoking, former smoking, and waist circumference), the risk of incident VTE if poor SRH decreased to 16% (HR 1.16, CI 0.84–1.61 p=0.370) and showed no significant difference for those not affected with incident VTE.

In the last and fully adjusted model where varicose veins and hypertension were added, the same pattern was displayed. Poor SRH showed a non-significantly increased risk of 18% (HR 1.18, CI 0.85–1.65 p=0.315). The last fully adjusted model only confirmed the well-known risk factors such as: smoking (HR 1.44, CI 1.02–2.03, p=0.037), waist circumference (HR 1.03, CI 1.02–1.04, p=0.000), and varicose veins (HR 2.60 CI1.40–4.80, p=0.002).

Table 5. Multivariate Cox regression with the confounding variables that showed a significantly increased incident VTE-risk in the univariate test.

Model	1	2	3
Total n	5529	4757	4575
Failures n	216	187	187
Self-rated health (poor/good)			
HR	1.51	1.17	1.20
CI	1.12-2.02	.85-1.63	.86-1.67
p	.006	.336	.282
Age			
HR	1.05	1.03	1.03
CI	1.00-1.09	.99-1.09	.99-1.08
p	.048	.166	.173
Physical activity (low/high)			
HR		1.29	.88
CI		.69-2.04	.65-1.18
p		.529	.387
Smoke (yes/no)			
HR		1.46	1.46
CI		1.05-2.03	1.05-2.03
p		.025	.026
Waist circumference			
HR		1.03	1.03
CI		1.02-1.04	1.02-1.04
p		.000	.000
Varicose veins (yes/no)			
HR			2.60
CI			1.40-4.81
p			.002
Hypertension (yes/no)			
HR			1.12
CI			.63-1.98
p			.691
Proportional hazard assumption test	0.0390	0.0689	0.1063

1st model adjusted by age and SRH. 2nd model adjusted by model 1, dichotomized level of physical activity, smoking former smoker and waist circumference. Third model is adjusted by model 2, varicose veins and hypertension. * reference is non-smoker. (Nymberg et.al., 2020)

Paper V

A total of 87 women were diagnosed with VTE during the follow-up time of 17.9 years. The sum of follow-up time was 31,073.123 years corresponding to a VTE incident rate of 2.8 (95% CI 2.3-3.4) per 1000 person-years.

There were significant differences in baseline characteristics between women who were or were not affected by VTE, both in this smaller cohort, as well as in the whole cohort (Paper IV). In the unadjusted Cox´s regression there was a non-significantly decreased risk of incident VTE, both among women with increased mtDNA-CN (HR=0.99, 95% CI 0.98-1.00, p=0.13), and those with mtDNA-CN

over the median (HR=0.76, 95% CI 0.50-1.17, p=0.21) using under the median as reference. Well-known risk factors showed statistically significant associations with risk of VTE; weight (HR=1.02, 95% CI 1.00-1.04 p=0.01), waist circumference (HR=1.02, 95% CI 1.00-1.04, p=0.01), hip circumference (HR=1.03 95% CI 1.00-1.06 p=0.02), and varicose veins (HR=2.89, 95% CI 1.17-7.13, p=0.02).

In this cohort, using unadjusted Cox´s regression, there were no significant associations between incident VTE and current smoking (HR=1.30, 95% CI 0.78-2.18, p=0.32), former smoking (HR=0.74, 95% CI 0.41-1.33 p=0.31), physical activity (HR=0.91, 95% CI 0.33-2.49 p=0.85), or SRH (HR=1.74, 95% CI 0.23-12.04 p=0.61).

When adjusting for age, the group with mtDNA-CN over median showed a non-significant decreased risk for VTE (95% CI 0.50-1.77) compared to mtDNA-CN under the median. There was a non-significantly decreased risk of 1%, for each increase in mtDNA-CN, when using mtDNA-CN as a continuous variable (95% CI 0.98-1.00) (table 6).

The fully adjusted model with confounders such as age, smoking, waist circumference, physical activity, and varicose veins showed that a mtDNA-CN over the median was associated with a 11% non-significantly decreased risk of incident VTE (95% CI 0.57-1.38) with the same reference as in previous models (table 6).

The Cox's regression with mtDNA-CN as a continuous variable, using the same adjustments, showed neither any decreased nor increased risk for incident VTE (95% CI 0.99-1.00) (table 6).

Table 6. Cox regression with mtDNA-CN, analyses with median and continuous were done in separate models. Exclusions were prevalent VTE, varicose veins, arterial CVD, and cancer, those who were living in nursing homes and those with treatment with anticoagulants. Censured for arterial CVD, and cancer before VTE diagnosis during follow-up.

Model	1	2	3
Total n Failures n	2117 87	2117 87	2003 82
mtDNA median* HR CI p	 .76 .49-1.17 .21	 .76 .50-1.17 .22	 .89 .57-1.38 .60
mtDNA(continuous) HR CI p	 .99 .98-1.00 .13	 .99 .98-1.00 .14	 1.00 .99-1.00 .34
	Model 1 mtDNA-CN	Model 2 mtDNA-CN and age	Model 3 mtDNA-CN, age, smoking, waist circumference physical activity and incident varicose veins

*reference is mtDNA-CN under the median. (Nymberg[2] et.al., 2021)

In the sensitivity analysis the only exclusions were the women with poor quality mtDNA-CN (541 women). The results of the sensitivity analysis showed the same

pattern as the main analysis with minor differences in HR and levels of significance between the main and sensitivity analysis.

Knowledge of family history of VTE was the only variable that differed between the sensitivity analysis and main analysis. The univariate sensitivity analysis showed an association between knowledge of family history of VTE and incident VTE (HR=1.67, 95% CI 1.05-2.68, p=0.03), which was not shown in the main analysis.

Discussion

This thesis studied interventions to promote lifestyle changes among primary care patients. It also investigated if poor SRH, lifestyle habits, and low mtDNA-CN are associated with increased risk of VTE.

Main findings

Patients in the focus-group interviews (Paper I) expressed an experienced sense of security when they visited the lifestyle clinic. This sense emerged to some extent from the confirmation of being healthy but also from the patient centred way that they were approached by. The disappointment with the lifestyle clinic that was experienced was due to unfulfilled expectations of the content in what was provided from the clinic.

The pilot-study (Paper II and III) revealed a need to remodel the mindfulness intervention, as there was low adherence to both the mindfulness course and the web-based training. There was neither a significant difference in change between the three groups in primary outcome nor the secondary outcome of the intervention, which may be due to the small sample size.

None of the two suggested predictors (SRH or mtDNA-CN; Paper IV and V), which are both related to lifestyle habits, showed any significant associations with incident VTE among women in ages 50-60 years at baseline. However, other lifestyle related already known risk-factors were confirmed.

Methodological considerations

An overview of used methods, both qualitative and quantitative are presented in Table 1 in the section describing the methods and material.

Paper I

The use of interviews instead of questionnaires was considered a reasonable method to capture the patients' experience of a nurse-led lifestyle clinic (paper I). The rationale for focus group interviews was the possibility to clarify experiences within each group and develop key points of the topic for discussion within the conversation (Krueger & Casey, 2009). The interviews with the patients should preferably have been done sooner after the visit, which may have contributed to a larger number of participants in the study. However, small focus groups can be preferable to large ones (Côté-Arsenault & Morrison-Beedy, 1999), in which the lower limit is set to four informants (Krueger & Casey, 2009). Whether the two interviews, with only three informants should be conducted or not, can be discussed. There is always a risk when inviting informants at the lower number that one of them does not show up. On the other hand, not using the information from those who showed up would not be ethically correct. Due to the limited material, the analysis was done manually in a systematic manner, which also ensures credibility and dependability. To strengthen the results in both credibility and confirmability, the authors' different results were compared and discussed until consensus was found. In this way the transferability was strengthened as well (Burnard, 1991).

Paper II & III

The findings from Paper I were used as grounds when planning the pilot study (Paper II & III), which is the first RCT using mindfulness as an extra motivator to PAP.

One of the differences between the lifestyle clinic in Paper I and the pilot-study (Paper II), was the inclusion criteria. In the pilot-study, the aim was to include those who were physically inactive between 40 to 65 years old regardless of previous diagnosis. In Paper I, healthy individuals were invited the year they became 40, 50, or 60 years, regardless of physical activity level.

As there was an expectation in Paper I regarding follow-ups, two follow-ups were planned in the pilot-study. For those in the intervention group only comprising mindfulness, there were eight course occasions. In the group with PAP a personalised number of follow-ups were planned, according to the concept of PAP, besides the three measurement points (baseline, three months, and six months). The combination group had the most contact with primary health care during the study; both eight weeks course and follow-ups regarding PAP.

The reasons for conducting a pilot-study were both as a matter of resources and that we wanted to test the feasibility. One purpose with studying the feasibility was to investigate if it was possible to implement the study design in routine care without taking advantage of any extra time. The evaluation of implementation ability was measured by recruitment rate and number of follow-ups.

Before conducting the full study there was also a need to collect some results for a proper power calculation. The reason was the very sparse number of studies that had change in activity level by PAP as outcome, measured with accelerometers. In the pilot-study, measurements of physical activity were done by both objective and subjective measures (Aparicio-Ugarriza et al., 2015; Ara et al., 2015; Plasqui & Westerterp, 2007).

Accelerometers were used as their measurements are suggested to correlate well with the golden standard; doubly labelled water (Plasqui & Westerterp, 2007). The accelerometers in present study were the same as in previous studies examining the concordance between objective and perceived walkability (Sundquist et al. 2011; Arvidsson et al, 2012). The questions about self-assessed time in physical activity and other lifestyle habits have been validated by the Public Health Agency in Sweden. For assessment of SRH with a single question, a five-step scale were used, as in previous research (Johansson et al., 2015; Sodergren et al., 2008).

Blood pressure measurements were done in a standardised way, although the measurements could have been affected by the "white coat effect". For a more secure result of the measurement, it could have been done with either 24-hour ambulatory blood pressure monitoring, or home blood pressure monitoring (Pioli et al., 2018; Johansson et al., 2021) and this may be worth considering in a full-scale study.

The reason for conducting an RCT with three groups all containing some intervention was the theoretical suggestion that mindfulness itself perhaps could lead to increased physical activity (Kang et al., 2017; Tsafou et al., 2016; Tsafou et al., 2016). The mindfulness programme, which was used in this study, was adapted to Swedish primary healthcare. The programme (in Swedish "Här och Nu" = Here and Now by the Swedish Mindfulness Centre; MFC) uses manuals and standardised techniques adapted and modified from both MBSR and MBCT, with guided meditations and yoga exercise. When used in other research, this mindfulness program has neither reported any short nor long-term adverse events, (Sundquist et al., 2015; Sundquist et al., 2019).

The instrument to evaluate change in mindfulness, FFMQ, has been tested for both reliability and validity in Swedish (Lilja et al., 2011). ISI is a validated instrument for evaluating insomnia (Bastien et al., 2001). In Sweden it is only validated among chronic pain patients (Dragioti et al.), but it has been used in research done in Sweden among various patient groups (Blom et al., 2015; Zou et al., 2019).

At the three participating health care centres (Paper III), all patients who were physically inactive were asked about their willingness to participate by the appointed health care personnel. The aim was to recruit 90 patients within 12 months, which meant about three patients per month/health care centre or one each month/healthcare centre and intervention group.

Despite reminders in the time schedule and discussing the recruitment at staff meetings, the recruitment lasted for about 30 months, even though there was a remuneration to the health care centre after each blood sampling.

The slow recruitment affected the mindfulness groups, which were supposed to contain 10 participants. To minimise the waiting list, some of the groups contained less than 10, and some more than 10 included participants. Long waiting times and group size are factors that potentially may influence the results, e.g., by affecting the motivation to exercise, but this is a speculation.

Paper IV & V

In the cohort studies (Paper IV and V), a well-defined group of women were followed from inclusion until development of VTE or another censoring event before first VTE i.e., cancer, arterial CVD, stroke, hypertension, varicose veins, or death. The women in the studies were classified on basis of exposure, SRH ratings (Paper IV), and high or low level of mtDNA-CN (Paper V). Even if cohort-based studies provide the opportunity to study multiple outcomes and exposures to calculate the risks (absolute and relative) for a disease, it is not enough to ensure causal inference (Bhopal, 2008; Hill, 2015).

One limitation with cohort studies is the risk of change in exposure status when only measured at baseline and without repeated measures. In Paper IV, the exposure variable SRH was collected only at baseline. However, SRH is quite stable until the age of 50 and then starts to decrease. Men often have better SRH at a younger age but with a more pronounced age-related decrease than women, which leads to similar ratings at older age between sexes (McCullough & Laurenceau, 2004; Sargent-Cox et al., 2010).

Poor SRH is a significantly better predictor of mortality among younger than in older individuals (Zajacova & Woo, 2016). Elderly people, above 75 years, often report their health as good even though there are several physical symptoms (Dening et al., 1998). Less than 45% of individuals seem to change their ratings over a decade, to either one step better or worse than the baseline assessment (Nery Guimarães et al., 2012; Wolinsky et al., 2008). Changed lifestyle with increased level of physical activity may affect the rating of SRH positively (Sargent-Cox et al., 2014).

Regarding change in mtDNA-CN, it is suggested to be altered with age, where older individuals have lower levels than younger, and those who suffer from different diseases have even lower levels (Mengel-From et al., 2014). Besides the decrease caused by ageing, a healthy lifestyle may affect the levels of mtDNA-CN and a positive change of lifestyle might increase the amount of mtDNA-CN (Cakir et al., 2007; Chang et al., 2016; Eluamai & Brooks, 2013; von Wurmb-Schwark et al., 2008).

Strengths and limitations

Paper I

The analysis was performed manually in a systematic manner to ensure both credibility and dependability. Both authors performed the analysis simultaneously, compared their analyses and discussed their result until consensus was reached. By this way of working the results were strengthened in terms of credibility and confirmability and suggests that the results would be transferable to a different lifestyle clinic in a similar context

A limitation with this study was the low recruitment rate in the focus group interviews. This may have been due to a long waiting time between the lifestyle clinic visits and the interviews.

Paper II & III

A strength with Paper II is that the proposed model has emerged from the experience and result of Paper I.

One strength of Paper III, which in fact is one of the first randomised trials investigating the proposed motivational effect of mindfulness to physical activity, was the use of both subjective and objective measurements. The study design combines already established methods in primary healthcare. The high recruitment rate and low dropout rate are also strengths of the study, as well as the fact that the sample contained only sedentary individuals, according to activity monitor data.
One limitation was the small sample size, meaning that the study was under powered and could not provide any convincing result. A limitation was also the low compliance regarding the activity monitors by the hip for at least four days. This compromises the reliability of the results. The ACTi Graph GT1X activity monitors have an inherent limitation since they do not capture all sorts of physical activity or intensity of, for example, weightlifting, biking, and swimming. This limitation with the activity monitors could have been less if the participants had kept a diary of their physical activity during the week when the activity level was measured.

Paper IV & V

The cohort in Paper IV and V includes a well-defined study population with both self-reported and anthropometric values combined with information from registers. To decrease the risk of influences on VTE- risk and poor SRH, we censored participants who were affected by cancer or any CVD before the first VTE occurrence during follow-up as well as diagnosed hypertension and varicose veins

after baseline. Paper V is, to our knowledge, the first study examining the association between mtDNA-CN and incident VTE.

One limitation with Paper IV is the lack of repeated measures of SRH, as SRH may change over time. There are limitations with both Paper IV and Paper V regarding the generalizability to a wider context, since the study was performed only in women with a narrow age span and from a certain area. The low number of VTE events limited the possibility to investigate and compare the occurrence of different VTE-forms between groups. For example, it was not possible to perform sub-analyses of provoked and unprovoked VTE. A major limitation with Paper V was that we do not have blood samples with mtDNA-CN from the whole cohort, thus rendering a smaller study population and, as with SHR, there was also a lack of repeated measures.

Considerations of the results

With a changed lifestyle, it is possible to decrease weight (Carolyn et al., 2020; Fitzpatrick et al., 2015; Goodpaster et al., 2010; Jarle et al., 2019), and on a population level to lower the incidence of diabetes (Knowler et al., 2002; Lindström et al., 2003; Pan et al., 1997; Roșescu et al., 2020; Sakane et al., 2014; Tuomilehto et al., 2001) and hypertension (Eriksson et al., 2006; Hinderliter et al., 2014; Mattila et al., 2003; Svetkey et al., 2009; Zanesco & Antunes, 2007; Zoellner et al., 2014). These results show the importance of promoting changes in lifestyle habits according to the recommendations, such as a healthy diet and the right amount of physical activity according to the healthcare regulations. Primary healthcare also has a responsibility to prevent noncommunicable diseases among the Swedish population (Hälso- och sjukvårdslag [HSL], 2017).

Paper I

The focus group interviews revealed patients' feeling of perceived integrity, when visiting the primary health care. The primary health care service was also considered to be a secure and independent actor to organise directed health check-ups. Patient-centeredness was considered important for the most beneficial consultation, and some individuals appreciated the personal chemistry (Hörnsten et al., 2014). This highlights the importance of extensively promoted consultation training by health care providers among those who are working with lifestyle changes (Lambe & Collins, 2010) to achieve the best results, and patient satisfaction (Drevenhorn et al., 2012).

An expectation of follow-ups was revealed through the interviews, even though several of the patients did not have any need for changed lifestyle habits. It is possible though that the patients may have been affected by this only visit (Persson & Friberg, 2009) by new insights, even if it did not lead to any major change of habits.

Measurements and blood samples were pronounced as an important part of a lifestyle clinic. Patients believed that blood samples would reflect the self-perceived health as a confirmation of the perceived wellbeing or validate an anticipated sickness. Blood samples measuring, e.g., fatty acids, blood sugar, and blood count should be and are often included when screening individuals in population-based studies (Lingfors et al., 2003; Norberg et al., 2010).

Paper II

Planning a pilot-study

The expectation of follow-ups, from Paper I, was considered when planning the pilot-study RCT (Paper II). When aiming to include physically inactive individuals and trying to motivate them to increase their physical activity level it is important to have follow-ups, which is also a part of the concept in PAP. There was not planned for any analysis of the number of follow-ups, which is a limitation; the number of follow-ups may have affected the result. When planning for the pilot-study the disappointment, noted in paper I, of not being blood sampled was taken into account. The blood sampling and anthropometric measurements were planned to be the same as in other studies with health dialogues in primary health care (Lingfors et al., 2009; Norberg et al., 2010).

The rationale for mindfulness groups

The aim with the pilot-study intervention was to tune up the effectiveness of PAP, by an addition of mindfulness in one of the intervention groups. If the intervention with the combination would be successful it should be easy to broaden and implement into the clinical care setting of primary health care. There are already, within primary health care, mindfulness groups led by health care providers targeting patients with stress reactions, insomnia, depression, and anxiety (Sundquist et al., 2015). Since there are studies implying the positive effect of physical activity to several of these diagnoses (Chekroud et al., 2018; Choi et al., 2019; Malm et al., 2019; Mammen & Faulkner, 2013; McDowell et al., 2019; Schuch et al., 2018) it would be easy to prescribe PAP for an additional effect. On the other hand, inactive patients could easily be included in the already established mindfulness groups.

Paper III

Inclusion and dropout

In Paper III, 62.5% of the included inactive patients were women, which is the same recruitment pattern as in other studies aiming for increased physical activity (Leijon et al., 2008). The feasibility goal for inclusion rate was fulfilled (paper III); 64.7% of eligible patients accepted to participate, compared to the anticipated 30%. This can be interpreted as an effect of seeing primary health care as a secure and reliable actor when patients shall discuss their lifestyle, and lifestyle changes, seen in Paper I. As previously described, patients have high expectations on lifestyle counselling and support with behavioural changes from primary health care (Jerdén et al., 2018). The low dropout rate of 20.4% may be due to the follow-up visits, which emerged as an expectation in Paper I.

Adherence to mindfulness

There was a surprisingly low attendance rate to the mindfulness courses, even if the course was outside working hours on a weekday. The loss of participants to the courses could preferably have been investigated, but we did not seek ethical permission for this purpose. The mindfulness groups and the web-based training programme were free of charge for the participants to minimise dropouts and increase the recruitment rate. The low compliance to mindfulness courses and the web-based training program can be due to a low interest or scepticism towards mindfulness. It can also be just a lack of time.

One possible explanation to the low attendance rate was the lack of a fee to participate in the course, thus possibly contributing to the loss of value to the participants and making it easy to skip. On the other hand, a cost for the mindfulness intervention may have resulted in hesitation to participate in the study, especially for those who consider mindfulness as a suspicious treatment. If only participants with a positive attitude towards mindfulness were to be included, there would be a risk of selection bias.

The low adherence to the web-based training is a major issue that can affect the measurements of the intervention effect, i.e., time in physical activity. Spending 20 minutes each day practising mindfulness can be hard when being randomised into a group you do not wish for.

To increase both the effect of, and adherence to, the mindfulness and PAP intervention it may be useful to include the spouses for a greater impact and better compliance over time. This has been shown to have a positive effect when promoting other beneficial lifestyle changes (Di Castelnuovo et al., 2007; Di Castelnuovo et al., 2009). However, this way will neither affect the compliance nor the effect of intervention among those living alone.

Before conducting a full-scale study, the mindfulness intervention must be redesigned. A suggestion could be a shorter version of the web-based training with daily reminders by short messages services (SMS) or such. The method with SMS-reminders has previously been shown to be a feasible way to promote smoking cessation (Whittaker et al., 2019), and lowering of blood sugar (Sahin et al., 2019). An ongoing study is analysing the use of lifestyle advice via SMS to help with lowering of blood pressure (Bolmsjö et al., 2020).

Primary outcome

We used two validated methods to measure the change of physical activity. Neither of them showed any significant differences between the three groups regarding change in physical activity during the follow-ups. There were changes of time in physical activity, both self-reported and measured with accelerometers, especially in the combination group. The increase was 2.4% in light physical activity in the combination group, which recalculated in time, corresponds to approximately 15 minutes per day. This calculation is based on a wear time of 600 minutes per day.

Even if the increase of light physical activity and decrease in sedentary time were small, this can be due to the short follow-up time. There may have been larger alterations in both light physical activity and moderate to vigorous physical activity with a longer follow-up time, but this is speculative. The lack of statistically significant differences in change, between intervention groups, can also be due to the repeated measurement where participants tend to overrate the self-assessment of their physical activity level irrespective to the intervention (Dyrstad et al., 2014; Forsen et al., 2010; Prince et al., 2008; Troiano et al., 2008).

The self-reported leisure time activity does not correspond exactly to the accelerometer data; there was a larger self-reported increase of time in leisure time activity than registered with the accelerometers. This inequality can be due to increased time in activities like weightlifting and swimming where the accelerometers do not collect correct data or cannot be used (Aparicio-Ugarriza et al., 2015). The low compliance to wearing the accelerometer by the hip could be one of the reasons to the absence of difference between the groups. In future studies it may be considered to use GPS-enabled mobile phone applications (Benson et al., 2015), as many people have their mobile phones with them everywhere. However, these may have the same limitations as accelerometers regarding e.g., weightlifting or swimming. In the combination group, there was an increase from an average activity level of 1.81 (range 0-6), which corresponds to about 30 to 60 minutes per week, to an average of 3.81, which corresponds to about 30 to 90 minutes per week (Figure 7). The other groups also increased the self-reported leisure time activity but not at the same amount. This can be due to the effect of expectation, when the participants in the combination group knew the purpose of the study and therefore had a tendency to overestimate their time in leisure time activity. In a full-scale

study, it would be of major interest to make the participants keep a physical activity diary to compare with the self-reported physical activity and accelerometer data.

According to the expected number needed to treat using a physical activity intervention, there should be about 2- 3 in each of the groups with PAP that increased their physical activity during the study. However, the number needed to treat with physical activity intervention has been calculated with one-year follow-up (Orrow et al., 2012; Williams et al., 2014) and in the pilot-study the follow up time was only six months. The short follow-up implies that a higher number of individuals should have increased their physical activity level, as it can be challenging to maintain an increased physical activity level over time (Leijon et al., 2009; Morgan, 2005; Onerup et al., 2018). Long-time adherence to an increased physical activity level may require a slow change over time (Hammar & Ostgren, 2013) together with a capability of taking autonomous decisions (Ludwig et al., 2020).

WHO states in their recommendations that all activity counts, and every minute less spent in a sedentary state is better (World Health Organization, 2020). These recommendations imply that even the small effect of the pilot-study might be useful as an addition with a positive effect of mindfulness when prescribing PAP, especially among those who are physically inactive. However, a lager study is needed to examine this, and the power calculation can be based on present study.

There can be differences concerning effectiveness of an intervention among different countries and cultures, which can result in a substantial cost without any effect if an intervention is not tested and adjusted before implementation (Isaranuwatchai et al., 2020). Even if a larger study shows significant increases of physical activity if mindfulness is added, there is a need to test the intervention in different populations and cultures.

Secondary outcomes

There were no significant differences in the score of FFMQ between the groups in Paper III. This might be due that physical activity may increase the level of mindfulness as much as mindfulness practice increases the level of mindfulness (Mothes et al., 2014). The small group size might have affected the results, and this is a major limitation of the study. The absence of changes in FFMQ score might also be due to the low adherence to the mindfulness course and web-based training.

There were neither any significant changes captured regarding sleep quality, measured with ISI. The low changes in physical activity among the participants can be a major cause, since there are previously described associations between increased amount of physical activity and decreased problems with insomnia (Hartescu et al., 2015; Kelley & Kelley, 2017). There are also suggested positive effects of practising mindfulness regarding sleep quality (Rusch et al., 2019), but

maybe due to the low adherence to mindfulness training and mindfulness group meetings, we did not find evidence of any changes.

SRH is considered a reliable measurement of some illnesses, such as arterial CVDs, and has also been associated with the amount of physical activity; higher amount of time in physical activity have resulted in higher ratings of the SRH (Södergren et al., 2008; Kerr et al., 2012). Even if there were small changes of time in physical activity, there were an increase of the SRH rating in all three groups which can be due to an expected effect by the participants. Ideally though, the explanation is that the participants actually felt better and answered honestly when rating SRH at follow-up.

The explanation of increased SRH ratings can be the increased attention from the health care service, where the participants were seen as individuals and were invited to discuss their health. In Paper 1 "not being seen as an individual" was one of the major disappointments, which may possibly affect the SRH. Considering that SRH are stable over time (Wolinsky et al., 2008) and the measurements were done within six months, the participants can be considered having had a positive effect of participating in the study regarding SRH at group level.

The weight loss tended to be slightly larger in the PAP group in a visual examination, although there were no significant differences between the groups. According to other research (Dalen et al., 2010; O'Reilly et al., 2014; Sojcher et al., 2012) claiming that mindfulness can affect negative eating behaviours, it could be expected a larger decrease of weight in any of the groups containing mindfulness. The PAP group had at baseline, the highest average weight which may explain the greater weight reduction in this group. One other explanation may be the previously discussed low adherence to the mindfulness course and web-based training. It can also depend on the low increase of physical activity in all three groups.

The absence of weight loss may explain why there were no significant differences in high density-lipoprotein cholesterol, low-density-lipoprotein cholesterol, total cholesterol, or triglycerides. Regarding blood pressure, there were not shown any significant differences either, which may be due to both the low increase of physical activity and small decreases of weight in the groups. This can be explained by the lack of change towards a low caloric diet. Besides the decrease in weight, a diet with caloric restrictions seems to increase both mean and maximum lifespan (Mercken et al., 2012). This has only been demonstrated primarily in rodents and lower species, but even in non-human primates there are positive outcomes with caloric restriction (Mercken et al., 2012). Even if the results with caloric restriction are positive, they should not be applied to all humans due to the increased risk of frailty that increases with age (Pifferi & Aujard, 2019).

Paper IV & V

Screening with predictors

When working with lifestyle changes, it is important to know if the same factors predispose for more than one disease. Particularly when the diseases, such e.g., arterial CVD and VTE, predispose for each other and both can be prevented with physical activity (Kunutsor et al., 2020; I. M. Lee et al., 2012). Both SRH and mtDNA-CN are suggested to be valid predictors of arterial CVDs (van der Linde et al., 2013; Waller et al., 2015; Yue et al., 2018), but the association with VTE has not been previously examined. This is the rationale for the cohort studies investigating the association between VTE and SRH, and between VTE and mtDNA-CN. The studies were especially challenging due to possible confounding. For example, both factors seem to be affected by physical activity, i.e., high levels of physical activity are associated with good SRH (Han et al., 2009; Jepsen et al., 2014; Kerr et al., 2012; Lahart et al., 2019; Smiley et al., 2020; Södergren et al., 2008) and high levels of mtDNA-CN (Chang et al., 2016; Eluamai & Brooks, 2013).

The study in Paper IV was, to our knowledge, the first study that examined the relation between SRH and incident VTE among middle-aged women. Previous studies of VTE have discussed the possibility that other diseases that increase the risk of VTE may affect SRH as well (Brækkan et al., 2016).

The mtDNA-CN level is regulated by heredity but can be decreased by low amount of physical activity, smoking and high alcohol consumption (Cakir et al., 2007; Chang et al., 2016; Eluamai & Brooks, 2013; von Wurmb-Schwark et al., 2008; Vyas et al., 2020). The lifestyle can be a possible explanation as to why poor SRH has been shown to be associated with low amount of mtDNA-CN (Takahashi et al., 2018).

It is a possibility that the participants in the WHILA-study have been affected by the questionnaires and physical examination and started to question their current lifestyle habits and changed them (Farnkvist et al., 2008; Lingfors et al., 2003; Persson & Friberg, 2009). Since choice of lifestyle habits affect the burden of illness (Yusuf et al., 2004), healthier habits may result in lower number of diseases in the registers. However, the incidence of VTE is quite similar in the WHILA study as in other studies (Goldhaber, 2012).

Even if some risk factors are shared, some risk factors (e.g., age, smoking) are stronger associated with arterial CVDs than VTE (Gregson et al., 2019). SRH may be a weak risk factor and larger studies comprising a wider age span and both sexes might find significant association with SRH, even if it may be weaker than for arterial CVDs. Even if SRH in larger studies should not show any significant associations and represent an additional risk factor, individuals with low SRH rating should be further examined and followed up.

Conclusion

Prevention in primary health care can be conducted through nurse led lifestyle clinics. The goal should be helping individuals to change unhealthy habits and keep the healthy ones. This requires frequent recurrent training in motivational interviewing by the nurses to secure a patient-centred holistic approach, including all aspects of the individual.

The visits to any lifestyle clinic should be based on screening forms, and include blood sampling, performed before the appointment.

There should be a clear proposition of follow-ups among those who are in need to change a lifestyle habit and require help with the modification.

Lifestyle conversations should include the assessment of both risk for arterial CVDs and VTE as these conditions predispose for each other and share many risk factors.

The pilot-study seems possible to conduct after adjustments of the mindfulness intervention. The web-based training should be shorter than in the pilot-study, possibly with SMS reminders each day, and perhaps web-based group meetings, or without any meetings at all. There should be a possibility for the study participants to choose between hip and wrist worn accelerometers.

There may be an additional effect on PAP with regular mindfulness training; this may also affect the rating of self-rated health in a positive direction more than both only PAP and only mindfulness.

Neither poor SRH nor low amount of mtDNA-CN seem to be useful predictors for incident VTE among women in age 50-64 years.

The presence of varicose veins should, as far as possible, be examined during a lifestyle consultation, for primary prevention of future VTE.

Future research

It is important to know if interventions to increase physical activity are cost effective. Therefore, prospective studies should evaluate the effect of physical activity on prescription using objective measurements with an addition of self-reported physical activity.

Regarding the implied increased physical activity when practising mindfulness needs to be investigated in the same way as the effect of physical activity on prescription.

The pilot-study presented in the thesis should be conducted in full-scale as it may reveal an important effect of mindfulness on physical activity. The full-scale study should contain different groups, healthy sedentary and those sedentary with different noncommunicable diseases, to further test if it is applicable in different individuals. There should be a minimum of one year of follow-up time with repeated measurements and blood sampling regarding epigenetics. The analysis should be adjusted by socioeconomic status.

Association between poor SRH, mtDNA-CN, and incident VTE should be investigated in a larger population containing both sexes in a broad age span. There is also a need to further investigate lifestyle habits and the association with incident VTE including the possibility to differ between different types i.e., PE and DVT.

Summary in Swedish /Sammanfattning

Inledning

En ohälsosam livsstil med låg fysisk aktivitet, tobaksbruk, högt alkoholintag och ohälsosamma matvanor ökar risken för övervikt, diabetes, högt blodtryck, cancer och hjärtkärlsjukdom. Förutom levnadsvanor har både lågt socioekonomiskt status och självskattad dålig hälsa starka kopplingar till ökad risk för sjukdom. Arteriella och venösa blodproppar har tidigare setts som två olika sjukdomar, dock har det visat sig att de har många gemensamma riskfaktorer. Riktade hälsosamtal är en effektiv metod för att hitta individer med ohälsosamma levnadsvanor. För att motivera de som är fysiskt inaktiva till en sundare livsstil med mer fysisk aktivitet använder hälso- och sjukvården fysisk aktivitet på recept. Ungefär 60% av dem som får fysisk aktivitet på recept ökar aktivitetsnivån, men förändringen håller inte i sig över tid och fungerar bäst hos dem som redan är aktiva. Mindfulness kan underlätta levnadsvaneförändring genom ökad motivation. Det har också påvisats samband mellan aktivitetsnivå och graden av medveten närvaro. WHOs rekommendation (2020), är fysisk aktivet med pulsökning i 150-300 minuter/ vecka, samt muskelstärkande aktivitet två gånger per vecka. Enligt folkhälsomyndigheten når 66 % av den svenska vuxna befolkningen WHO:s tidigare rekommendation (2011) med minst 150 minuter pulsökande fysisk aktivitet per vecka. Dock har en studie med hjälp av aktivitetsmätare bland svenska 50-64 -åringar visat att endast ca 7 % når rekommendationen. Därför är det viktigt att studera metoder som kan leda till ökad fysisk aktivitet hos inaktiva individer, men också om faktorer (självskattad hälsa & mitokondrie-DNA) som predikterar blodproppar i artärer och påverkas av fysisk aktivitet kan förutsäga risken för blodproppar i venösa kärl.

Det övergripande syftet med avhandlingen var att studera livsstilsförändring hos primärvårdspatienter både avseende upplevelse av samtal kring levnadsvanor och huruvida det går att öka den fysiska aktivitetsnivån ytterligare med hjälp av mindfulness i kombination med fysisk aktivitet på recept jämfört med var för sig. Ytterligare syfte var att studera sambanden mellan risken att drabbas av blodproppar i vener och faktorer (självskattad hälsa och mitokondrie-DNA) som påverkas av mängden fysisk aktivitet.

Metoder

Delarbete I baserades på fokusgruppsintervjuer med totalt 14 patienter som besökt en distriktssköterskeledd levnadsvanemottagning. Syftet var att undersöka patienternas upplevelse av att diskutera sina levnadsvanor. Fokusgruppsintervjuerna analyserades med manifest innehållsanalys.

Delarbete II är en projektplan för en planerad randomiserad kontrollerad pilotstudie hos inaktiva patienter med tre olika grupper, 1) fysisk aktivitet på recept, 2) mindfulness och 3) en kombination av båda föregående grupperna. Här beskrivs tillvägagångssätt, patientrekrytering, provtagning, mindfulness-intervention, mätpunkter med mera. Delarbetet innehåller också beskrivning på mått för en lyckad pilotstudie.

Delarbete III utvärderade pilotstudien avseende rekrytering, avhopp och följsamhet till mindfulness-interventionen. För att utvärdera effekten mellan de tre interventionerna (mindfulness, fysisk aktivitet på recept och kombinationen) och de tre mättillfällena analyserades det insamlade materialet med hjälp av en linjär blandad regressionsmodell.

Delarbete IV undersökte med överlevnadsanalys (Cox's regression) sambandet mellan självskattad hälsa och risken att drabbas av venös blodpropp. Studien utfördes på ett tidigare insamlat material bestående av 6917 kvinnor mellan 50-64 år från ett område kring Lundabygden, vilka följdes under 20 år. Det insamlade materialet kopplades till olika register för att inhämta information om bland annat diagnostiserade sjukdomar.

Delarbete V undersökte med hjälp av överlevnadsanalys (Cox's regression) sambandet mellan mängden mitokondrie-DNA och risken att under uppföljningstiden drabbas av venös blodpropp. Denna studie omfattade de 2521 kvinnor som hade lämnat blod avseende DNA-analyser från kohorten som användes i delstudie IV.

Resultat

Delarbete I visade att patienterna upplevde en *känsla av säkerhet*, vilken kom från att primärvården anses vara en tillförlitlig aktör jämfört med till exempel företagshälsovården. Känslan av att vara på samma nivå som distriktssköterskan var viktig för vissa, för andra var kompetens och den kommunikativa förmågan avgörande. Ett kvitto på att vara frisk bidrog också till känslan av säkerhet. Det fanns även negativa upplevelser vilka kategoriserades som *ouppfyllda förväntningar*. De negativa upplevelserna handlade om bristfällig information kring innehåll och oprofessionellt förhållningssätt. Patienterna ville vara förberedda och

förväntade sig att distriktssköterskan också skulle vara det. De saknade också både provtagning av bland annat blodfetter samt uppföljning.

Delarbetet II och III: Under en period på ca 30 månader accepterade 88 av 136 tillfrågade patienter att delta i pilotstudien, vilket är en mycket högre rekryteringsgrad (64,7 %) än den förväntade på ca 30 %. Det var under studietiden 20,4 % avhopp vilket är lägre än beräknat (30 %). Det förväntades att 70 % av de som randomiserats till mindfulness skulle delta vid minst 6 av de 8 gruppträffarna, dock visade det sig att endast 52 % gjorde det. Bland deltagarna i mindfulnessgrupperna beräknades att 70 % av deltagarna skulle öva minst 800 minuter med den webbaserade träningen. Dock var det bara sju individer som nådde upp till 800 minuter eller mer. Resultatet visade små indikationer på att kombinationen av mindfulness och fysisk aktivitet på recept gav bättre effekt än interventionerna var för sig. Kombinationen uppvisade en lite större ökning av lätt fysisk aktivitet mätt både med aktivitetsmätare och självrapportering, men även bättre självskattad hälsa. Det fanns dock inga statistiskt signifikanta skillnader, vilket kan bero på att deltagarantalet var för lågt för att eventuella skillnader skulle kunna upptäckas.

I **delarbete IV** med en uppföljningstid på 20,4 år drabbades 220 kvinnor av venös blodpropp, vilket ger 3,9 % nya fall per 1000 personår. De som drabbades av venösblodpropp var i medeltal både längre och tyngre med större midjemått än de som inte drabbades. De var också mindre hälsosamma avseende både kost och motion och fler var rökare. Överlevnadsanalysen visade en viss ökad risk för venös blodpropp om den självskattade hälsan skattades som dålig, denna risk var inte statistiskt signifikant efter justering av kända riskfaktorer. Denna studie bekräftade att, rökning, stort midjeomfång och åderbråck är riskfaktorer för venösa proppar.

I **delarbete V** diagnostiserades 87 kvinnor med venösblodpropp, vilket ger 2,8 % nya fall per 1000 personår. Avseende baslinje mått sågs samma skillnader gällande antropometriska mått och levnadsvanor i denna mindre kohort som i delarbete IV. Högre antal mitokondrie-DNA-molekyler än median antalet vid studiens start, visade en liten reducerad risk för venös blodpropp under uppföljningstiden. Denna riskminskning var inte statistiskt signifikant. Det gick inte heller att se någon kontinuerligt minskad risk för venös blodpropp med stigande antal mitokondrie-DNA-molekyler.

Slutsatser

Prevention i primärvård kan med fördel arrangeras via sjuksköterskeledda levnadsvanemottagningar. Dock krävs kontinuerlig träning i samtalsmetodik för att säkerställa en holistisk syn på individen. Besöket på levnadsvanemottagning bör omfatta blodprovstagning och mätningar som är relevanta för prediktion av sjukdom

och kan påverkas av levnadsvanor. För ett konstruktivt möte bör patienterna vara förbereda genom att besvarat frågeformulär innan besöket för att förbereda både sig själv och sjuksköterskan. Det kan också vara en fördel med att generöst erbjuda uppföljning till de som så önskar, och har behov av stöd.

Levnadsvanesamtal bör innehålla riskskattning för både arteriella och venösa blodproppar då de har liknande riskfaktorer, och predisponerar för varandra. Förekomsten av åderbråck bör undersökas under ett levnadsvanebesök för att kunna hjälpa till med förebyggande åtgärder mot venösa blodproppar.

Pilotstudien (delarbete II & III) visar sig möjlig att genomföra som en fullskalig studie efter vissa justeringar, dock behövs en modifiering av mindfulness-interventionen för att öka deltagandet, både i gruppaktiviteterna och den webbaserade träningen. Det kan kanske fungera med dagliga SMS-påminnelser för ökad mängd träning och kanske även webbaserade gruppträffar.

Konceptet med mindfulness som tillägg till fysisk aktivitet på recept hos inaktiva individer kan kanske öka aktivitetsnivån mer än fysisk aktivitet på recept eller mindfulness var för sig.

Varken självskattad hälsa eller mitokondrie-DNA-antal är användbara till att förutsäga insjuknandet i venös blodpropp i denna population av 50-64- åriga kvinnor på ett tillförlitligt sätt.

Acknowledgements

There are many friends, co-workers, and other PhD-students who have supported and encouraged me during my PhD-studies. There has been a lot of coffee drinking and laughs. However, there are a few people I especially wish to express my greatest gratitude to:

My head supervisor, Professor **Bengt Zöller,** for the ability to mediate the feeling of never being disturbed, regardless of the question. You have guided me through the study time with a firm hand, always getting me back on track when I got lost in the epidemiology or other things. Thank you for your fabulous support and supervising.

Professor **Kristina Sundquist** for excellent supervising and always being there when needed. You have always interesting things to discuss, everything from animals, study designs, travels, and many other things.

Professor **Jan Sundquist** for believing in me and giving me the opportunity to try out research and introducing me to a new way to see the world by mindfulness. Thank you for great ideas and encouraging me to keep on going.

Co-supervisor **Emelie Stenman**, for always having an encouraging word to say, you have the incredible ability to give feedback in a very pleasant way without making anyone depressed. And thank you for all the laughs by the coffee table outside my workstation at CRC.

Associate professor **Susanna Calling**, for your calm, expertise, and wisdom in many areas, and for your flexibility when needed.

Professor **Eva Ekvall Hansson**, for all fantastic input and always answering a question by email with the speed of a rocket.

Associate Professor **Ashfaque Memon**, for your valuable input regarding the small but important things like mtDNA-CN.

Statistician **Karolina Palmér**, for always urging, "try and see what happens". This has given me good training in statistics. You have always tried to explain in a language which I can understand.

Helene Rosenqvist for keeping all the non-perfumed mail safe until I could fetch them, and all other, both small and big things, you have helped me out with. It is always nice to talk to you.

My always caring parents **Ingrid and Bengt** for always allowing and encouraging me to go my own way. Thank you for being there.

The youngsters (**Klara**, **Maria**, **Paula** & **Emil**) at home for their often-brutal way of bringing me back to reality from my studies.

My beloved wife **Vera,** for endless discussions over the dinner table about everything and nothing. Thank you for putting up with me. What should a stubborn crossbreed of a turtle and a donkey like me do without you?

References

Ageno, W., Becattini, C., Brighton, T., Selby, R., & Kamphuisen, P. W. (2008). Cardiovascular risk factors and venous thromboembolism: a meta-analysis. *Circulation*, *117*(1), 93-102. https://doi.org/10.1161/CIRCULATIONAHA.107.709204

Alegría-Torres, J. A., Baccarelli, A., & Bollati, V. (2011). Epigenetics and lifestyle. *Epigenomics*, *3*(3), 267-277. https://doi.org/10.2217/epi.11.22

Ancellin, R. (2019). [Benefits of physical activity for cancer patients]. *Rev Prat*, *69*(4), 438-443. (Bénéfices de l'activité physique pour les patients atteints de cancer.)

Aparicio-Ugarriza, R., Mielgo-Ayuso, J., Benito, P. J., Pedrero-Chamizo, R., Ara, I., & González-Gross, M. (2015). Physical activity assessment in the general population; instrumental methods and new technologies. *Nutr Hosp*, *31 Suppl 3*, 219-226. https://doi.org/10.3305/nh.2015.31.sup3.8769

Ara, I., Aparicio-Ugarriza, R., Morales-Barco, D., Nascimento de Souza, W., Mata, E., & González-Gross, M. (2015). Physical activity assessment in the general population; validated self-report methods. *Nutr Hosp*, *31 Suppl 3*, 211-218. https://doi.org/10.3305/nh.2015.31.sup3.8768

Armstrong, M. E., Green, J., Reeves, G. K., Beral, V., & Cairns, B. J. (2015). Frequent physical activity may not reduce vascular disease risk as much as moderate activity: large prospective study of women in the United Kingdom. *Circulation*, *131*(8), 721-729. https://doi.org/10.1161/circulationaha.114.010296

Arvidsson D, Kawakami N, Ohlsson H, Sundquist K. (2012) Physical activity and concordance between objective and perceived walkability. Med Sci Sports Exerc. 44(2):280-7. doi: 10.1249/MSS.0b013e31822a9289. PMID: 21716148

Baer, R. A., Smith, G. T., Hopkins, J., Krietemeyer, J., & Toney, L. (2006). Using self-report assessment methods to explore facets of mindfulness. *Assessment*, *13*(1), 27-45. https://doi.org/10.1177/1073191105283504

Baer, R. A., Smith, G. T., Lykins, E., Button, D., Krietemeyer, J., Sauer, S., Walsh, E., Duggan, D., & Williams, J. M. (2008). Construct validity of the five-facet mindfulness questionnaire in meditating and nonmeditating samples. *Assessment*, *15*(3), 329-342. https://doi.org/10.1177/1073191107313003

Baldwin, A. S., Rothman, A. J., Hertel, A. W., Linde, J. A., Jeffery, R. W., Finch, E. A., & Lando, H. A. (2006). Specifying the determinants of the initiation and maintenance of behavior change: an examination of self-efficacy, satisfaction, and smoking cessation. *Health Psychol*, *25*(5), 626-634. https://doi.org/10.1037/0278-6133.25.5.626

Baldwin, A. S., Rothman, A. J., & Jeffery, R. W. (2009). Satisfaction with weight loss: examining the longitudinal covariation between people's weight-loss-related outcomes and experiences and their satisfaction. *Ann Behav Med*, *38*(3), 213-224. https://doi.org/10.1007/s12160-009-9148-x

Baldwin, A. S., Baldwin, S. A., Loehr, V. G., Kangas, J. L., & Frierson, G. M. (2013). Elucidating satisfaction with physical activity: an examination of the day-to-day associations between experiences with physical activity and satisfaction during physical activity initiation. *Psychol Health*, *28*(12), 1424-1441. https://doi.org/10.1080/08870446.2013.822078

Barnes, R. D., Ivezaj, V., Martino, S., Pittman, B. P., Paris, M., & Grilo, C. M. (2020). 12 Months later: Motivational interviewing plus nutrition psychoeducation for weight loss in primary care. *Eat Weight Disord*. https://doi.org/10.1007/s40519-020-00994-5

Barry, K., & Finke, J. (2020). Nicotine Replacement Therapy for Smoking Cessation. *Am Fam Physician*, *102*(1), 17-18.

Bastien, C. H., Vallieres, A., & Morin, C. M. (2001). Validation of the Insomnia Severity Index as an outcome measure for insomnia research. *Sleep Med*, *2*(4), 297-307.

Baćak, V., & Ólafsdóttir, S. (2017). Gender and validity of self-rated health in nineteen European countries. *Scandinavian Journal of Public Health*, *45*(6), 647-653. https://doi.org/10.1177/1403494817717405

Benson, A. C., Bruce, L., & Gordon, B. A. (2015). Reliability and validity of a GPS-enabled iPhoneTM "app" to measure physical activity. *Journal of Sports Sciences*, *33*(14), 1421-1428. https://doi.org/10.1080/02640414.2014.994659

Bhopal, R. S. (2008). *Concepts of Epidemiology Integrating the ideas, theories, principles, and methods of epidemiology* [Online Electronic document]. Oxford University Press.

Bishop, S. R., Lau, M., Shapiro, S., Carlson, L., Anderson, N. D., Carmody, J., Segal, Z. V., Abbey, S., Speca, M., Velting, D., & Devins, G. (2004). Mindfulness: A proposed operational definition. *Clinical Psychology: Science and Practice*, *11*(3), 230-241. https://doi.org/10.1093/clipsy.bph077

Blom, K., Tarkian Tillgren, H., Wiklund, T., Danlycke, E., Forssén, M., Söderström, A., Johansson, R., Hesser, H., Jernelöv, S., Lindefors, N., Andersson, G., & Kaldo, V. (2015). Internet-vs. group-delivered cognitive behavior therapy for insomnia: A randomized controlled non-inferiority trial. *Behav Res Ther*, *70*, 47-55. https://doi.org/10.1016/j.brat.2015.05.002

Blomstedt, Y., Norberg, M., Stenlund, H., Nyström, L., Lönnberg, G., Boman, K., Wall, S., & Weinehall, L. (2015). Impact of a combined community and primary care prevention strategy on all-cause and cardiovascular mortality: a cohort analysis based on 1 million person-years of follow-up in Västerbotten County, Sweden, during 1990-2006. *BMJ open*, *5*(12), e009651. https://doi.org/10.3402/gha.v4i0.5613. (PMID: 21695071)

Boecker, H., & Dishman, R. K. (2013). Physical activity and reward: The role of endogenous opioids. In *Routledge handbook of physical activity and mental health.* (pp. 57-70). Routledge/Taylor & Francis Group.

Bolmsjö, B. B., Wolff, M., Nymberg, V. M., Sandberg, M., Midlöv, P., & Calling, S. (2020). Text message-based lifestyle intervention in primary care patients with hypertension: a randomized controlled pilot trial. *Scandinavian Journal of Primary Health Care*, *38*(3), 300-307. https://doi.org/10.1080/02813432.2020.1794392

Borch, K. H., Braekkan, S. K., Mathiesen, E. B., Njølstad, I., Wilsgaard, T., Størmer, J., & Hansen, J. B. (2010). Anthropometric measures of obesity and risk of venous thromboembolism: the Tromso study. *Arterioscler Thromb Vasc Biol*, *30*(1), 121-127. https://doi.org/10.1161/ATVBAHA.109.188920

Bouchard, C., Blair, S. N., & Katzmarzyk, P. T. (2015). Less Sitting, More Physical Activity, or Higher Fitness? *Mayo Clin Proc*, *90*(11), 1533-1540. https://doi.org/10.1016/j.mayocp.2015.08.005

Brewer, J. A., Elwafi, H. M., & Davis, J. H. (2014). Craving to quit: Psychological models and neurobiological mechanisms of mindfulness training as treatment for addictions. *Translational Issues in Psychological Science*, *1*(S), 70-90. https://doi.org/10.1037/2332-2136.1.S.70

Brown, K. W., & Ryan, R. M. (2003). The benefits of being present: mindfulness and its role in psychological well-being. *J Pers Soc Psychol*, *84*(4), 822-848.

Browne, R. H. (1995). On the use of a pilot sample for sample size determination. *Stat Med*, *14*(17), 1933-1940. https://doi.org/10.1002/sim.4780141709

Brækkan, S. K., Grosse, S. D., Okoroh, E. M., Tsai, J., Cannegieter, S. C., Næss, I. A., Krokstad, S., Hansen, J. B., & Skjeldestad, F. E. (2016). Venous thromboembolism and subsequent permanent work-related disability [https://doi.org/10.1111/jth.13411]. *Journal of Thrombosis and Haemostasis*, *14*(10), 1978-1987. https://doi.org/https://doi.org/10.1111/jth.13411

Bull, F. C., Al-Ansari, S. S., Biddle, S., Borodulin, K., Buman, M. P., Cardon, G., Carty, C., Chaput, J.-P., Chastin, S., Chou, R., Dempsey, P. C., DiPietro, L., Ekelund, U., Firth, J., Friedenreich, C. M., Garcia, L., Gichu, M., Jago, R., Katzmarzyk, P. T., Lambert, E., Leitzmann, M., Milton, K., Ortega, F. B., Ranasinghe, C., Stamatakis, E., Tiedemann, A., Troiano, R. P., van der Ploeg, H. P., Wari, V., & Willumsen, J. F. (2020). World Health Organization 2020 guidelines on physical activity and sedentary behaviour. *British Journal of Sports Medicine*, *54*(24), 1451. https://doi.org/10.1136/bjsports-2020-102955

Burnard, P. (1991). A method of analysing interview transcripts in qualitative research. *Nurse Educ Today*, *11*(6), 461-466. https://doi.org/10.1016/0260-6917(91)90009-y

Cakir, Y., Yang, Z., Knight, C. A., Pompilius, M., Westbrook, D., Bailey, S. M., Pinkerton, K. E., & Ballinger, S. W. (2007). Effect of alcohol and tobacco smoke on mtDNA damage and atherogenesis. *Free Radic Biol Med*, *43*(9), 1279-1288. https://doi.org/10.1016/j.freeradbiomed.2007.07.015

Cambridge dictionary (no year). Lifestyle. Retrieved March the 7th 2021 from https://www.dictionary.cambridge.org/dictionary/english/lifestyle.

Carlsson, A. C., Wandell, P. E., Gigante, B., Leander, K., Hellenius, M. L., & de Faire, U. (2013). Seven modifiable lifestyle factors predict reduced risk for ischemic cardiovascular disease and all-cause mortality regardless of body mass index: A

cohort study. *International Journal of Cardiology*, *168*(2), 946-952. https://doi.org/DOI 10.1016/j.ijcard.2012.10.045

Castellani, C. A., Longchamps, R. J., Sun, J., Guallar, E., & Arking, D. E. (2020). Thinking outside the nucleus: Mitochondrial DNA copy number in health and disease. *Mitochondrion*, *53*, 214-223. https://doi.org/10.1016/j.mito.2020.06.004https://doi.org/DOI 10.1016/j.ijcard.2012.10.045

Carolyn, T. B., Rachel, L. J. T., Scott, J. P., Nisa, M. M., Maya, V., & Jeanne, M. C. (2020). Parents lose less weight than nonparents in an intensive lifestyle intervention [article]. *Obesity Science & Practice*, *6*(5), 494-506. https://doi.org/10.1002/osp4.436

Caspersen, C. J., Powell, K. E., & Christenson, G. M. (1985). Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research. *Public Health Rep*, *100*(2), 126-131.

Cech, D. J., & Martin, S. T. (2012). Chapter 15 - Health and Fitness Chapter 15- Health and Fitness. In *Functional Movement Development Across the Life Span* (Third edition ed.). Elsevier.

Chang, Y. K., Kim, D. E., Cho, S. H., & Kim, J. H. (2016). Association between Leukocyte Mitochondrial DNA Copy Number and Regular Exercise in Postmenopausal Women. *Korean J Fam Med*, *37*(6), 334-339. https://doi.org/10.4082/kjfm.2016.37.6.334

Chekroud, S. R., Gueorguieva, R., Zheutlin, A. B., Paulus, M., Krumholz, H. M., Krystal, J. H., & Chekroud, A. M. (2018). Association between physical exercise and mental health in 1·2 million individuals in the USA between 2011 and 2015: a cross-sectional study. *Lancet Psychiatry*, *5*(9), 739-746. https://doi.org/10.1016/s2215-0366(18)30227-x

Chiuve, S. E., Cook, N. R., Shay, C. M., Rexrode, K. M., Albert, C. M., Manson, J. E., Willett, W. C., & Rimm, E. B. (2014). Lifestyle-based prediction model for the prevention of CVD: the Healthy Heart Score. *J Am Heart Assoc*, *3*(6), e000954. https://doi.org/10.1161/jaha.114.000954

Choi, K. W., Chen, C.-Y., Stein, M. B., Klimentidis, Y. C., Wang, M.-J., Koenen, K. C., Smoller, J. W., & Consortium, f. t. M. D. D. W. G. o. t. P. G. (2019). Assessment of Bidirectional Relationships Between Physical Activity and Depression Among Adults: A 2-Sample Mendelian Randomization Study. *JAMA Psychiatry*, *76*(4), 399-408. https://doi.org/10.1001/jamapsychiatry.2018.4175

Chudasama, Y. V., Khunti, K. K., Zaccardi, F., Rowlands, A. V., Yates, T., Gillies, C. L., Davies, M. J., & Dhalwani, N. N. (2019). Physical activity, multimorbidity, and life expectancy: a UK Biobank longitudinal study. *BMC Med*, *17*(1), 108. https://doi.org/10.1186/s12916-019-1339-0

Crous-Bou, M., Harrington, L. B., & Kabrhel, C. (2016). Environmental and Genetic Risk Factors Associated with Venous Thromboembolism. *Semin Thromb Hemost*, *42*(8), 808-820. https://doi.org/10.1055/s-0036-1592333

Côté-Arsenault, D., & Morrison-Beedy, D. (1999). Practical advice for planning and conducting focus groups. *Nursing research*, *48*(5), 280-283.

Dalen, J., Smith, B. W., Shelley, B. M., Sloan, A. L., Leahigh, L., & Begay, D. (2010). Pilot study: Mindful Eating and Living (MEAL): weight, eating behavior, and psychological outcomes associated with a mindfulness-based intervention for people with obesity. *Complement Ther Med*, *18*(6), 260-264. https://doi.org/10.1016/j.ctim.2010.09.008

Darren, E. R. W., & Shannon, S. D. B. (2019). Health Benefits of Physical Activity: A Strengths-Based Approach [article]. *Journal of Clinical Medicine*, *8*(12), 2044-2044. https://doi.org/10.3390/jcm8122044

Deckers, L. (2005). *Motivation: Biological, psychological, and environmental., 2nd ed*. Pearson Education New Zealand.

Deflandre, E., Degey, S., Opsomer, N., Brichant, J. F., & Joris, J. (2016). Obstructive Sleep Apnea and Smoking as a Risk Factor for Venous Thromboembolism Events: Review of the Literature on the Common Pathophysiological Mechanisms. *Obes Surg*, *26*(3), 640-648. https://doi.org/10.1007/s11695-015-2012-0

Dening, T. R., Chi, L.-Y., Brayne, C., Huppert, F. A., Paykel, E. S., & O'Connor, D. W. (1998). Changes in self-rated health, disability and contact with services in a very elderly cohort: a 6-year follow-up study. *Age and Ageing*, *27*(1), 23-33. https://doi.org/10.1093/ageing/27.1.23

DeSalvo, K. B., Fan, V. S., McDonell, M. B., & Fihn, S. D. (2005). Predicting mortality and healthcare utilization with a single question. *Health Serv Res*, *40*(4), 1234-1246. https://doi.org/10.1111/j.1475-6773.2005.00404.x

Dexter, L. (1973). The chair and venous thrombosis. *Trans Am Clin Climatol Assoc*, *84*, 1-15.

Di Castelnuovo, A., Quacquaruccio, G., Arnout, J., Cappuccio, F. P., de Lorgeril, M., Dirckx, C., Donati, M. B., Krogh, V., Siani, A., van Dongen, M. C., Zito, F., de Gaetano, G., & Iacoviello, L. (2007). Cardiovascular risk factors and global risk of fatal cardiovascular disease are positively correlated between partners of 802 married couples from different European countries. Report from the IMMIDIET project. Thromb Haemost, 98(3), 648-655.

Di Castelnuovo, A., Quacquaruccio, G., Donati, M. B., de Gaetano, G., & Iacoviello, L. (2009). Spousal concordance for major coronary risk factors: a systematic review and meta-analysis. *Am J Epidemiol*, *169*(1), 1-8. https://doi.org/10.1093/aje/kwn234

Dragioti, E., Wiklund, T., Alföldi, P., & Gerdle, B. The Swedish version of the Insomnia Severity Index: Factor structure analysis and psychometric properties in chronic pain patients. *Scandinavian Journal of Pain*, *9*, 22-27. https://doi.org/10.1016/j.sjpain.2015.06.001

Drevenhorn, E., Bengtson, A., & Kjellgren, K. I. (2014). To be motivated or only comply – patients' views of hypertension care after consultation training for nurses. *Health Education Journal*, *74*(1), 28-36. https://doi.org/10.1177/0017896913517106

Drevenhorn, E., Bengtson, A., Nilsson, P. M., Nyberg, P., & Kjellgren, K. I. (2012). Consultation training of nurses for cardiovascular prevention - a randomized study of 2 years duration. *Blood Press*, *21*(5), 293-299. https://doi.org/10.3109/08037051.2012.680734

Duaso, M. J., & Cheung, P. (2002). Health promotion and lifestyle advice in a general practice: what do patients think? *Journal of Advanced Nursing*, *39*(5), 472-479. https://doi.org/DOI 10.1046/j.1365-2648.2002.02312.x

Dyrstad, S. M., Hansen, B. H., Holme, I. M., & Anderssen, S. A. (2014). Comparison of self-reported versus accelerometer-measured physical activity. *Med Sci Sports Exerc*, *46*(1), 99-106. https://doi.org/10.1249/MSS.0b013e3182a0595f

Edwardson, C. L., Gorely, T., Davies, M. J., Gray, L. J., Khunti, K., Wilmot, E. G., Yates, T., & Biddle, S. J. (2012). Association of sedentary behaviour with metabolic syndrome: a meta-analysis. *PLoS One*, *7*(4), e34916. https://doi.org/10.1371/journal.pone.0034916

Ekblom-Bak, E., Olsson, G., Ekblom, O., Ekblom, B., Bergstrom, G., & Borjesson, M. (2015). The Daily Movement Pattern and Fulfilment of Physical Activity Recommendations in Swedish Middle-Aged Adults: The SCAPIS Pilot Study. *PLoS One*, *10*(5), e0126336. https://doi.org/10.1371/journal.pone.0126336

Eluamai, A., & Brooks, K. (2013). Effect of aerobic exercise on mitochondrial DNA and aging. *Journal of Exercise Science & Fitness*, *11*(1), 1-5. https://doi.org/https://doi.org/10.1016/j.jesf.2013.03.003

Emmelin, M., Nafziger, A. N., Stenlund, H., Weinehall, L., & Wall, S. (2006). Cardiovascular risk factor burden has a stronger association with self-rated poor health in adults in the US than in Sweden, especially for the lower educated. *Scand J Public Health*, *34*(2), 140-149. https://doi.org/10.1080/14034940510032365

Epstein, R. M. (1999). Mindful practice. *JAMA*, *282*(9), 833-839.

Eriksson, K. M., Westborg, C. J., & Eliasson, M. C. E. (2006). A randomized trial of lifestyle intervention in primary healthcare for the modification of cardiovascular risk factors - The Bjorknas study. *Scandinavian Journal of Public Health*, *34*(5), 453-461. https://doi.org/Doi 10.1080/14034940500489826

Farnkvist, L., Olofsson, N., & Weinehall, L. (2008). Did a health dialogue matter? Self-reported cardiovascular disease and diabetes 11 years after health screening. *Scand J Prim Health Care*, *26*(3), 135-139. https://doi.org/10.1080/02813430802113029

Fitzpatrick, S. L., Coughlin, J. W., Appel, L. J., Tyson, C., Stevens, V. J., Jerome, G. J., Dalcin, A., Brantley, P. J., & Hill-Briggs, F. (2015). Application of Latent Class Analysis to Identify Behavioral Patterns of Response to Behavioral Lifestyle Interventions in Overweight and Obese Adults. *Int J Behav Med*, *22*(4), 471-480. https://doi.org/10.1007/s12529-014-9446-y

Forouzanfar, M. H., Alexander, L., Anderson, H. R., Bachman, V. F., Biryukov, S., Brauer, M., Burnett, R., Casey, D., Coates, M. M., Cohen, A., Delwiche, K., Estep, K., Frostad, J. J., Astha, K. C., Kyu, H. H., Moradi-Lakeh, M., Ng, M., Slepak, E. L., Thomas, B. A., Wagner, J.,… Murray, C. J., & Collaborators, G. R. F. (2015). Global, regional, and national comparative risk assessment of 79 behavioural, environmental, and occupational, and metabolic risks or clusters of risks in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet*, *386*(10010), 2287-2323. https://doi.org/10.1016/S0140-6736(15)00128-2

Forsberg, L., Berglind, O., Statens, f., & Forsberg, K. (2009). *Motiverande samtal: för att uppmuntra fysisk aktivitet: manual* [Non-fiction]. Statens folkhälsoinstitut.

Forsen, L., Loland, N. W., Vuillemin, A., Chinapaw, M. J., van Poppel, M. N., Mokkink, L. B., van Mechelen, W., & Terwee, C. B. (2010). Self-administered physical activity questionnaires for the elderly: a systematic review of measurement properties. *Sports Med*, *40*(7), 601-623. https://doi.org/10.2165/11531350-000000000-00000

Francesconi, C., Niebauer, J., Haber, P., Weitgasser, R., & Lackinger, C. (2019). [Lifestyle: physical activity and training as prevetion and therapy of type 2 diabetes mellitus (Update 2019)]. *Wien Klin Wochenschr*, *131*(Suppl 1), 61-66. https://doi.org/10.1007/s00508-019-1457-x (Lebensstil: körperliche Aktivität und Training in der Prävention und Therapie des Typ 2 Diabetes mellitus (Update 2019).)

Franchini, M., & Mannucci, P. M. (2008). Venous and arterial thrombosis: different sides of the same coin? *Eur J Intern Med*, *19*(7), 476-481. https://doi.org/10.1016/j.ejim.2007.10.019

Fylkesnes, K., & Forde, O. H. (1991). The Tromso Study: predictors of self-evaluated health--has society adopted the expanded health concept? *Soc Sci Med*, *32*(2), 141-146.

Füzéki, E., Engeroff, T., & Banzer, W. (2017). Health Benefits of Light-Intensity Physical Activity: A Systematic Review of Accelerometer Data of the National Health and Nutrition Examination Survey (NHANES). *Sports Med*, *47*(9), 1769-1793. https://doi.org/10.1007/s40279-017-0724-0

Gerovasili, V., Agaku, I. T., Vardavas, C. I., & Filippidis, F. T. (2015). Levels of physical activity among adults 18-64 years old in 28 European countries. *Prev Med*, *81*, 87-91. https://doi.org/10.1016/j.ypmed.2015.08.005

Gluck, T. M., & Maercker, A. (2011). A randomized controlled pilot study of a brief web-based mindfulness training. *BMC Psychiatry*, *11*, 175. https://doi.org/10.1186/1471-244x-11-175

Glynn, R. J., & Rosner, B. (2005). Comparison of risk factors for the competing risks of coronary heart disease, stroke, and venous thromboembolism. *Am J Epidemiol*, *162*(10), 975-982. https://doi.org/10.1093/aje/kwi309

Goldberg, A. D., Allis, C. D., & Bernstein, E. (2007). Epigenetics: a landscape takes shape. *Cell*, *128*(4), 635-638. https://doi.org/10.1016/j.cell.2007.02.006

Goldhaber SZ. Venous thromboembolism: epidemiology and magnitude of the problem. Best Pract Res Clin Haematol. 2012 Sep;25(3):235-42. doi: 10.1016/j.beha.2012.06.007. Epub 2012 Aug 9. PMID: 22959540

Goodpaster, B. H., DeLany, J. P., Otto, A. D., Kuller, L., Vockley, J., South-Paul, J. E., Thomas, S. B., Brown, J., McTigue, K., Hames, K. C., Lang, W., & Jakicic, J. M. (2010). Effects of Diet and Physical Activity Interventions on Weight Loss and Cardiometabolic Risk Factors in Severely Obese Adults A Randomized Trial. *Jama-Journal of the American Medical Association*, *304*(16), 1795-1802. https://doi.org/DOI 10.1001/jama.2010.1505

Graneheim, U. H., & Lundman, B. (2004). Qualitative content analysis in nursing research: concepts, procedures, and measures to achieve trustworthiness. *Nurse Educ Today*, *24*(2), 105-112. https://doi.org/10.1016/j.nedt.2003.10.001

Gregson, J., Kaptoge, S., Bolton, T., Pennells, L., Willeit, P., Burgess, S., Bell, S., Sweeting, M., Rimm, E. B., Kabrhel, C., Zöller, B., Assmann, G., Gudnason, V., Folsom, A. R., Arndt, V., Fletcher, A., Norman, P. E., Nordestgaard, B. G., Kitamura, A., Mahmoodi, B. K., …Meade, T. (2019). Cardiovascular Risk Factors Associated With Venous Thromboembolism. *JAMA Cardiol*, *4*(2), 163-173. https://doi.org/10.1001/jamacardio.2018.4537

Hallgrímsson, B., & Hall, B. k. (2011). Epigenetics : Linking Genotype and Phenotype in Development and Evolution. University of California Press

Hammar, M., & Ostgren, C. J. (2013). Healthy aging and age-adjusted nutrition and physical fitness. Best Pract Res Clin Obstet Gynaecol, 27(5), 741-752. https://doi.org/10.1016/j.bpobgyn.2013.01.004

Han, M. A., Kim, K. S., Park, J., Kang, M. G., & Ryu, S. Y. (2009). Association between levels of physical activity and poor self-rated health in Korean adults: The Third Korea National Health and Nutrition Examination Survey (KNHANES), 2005. *Public Health*, *123*(10), 665-669. https://doi.org/10.1016/j.puhe.2009.08.005

Hansen-Krone, I. J., Enga, K. F., Südduth-Klinger, J. M., Mathiesen, E. B., Njølstad, I., Wilsgaard, T., Watkins, S., Brækkan, S. K., & Hansen, J. B. (2014). High fish plus fish oil intake is associated with slightly reduced risk of venous thromboembolism: the Tromsø Study. *J Nutr*, *144*(6), 861-867. https://doi.org/10.3945/jn.113.189548

Hartescu, I., Morgan, K., & Stevinson, C. D. (2015). Increased physical activity improves sleep and mood outcomes in inactive people with insomnia: a randomized controlled trial. *J Sleep Res*, *24*(5), 526-534. https://doi.org/10.1111/jsr.12297

Helgadottir, B., Forsell, Y., & Ekblom, O. (2015). Physical activity patterns of people affected by depressive and anxiety disorders as measured by accelerometers: a cross-sectional study. *PLoS One*, *10*(1), e0115894. https://doi.org/10.1371/journal.pone.0115894

Hill, A. B. (2015). The environment and disease: association or causation? *Journal of the Royal Society of Medicine*, *108*(1), 32-37. https://doi.org/10.1177/0141076814562718

Hinderliter, A. L., Sherwood, A., Craighead, L. W., Lin, P. H., Watkins, L., Babyak, M. A., & Blumenthal, J. A. (2014). The long-term effects of lifestyle change on blood pressure: One-year follow-up of the ENCORE study. *Am J Hypertens*, *27*(5), 734-741. https://doi.org/10.1093/ajh/hpt183

Hindson, C. M., Chevillet, J. R., Briggs, H. A., Gallichotte, E. N., Ruf, I. K., Hindson, B. J., Vessella, R. L., & Tewari, M. (2013). Absolute quantification by droplet digital PCR versus analog real-time PCR. *Nat Methods*, *10*(10), 1003-1005. https://doi.org/10.1038/nmeth.2633

Holm Ivarsson, B. (2013). *MI - motiverande samtal: praktisk handbok för hälso- och sjukvården: tobaksbruk, riskbruk av alkohol, otillräcklig fysisk aktivitet, ohälsosamma matvanor* (2., [omarb.] uppl. ed.) [Non-fiction]. Gothia.

Huang, C. H., Su, S. L., Hsieh, M. C., Cheng, W. L., Chang, C. C., Wu, H. L., Kuo, C. L., Lin, T. T., & Liu, C. S. (2011). Depleted leukocyte mitochondrial DNA copy

number in metabolic syndrome. *J Atheroscler Thromb*, *18*(10), 867-873. https://doi.org/10.5551/jat.8698

Hälso- och sjukvårdslag (SFS 2017:30). Socialdepartementet. https://www.riksdagen.se/sv/dokument-lagar/dokument/svensk-forfattningssamling/halso--och-sjukvardslag_sfs-2017-30

Hörnsten, Å., Lindahl, K., Persson, K., & Edvardsson, K. (2014). Strategies in health-promoting dialogues: primary healthcare nurses' perspectives: a qualitative study [Artikel]. *Scandinavian Journal of Caring Sciences*, *28*(2), 235-244. https://doi.org/10.1111/scs.12045

Idler, E. L., & Benyamini, Y. (1997). Self-rated health and mortality: a review of twenty-seven community studies. *J Health Soc Behav*, *38*(1), 21-37.

Isaranuwatchai, W., Teerawattananon, Y., Archer, R. A., Luz, A., Sharma, M., Rattanavipapong, W., Anothaisintawee, T., Bacon, R. L., Bhatia, T., Bump, J., Chalkidou, K., Elshaug, A. G., Kim, D. D., Reddiar, S. K., Nakamura, R., Neumann, P. J., Shichijo, A., Smith, P. C., & Culyer, A. J. (2020). Prevention of non-communicable disease: best buys, wasted buys, and contestable buys. *BMJ*, *368*, m141. https://doi.org/10.1136/bmj.m141

Jarle, B., Øyvind, S., Jens, K. H., Espen, G., Milada Cvancarova, S., & Jøran, H. (2019). Associations between cardiorespiratory fitness and weight loss in patients with severe obesity undergoing an intensive lifestyle intervention program: retrospective cohort study [article]. *BMC Endocrine Disorders*, *19*(1), 1-9. https://doi.org/10.1186/s12902-019-0394-z

Jepsen, R., Dogisso, T. W., Dysvik, E., Andersen, J. R., & Natvig, G. K. (2014). A cross-sectional study of self-reported general health, lifestyle factors, and disease: the Hordaland Health Study. *PeerJ*, *2*, e609. https://doi.org/10.7717/peerj.609

Jerdén, L., Dalton, J., Johansson, H., Sorensen, J., Jenkins, P., & Weinehall, L. (2018). Lifestyle counseling in primary care in the United States and Sweden: a comparison of patients' expectations and experiences. *Glob Health Action*, *11*(1), 1438238. https://doi.org/10.1080/16549716.2018.1438238

Johansson, M. A. K., Östgren, C. J., Engvall, J., Swahn, E., Wijkman, M., & Nystrom, F. H. (2021). Relationships between cardiovascular risk factors and white-coat hypertension diagnosed by home blood pressure recordings in a middle-aged population. J Hypertens. https://doi.org/10.1097/hjh.0000000000002888

Johansson, M., Johansson, L., Wennberg, P., & Lind, M. (2019). Physical activity and risk of first-time venous thromboembolism. *Eur J Prev Cardiol*, *26*(11), 1181-1187. https://doi.org/10.1177/2047487319829310

Johansson, S. E., Midlov, P., Sundquist, J., Sundquist, K., & Calling, S. (2015). Longitudinal trends in good self-rated health: effects of age and birth cohort in a 25-year follow-up study in Sweden. *Int J Public Health*, *60*(3), 363-373. https://doi.org/10.1007/s00038-015-0658-y

Juul, S., & Frydenberg, M. (2014). *An introduction to Stata for health researchers*.

Jylha, M. (2009). What is self-rated health and why does it predict mortality? Towards a unified conceptual model. *Social Science & Medicine*, *69*(3), 307-316. https://doi.org/DOI 10.1016/j.socscimed.2009.05.013

Kabat-Zinn, J. (1994). *Wherever you go, there you are : mindfulness meditation for everyday life*. Piatkus.

Kabat-Zinn, J. (2003). Mindfulness-Based Interventions in Context: Past, Present, and Future [https://doi.org/10.1093/clipsy.bpg016]. Clinical Psychology: Science and Practice, 10(2), 144-156. https://doi.org/https://doi.org/10.1093/clipsy.bpg016

Kabat-Zinn, J. (2013). *Full catastrophe living : using the wisdom of your body and mind to face stress, pain, and illness* (Rev. and updated edition, Bantam Books trade paperback edition. ed.). Bantam Books.

Kallings, L., V. (2011). *FaR® : individanpassad skriftlig ordination av fysisk aktivitet*.

Kang, Y., O'Donnell, M. B., Strecher, V. J., & Falk, E. B. (2017). Dispositional Mindfulness Predicts Adaptive Affective Responses to Health Messages and Increased Exercise Motivation. *Mindfulness (N Y)*, *8*(2), 387-397. https://doi.org/10.1007/s12671-016-0608-7

Kelley, G. A., & Kelley, K. S. (2017). Exercise and sleep: a systematic review of previous meta-analyses. *J Evid Based Med*, *10*(1), 26-36. https://doi.org/10.1111/jebm.12236

Kerr, J., Sallis, J. F., Saelens, B. E., Cain, K. L., Conway, T. L., Frank, L. D., & King, A. C. (2012). Outdoor physical activity and self rated health in older adults living in two regions of the U.S. *Int J Behav Nutr Phys Act*, *9*, 89. https://doi.org/10.1186/1479-5868-9-89

King, A. C., Haskell, W. L., Taylor, C. B., Kraemer, H. C., & DeBusk, R. F. (1991). Group-vs home-based exercise training in healthy older men and women. A community-based clinical trial. *Jama*, *266*(11), 1535-1542.

Kirkwood, B. R., & Sterne, J. A. C. (2003). *Essential medical statistics* (2. ed. ed.) [Bibliographies Non-fiction]. Blackwell Science.

Knowler, W. C., Barrett-Connor, E., Fowler, S. E., Hamman, R. F., Lachin, J. M., Walker, E. A., Nathan, D. M., & Diabetes Prevention Program Research, G. (2002). Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med*, *346*(6), 393-403. https://doi.org/10.1056/NEJMoa012512

Krueger, R. A., & Casey, M. A. (2009). *Focus groups : a practical guide for applied research* (4. [updated] ed. ed.) [Non-fiction]. Sage Publications.

Kruk, J. (2007). Physical activity in the prevention of the most frequent chronic diseases: an analysis of the recent evidence. *Asian Pac J Cancer Prev*, *8*(3), 325-338.

Kubota, Y., Cushman, M., Zakai, N., Rosamond, W. D., & Folsom, A. R. (2018). TV viewing and incident venous thromboembolism: the Atherosclerotic Risk in Communities Study. *Journal of thrombosis and thrombolysis*, *45*(3), 353-359. https://doi.org/10.1007/s11239-018-1620-7

Kunutsor, S. K., Mäkikallio, T. H., Seidu, S., de Araújo, C. G. S., Dey, R. S., Blom, A. W., & Laukkanen, J. A. (2020). Physical activity and risk of venous thromboembolism: systematic review and meta-analysis of prospective cohort studies. *Eur J Epidemiol*, *35*(5), 431-442. https://doi.org/10.1007/s10654-019-00579-2

Kvale, S., & Brinkmann, S. (2009). *InterViews : learning the craft of qualitative research interviewing* (2. ed. ed.) [Non-fiction]. Sage Publications.

Kärner, A., Tingström, P., Abrandt-Dahlgren, M., & Bergdahl, B. (2005). Incentives for lifestyle changes in patients with coronary heart disease. *J Adv Nurs*, *51*(3), 261-275. https://doi.org/10.1111/j.1365-2648.2005.03467.x

Lahart, I., Darcy, P., Gidlow, C., & Calogiuri, G. (2019). The Effects of Green Exercise on Physical and Mental Wellbeing: A Systematic Review. *Int J Environ Res Public Health*, *16*(8). https://doi.org/10.3390/ijerph16081352

Lambe, B., & Collins, C. (2010). A qualitative study of lifestyle counselling in general practice in Ireland. *Family Practice*, *27*(2), 219-223. https://doi.org/10.1093/fampra/cmp086

Leão, T. S., Sundquist, J., Johansson, S. E., & Sundquist, K. (2009). The influence of age at migration and length of residence on self-rated health among Swedish immigrants: a cross-sectional study. Ethn Health, 14(1), 93-105. https://doi.org/10.1080/13557850802345973

Lee, I. M., Shiroma, E. J., Lobelo, F., Puska, P., Blair, S. N., & Katzmarzyk, P. T. (2012). Effect of physical inactivity on major non-communicable diseases worldwide: an analysis of burden of disease and life expectancy. *Lancet*, *380*(9838), 219-229. https://doi.org/10.1016/s0140-6736(12)61031-9

Lee, J.-Y., Lee, D.-C., Im, J.-A., & Lee, J.-W. (2014). Mitochondrial DNA Copy Number in Peripheral Blood Is Independently Associated with Visceral Fat Accumulation in Healthy Young Adults. *International Journal of Endocrinology*, *2014*, 586017. https://doi.org/10.1155/2014/586017

Lee, W., Reeve, J., Xue, Y., & Xiong, J. (2012). Neural differences between intrinsic reasons for doing versus extrinsic reasons for doing: An fMRI study. *Neuroscience Research*, *73*(1), 68-72. https://doi.org/https://doi.org/10.1016/j.neures.2012.02.010

Leijon, M. E., Bendtsen, P., Nilsen, P., Ekberg, K., & Stahle, A. (2008). Physical activity referrals in Swedish primary health care - prescriber and patient characteristics, reasons for prescriptions, and prescribed activities. *BMC Health Serv Res*, *8*, 201. https://doi.org/10.1186/1472-6963-8-201

Leijon, M. E., Bendtsen, P., Nilsen, P., Festin, K., & Stahle, A. (2009). Does a physical activity referral scheme improve the physical activity among routine primary health care patients? *Scand J Med Sci Sports*, *19*(5), 627-636. https://doi.org/10.1111/j.1600-0838.2008.00820.x

Leon, A. C., Davis, L. L., & Kraemer, H. C. (2011). The role and interpretation of pilot studies in clinical research. *J Psychiatr Res*, *45*(5), 626-629. https://doi.org/10.1016/j.jpsychires.2010.10.008

Lijfering, W. M., Flinterman, L. E., Vandenbroucke, J. P., Rosendaal, F. R., & Cannegieter, S. C. (2011). Relationship between venous and arterial thrombosis: a review of the literature from a causal perspective. *Semin Thromb Hemost*, *37*(8), 885-896. https://doi.org/10.1055/s-0031-1297367

Lilja, J. L., Frodi-Lundgren, A., Hanse, J. J., Josefsson, T., Lundh, L. G., Skold, C., Hansen, E., & Broberg, A. G. (2011). Five Facets Mindfulness Questionnaire--reliability and factor structure: a Swedish version. *Cogn Behav Ther*, *40*(4), 291-303. https://doi.org/10.1080/16506073.2011.580367

Lindström, J., Louheranta, A., Mannelin, M., Rastas, M., Salminen, V., Eriksson, J., Uusitupa, M., & Tuomilehto, J. (2003). The Finnish Diabetes Prevention Study (DPS). *Diabetes Care*, *26*(12), 3230. https://doi.org/10.2337/diacare.26.12.3230

Lingfors, H., Lindstrom, K., Persson, L. G., Bengtsson, C., & Lissner, L. (2003). Lifestyle changes after a health dialogue. Results from the Live for Life health promotion programme. *Scand J Prim Health Care*, *21*(4), 248-252.

Lingfors, H., & Persson, L.-G. (2019). All-cause mortality among young men 24-26 years after a lifestyle health dialogue in a Swedish primary care setting: a longitudinal follow-up register study [Artikel]. *BMJ Open*, *9*(1). https://doi.org/10.1136/bmjopen-2018-022474

Lingfors, H., Persson, L. G., Lindstrom, K., Bengtsson, C., & Lissner, L. (2009). Effects of a global health and risk assessment tool for prevention of ischemic heart disease in an individual health dialogue compared with a community health strategy only Results from the Live for Life health promotion programme. *Preventive Medicine*, *48*(1), 20-24. https://doi.org/DOI 10.1016/j.ypmed.2008.10.009

Lippi, G., Mattiuzzi, C., & Franchini, M. (2015). Sleep apnea and venous thromboembolism. A systematic review. *Thromb Haemost*, *114*(5), 958-963. https://doi.org/10.1160/TH15-03-0188

Loucks, E. B., Britton, W. B., Howe, C. J., Eaton, C. B., & Buka, S. L. (2015). Positive Associations of Dispositional Mindfulness with Cardiovascular Health: the New England Family Study. *Int J Behav Med*, *22*(4), 540-550. https://doi.org/10.1007/s12529-014-9448-9

Loucks, E. B., Schuman-Olivier, Z., Britton, W. B., Fresco, D. M., Desbordes, G., Brewer, J. A., & Fulwiler, C. (2015). Mindfulness and Cardiovascular Disease Risk: State of the Evidence, Plausible Mechanisms, and Theoretical Framework. *Curr Cardiol Rep*, *17*(12), 112. https://doi.org/10.1007/s11886-015-0668-7

Lowe, G. D. (2008). Common risk factors for both arterial and venous thrombosis. *Br J Haematol*, *140*(5), 488-495. https://doi.org/10.1111/j.1365-2141.2007.06973.x

Loyen, A., Van Hecke, L., Verloigne, M., Hendriksen, I., Lakerveld, J., Steene-Johannessen, J., Vuillemin, A., Koster, A., Donnelly, A., Ekelund, U., Deforche, B., De Bourdeaudhuij, I., Brug, J., van der Ploeg, H. P., & consortium, D. (2016). Variation in population levels of physical activity in European adults according to cross-European studies: a systematic literature review within DEDIPAC. *Int J Behav Nutr Phys Act*, *13*, 72. https://doi.org/10.1186/s12966-016-0398-2

Ludwig, D. S., & Kabat-Zinn, J. (2008). Mindfulness in medicine. *JAMA*, *300*(11), 1350-1352. https://doi.org/10.1001/jama.300.11.1350

Ludwig, V. U., Brown, K. W., & Brewer, J. A. (2020). Self-Regulation Without Force: Can Awareness Leverage Reward to Drive Behavior Change? *Perspect Psychol Sci*, *15*(6), 1382-1399. https://doi.org/10.1177/1745691620931460

Malm, C., Jakobsson, J., & Isaksson, A. (2019). Physical Activity and Sports-Real Health Benefits: A Review with Insight into the Public Health of Sweden. *Sports (Basel)*, *7*(5). https://doi.org/10.3390/sports7050127

Mammen, G., & Faulkner, G. (2013). Physical activity and the prevention of depression: a systematic review of prospective studies. *Am J Prev Med*, *45*(5), 649-657. https://doi.org/10.1016/j.amepre.2013.08.001

Matthews, C. E., Chen, K. Y., Freedson, P. S., Buchowski, M. S., Beech, B. M., Pate, R. R., & Troiano, R. P. (2008). Amount of time spent in sedentary behaviors in the United States, 2003-2004. *Am J Epidemiol*, *167*(7), 875-881. https://doi.org/10.1093/aje/kwm390

Mattila, R., Malmivaara, A., Kastarinen, M., Kivela, S. L., & Nissinen, A. (2003). Effectiveness of multidisciplinary lifestyle intervention for hypertension: a randomised controlled trial [Article]. *Journal of Human Hypertension*, *17*(3), 199. https://doi.org/10.1038/sj.jhh.1001531

Maximov, V. N., Malyutina, S. K., Orlov, P. S., Ivanoschuk, D. E., Mikhailova, S. V., Shapkina, M. Y., Hubacek, J., Holmes, M., Bobak, M., & Voevoda, M. I. (2019). [Mitochondrial DNA copy number of leucocytes as ageing marker and risk factors for age-related diseases in human.]. *Adv Gerontol*, *32*(3), 422-430.

McCoach, D. B., & Flake, J. K. (2018). The role of motivation. In S. I. Pfeiffer, E. Shaunessy-Dedrick, & M. Foley-Nicpon (Eds.), *APA handbook of giftedness and talent.* (pp. 201-213). American Psychological Association. https://doi.org/10.1037/0000038-013

McCullough, M. E., & Laurenceau, J.-P. (2004). Gender and the Natural History of Self-Rated Health: A 59-Year Longitudinal Study. *Health Psychology*, *23*(6), 651-655.

McDoniel, S. O., Wolskee, P., & Shen, J. (2010). Treating obesity with a novel hand-held device, computer software program, and Internet technology in primary care: the SMART motivational trial. *Patient Educ Couns*, *79*(2), 185-191. https://doi.org/10.1016/j.pec.2009.07.034

McDowell, C. P., Dishman, R. K., Gordon, B. R., & Herring, M. P. (2019). Physical Activity and Anxiety: A Systematic Review and Meta-analysis of Prospective Cohort Studies. *Am J Prev Med*, *57*(4), 545-556. https://doi.org/10.1016/j.amepre.2019.05.012

McNamara, C. L., Balaj, M., Thomson, K. H., Eikemo, T. A., Solheim, E. F., & Bambra, C. (2017). The socioeconomic distribution of non-communicable diseases in Europe: findings from the European Social Survey (2014) special module on the social determinants of health. *European Journal of Public Health*, *27*, 22-26. https://doi.org/10.1093/eurpub/ckw222

McTiernan, A., Friedenreich, C. M., Katzmarzyk, P. T., Powell, K. E., Macko, R., Buchner, D., Pescatello, L. S., Bloodgood, B., Tennant, B., Vaux-Bjerke, A., George, S. M., Troiano, R. P., Piercy, K. L., & COMMITTEE*, P. A. G. A. (2019). Physical Activity in Cancer Prevention and Survival: A Systematic Review. *Med Sci Sports Exerc*, *51*(6), 1252-1261. https://doi.org/10.1249/MSS.0000000000001937

Memon, A. A., Zöller, B., Hedelius, A., Wang, X., Stenman, E., Sundquist, J., & Sundquist, K. (2017). Quantification of mitochondrial DNA copy number in suspected cancer patients by a well optimized ddPCR method. *Biomol Detect Quantif*, *13*, 32-39. https://doi.org/10.1016/j.bdq.2017.08.001

Mengel-From, J., Thinggaard, M., Dalgård, C., Kyvik, K. O., Christensen, K., & Christiansen, L. (2014). Mitochondrial DNA copy number in peripheral blood cells declines with age and is associated with general health among elderly. *Hum Genet*, *133*(9), 1149-1159. https://doi.org/10.1007/s00439-014-1458-9

Mercken, E. M., Carboneau, B. A., Krzysik-Walker, S. M., & de Cabo, R. (2012). Of mice and men: the benefits of caloric restriction, exercise, and mimetics. *Ageing Res Rev*, *11*(3), 390-398. https://doi.org/10.1016/j.arr.2011.11.005

Meyer, J. D., Torres, E. R., Grabow, M. L., Zgierska, A. E., Teng, H. Y., Coe, C. L., & Barrett, B. P. (2018). Benefits of 8-wk Mindfulness-based Stress Reduction or Aerobic Training on Seasonal Declines in Physical Activity. *Med Sci Sports Exerc*, *50*(9), 1850-1858. https://doi.org/10.1249/MSS.0000000000001636

Miller, W. R., & Rollnick, S. (2013). *Motiverande samtal : att hjälpa människor till förändring* (3., rev. och utök. utg. [dvs 4 svenska utg.] ed.) [Non-fiction]. Natur & kultur.

Mohammed, W. A., Pappous, A., & Sharma, D. (2018). Effect of Mindfulness Based Stress Reduction (MBSR) in Increasing Pain Tolerance and Improving the Mental Health of Injured Athletes. *Front Psychol*, *9*, 722. https://doi.org/10.3389/fpsyg.2018.00722

Moren, C., Welmer, A. K., Hagstromer, M., Karlsson, E., & Sommerfeld, D. K. (2016). The Effects of "Physical Activity on Prescription" in Persons With Transient Ischemic Attack: A Randomized Controlled Study. *J Neurol Phys Ther*, *40*(3), 176-183. https://doi.org/10.1097/NPT.0000000000000134

Morgan, O. (2005). Approaches to increase physical activity: reviewing the evidence for exercise-referral schemes. *Public Health*, *119*(5), 361-370. https://doi.org/10.1016/j.puhe.2004.06.008

Mothes, H., Klaperski, S., Seelig, H., Schmidt, S., & Fuchs, R. (2014). Regular aerobic exercise increases dispositional mindfulness in men: A randomized controlled trial [Article]. *Mental Health and Physical Activity*, *7*, 111-119. https://doi.org/10.1016/j.mhpa.2014.02.003

Nass, M. M., & Nass, S. (1963). INTRAMITOCHONDRIAL FIBERS WITH DNA CHARACTERISTICS. I. FIXATION AND ELECTRON STAINING REACTIONS. *J Cell Biol*, *19*(3), 593-611. https://doi.org/10.1083/jcb.19.3.593

United Nations. (2015). *Transforming our World: The 2030 Agenda for Sustainable Development.* https://sustainabledevelopment.un.org/post2015/transformingourworld/publication

Nery Guimarães, J. M., Chor, D., Werneck, G. L., Carvalho, M. S., Coeli, C. M., Lopes, C. S., & Faerstein, E. (2012). Association between self-rated health and mortality: 10 years follow-up to the Pró-Saúdecohort study. *BMC Public Health*, *12*(1), 676. https://doi.org/10.1186/1471-2458-12-676

Noordman, J., Koopmans, B., Korevaar, J. C., van der Weijden, T., & van Dulmen, S. (2013). Exploring lifestyle counselling in routine primary care consultations: the professionals' role. *Fam Pract*, *30*(3), 332-340. https://doi.org/10.1093/fampra/cms077

Norberg, M., Wall, S., Boman, K., & Weinehall, L. (2010). The Västerbotten Intervention Programme: background, design, and implications. *Global Health Action*, *3*(1), 4643. https://doi.org/10.3402/gha.v3i0.4643

Nymberg, P., & Drevenhorn, E. (2016). Patients' experience of a nurse-led lifestyle clinic at a Swedish health centre. Scandinavian Journal of Caring Sciences, 30(2), 349-355. https://doi.org/10.1111/scs.12254

Nymberg, P., Ekvall Hansson, E., Stenman, E., Calling, S., Sundquist, K., Sundquist, J., & Zoller, B. (2018). Pilot study on increased adherence to physical activity on prescription (PAP) through mindfulness: study protocol. *Trials*, 19(1), 563. https://doi.org/10.1186/s13063-018-2932-9

Nymberg, P., Stenman, E., Calling, S., Sundquist, J., Sundquist, K., & Zöller, B. (2020). Self-rated health and venous thromboembolism among middle-aged women: a population-based cohort study. *J Thromb Thrombolysis*, 49(3), 344-351. https://doi.org/10.1007/s11239-019-01995-7

Nymberg[1], P., Calling,S., Stenman,E., Palmér,K., Ekvall Hansson,E., Sundquist,K., Sundquist,J., Zöller,B. (2021), Effect of mindfulness on physical activity in primary healthcare patients: a randomised controlled trial pilot study. Pilot and Feasibility Studies, 7(1), 70. https://doi.org/10.1186/s40814-021-00810-6

Nymberg[2], P., Memon,A.A., Sundquist,J., Sundquist,K., Zöller,B. (2021). Mitochondria-DNA copy-number and incident venous thromboembolism among middle-aged women: a population-based cohort study. J Thromb Thrombolysis. https://doi.org/10.1007/s11239-021-02446-y. April 15 Online ahead of print

O'Reilly, G. A., Cook, L., Spruijt-Metz, D., & Black, D. S. (2014). Mindfulness-based interventions for obesity-related eating behaviours: a literature review. *Obes Rev*, 15(6), 453-461. https://doi.org/10.1111/obr.12156

Olson, N. C., Cushman, M., Judd, S. E., McClure, L. A., Lakoski, S. G., Folsom, A. R., Safford, M. M., & Zakai, N. A. (2015). American Heart Association's Life's Simple 7 and risk of venous thromboembolism: the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study. *J Am Heart Assoc*, 4(3), e001494. https://doi.org/10.1161/jaha.114.001494

Onerup, A., Arvidsson, D., Blomqvist, A., Daxberg, E. L., Jivegard, L., Jonsdottir, I. H., Lundqvist, S., Mellen, A., Persson, J., Sjogren, P., Svanberg, T., & Borjesson, M. (2018). Physical activity on prescription in accordance with the Swedish model increases physical activity: a systematic review. *Br J Sports Med*. https://doi.org/10.1136/bjsports-2018-099598

Orrow, G., Kinmonth, A. L., Sanderson, S., & Sutton, S. (2012). Effectiveness of physical activity promotion based in primary care: systematic review and meta-analysis of randomised controlled trials. *BMJ*, 344, e1389. https://doi.org/10.1136/bmj.e1389

Pan, X. R., Li, G. W., Hu, Y. H., Wang, J. X., Yang, W. Y., An, Z. X., Hu, Z. X., Lin, J., Xiao, J. Z., Cao, H. B., Liu, P. A., Jiang, X. G., Jiang, Y. Y., Wang, J. P., Zheng, H., Zhang, H., Bennett, P. H., & Howard, B. V. (1997). Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance. The Da Qing IGT and Diabetes Study. *Diabetes Care*, 20(4), 537-544.

Parahoo, K. (2006). *Nursing research: principles, process, and issues* (2. ed. ed.) [Non-fiction]. Palgrave Macmillan.

Pasanen, T., Tolvanen, S., Heinonen, A., & Kujala, U. M. (2017). Exercise therapy for functional capacity in chronic diseases: an overview of meta-analyses of randomised controlled trials. *Br J Sports Med*, 51(20), 1459-1465. https://doi.org/10.1136/bjsports-2016-097132

Pate, R. R., Pratt, M., Blair, S. N., Haskell, W. L., Macera, C. A., Bouchard, C., Buchner, D., Ettinger, W., Heath, G. W., & King, A. C. (1995). Physical activity and public health. A recommendation from the Centers for Disease Control and Prevention and the American College of Sports Medicine. *JAMA*, *273*(5), 402-407. https://doi.org/10.1001/jama.273.5.402

Peluso, M. A., & Guerra de Andrade, L. H. (2005). Physical activity and mental health: the association between exercise and mood. *Clinics (Sao Paulo)*, *60*(1), 61-70. https://doi.org/10.1590/s1807-59322005000100012

Persson, M., & Friberg, F. (2009). The dramatic encounter: experiences of taking part in a health conversation. *J Clin Nurs*, *18*(4), 520-528. https://doi.org/10.1111/j.1365-2702.2008.02535.x

Pifferi, F., & Aujard, F. (2019). Caloric restriction, longevity, and aging: Recent contributions from human and non-human primate studies. *Prog Neuropsychopharmacol Biol Psychiatry*, *95*, 109702. https://doi.org/10.1016/j.pnpbp.2019.109702

Pioli, M. R., Ritter, A. M., de Faria, A. P., & Modolo, R. (2018). White coat syndrome and its variations: differences and clinical impact. *Integr Blood Press Control*, *11*, 73-79. https://doi.org/10.2147/ibpc.s152761

Plasqui, G., & Westerterp, K. R. (2007). Physical activity assessment with accelerometers: an evaluation against doubly labeled water. *Obesity (Silver Spring)*, *15*(10), 2371-2379. https://doi.org/10.1038/oby.2007.281

Pocock, S. J., & Simon, R. (1975). Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. *Biometrics*, *31*(1), 103-115.

Pontzer, H., Durazo-Arvizu, R., Dugas, L. R., Plange-Rhule, J., Bovet, P., Forrester, T. E., Lambert, E. V., Cooper, R. S., Schoeller, D. A., & Luke, A. (2016). Constrained Total Energy Expenditure and Metabolic Adaptation to Physical Activity in Adult Humans. *Curr Biol*, *26*(3), 410-417. https://doi.org/10.1016/j.cub.2015.12.046

Poskiparta, M., Kasila, K., & Kiuru, P. (2006). Dietary and physical activity counselling on Type 2 diabetes and impaired glucose tolerance by physicians and nurses in primary healthcare in Finland. *Scandinavian Journal of Primary Health Care*, *24*(4), 206-210. https://doi.org/Doi 10.1080/02813430600866463

Powell, K. E., Paluch, A. E., & Blair, S. N. (2011). Physical activity for health: What kind? How much? How intense? On top of what? *Annu Rev Public Health*, *32*, 349-365. https://doi.org/10.1146/annurev-publhealth-031210-101151

Prandoni, P. (2017). Venous and Arterial Thrombosis: Is There a Link? *Adv Exp Med Biol*, *906*, 273-283. https://doi.org/10.1007/5584_2016_121

Prince, S. A., Adamo, K. B., Hamel, M. E., Hardt, J., Connor Gorber, S., & Tremblay, M. (2008). A comparison of direct versus self-report measures for assessing physical activity in adults: a systematic review. *Int J Behav Nutr Phys Act*, *5*, 56. https://doi.org/10.1186/1479-5868-5-56

Public health agency of Sweden (2020)-National health survey. (Folkhälsomyndigheten. (2020). Nationella folkhälsoenkäten - Hälsa på lika villkor.)

Rose, G. (2001). Sick individuals and sick populations. *Int J Epidemiol*, *30*(3), 427-432; discussion 433-424. https://doi.org/10.1093/ije/30.3.427

Roshanaei-Moghaddam, B., Katon, W. J., & Russo, J. (2009). The longitudinal effects of depression on physical activity. *Gen Hosp Psychiatry*, *31*(4), 306-315. https://doi.org/10.1016/j.genhosppsych.2009.04.002

Roșescu, R., Martin-Hadmaș, R. M., & Tarcea, M. (2020). Is there a link between physical activity, body mass index, Finnish Diabetes Risk Score (FINDRISC) and blood pressure? [Article]. *Palestrica of the Third Millennium Civilization & Sport*, *21*(3), 174-178. https://doi.org/10.26659/pm3.2020.21.3.174

Ruffault, A., Bernier, M., Juge, N., & Fournier, J. F. (2016). Mindfulness May Moderate the Relationship Between Intrinsic Motivation and Physical Activity: A Cross-Sectional Study [journal article]. *Mindfulness*, *7*(2), 445-452. https://doi.org/10.1007/s12671-015-0467-7

Rusch, H. L., Rosario, M., Levison, L. M., Olivera, A., Livingston, W. S., Wu, T., & Gill, J. M. (2019). The effect of mindfulness meditation on sleep quality: a systematic review and meta-analysis of randomized controlled trials. *Ann N Y Acad Sci*, *1445*(1), 5-16. https://doi.org/10.1111/nyas.13996

Ryan, R. M., & Deci, E. L. (2000). Self-Determination Theory and the Facilitation of Intrinsic Motivation, Social Development, and Well-Being [Article]. *American Psychologist*, *55*(1), 68. https://doi.org/10.1037/0003-066X.55.1.68

Sahin, C., Courtney, K. L., Naylor, P. J., & E Rhodes, R. (2019). Tailored mobile text messaging interventions targeting type 2 diabetes self-management: A systematic review and a meta-analysis. *Digital health*, *5*, 2055207619845279-2055207619845279. https://doi.org/10.1177/2055207619845279

Sakane, N., Sato, J., Tsushita, K., Tsujii, S., Kotani, K., Tominaga, M., Kawazu, S., Sato, Y., Usui, T., Kamae, I., Yoshida, T., Kiyohara, Y., Sato, S., Tsuzaki, K., Takahashi, K., Kuzuya, H., & Group, J. D. P. P. J. R. (2014). Effect of baseline HbA1c level on the development of diabetes by lifestyle intervention in primary healthcare settings: insights from subanalysis of the Japan Diabetes Prevention Program. *BMJ Open Diabetes Res Care*, *2*(1), e000003. https://doi.org/10.1136/bmjdrc-2013-000003

Samsioe, G., Lidfeldt, J., Nerbrand, C., & Nilsson, P. (2010). The women's health in the Lund area (WHILA) study--an overview. *Maturitas*, *65*(1), 37-45. https://doi.org/10.1016/j.maturitas.2009.11.009

Sand, O., Bjålie, J. G., Sjaastad, Ø. V., & Haug, E. (2007). *Människokroppen: fysiologi och anatomi* (2. upplagan [översättning: Inger Bolinder-Palmér ...] ed.) [Non-fiction]. Liber.

Sargent-Cox, K., Cherbuin, N., Morris, L., Butterworth, P., & Anstey, K. J. (2014). The effect of health behavior change on self-rated health across the adult life course: a longitudinal cohort study. *Prev Med*, *58*, 75-80. https://doi.org/10.1016/j.ypmed.2013.10.017

Sargent-Cox, K. A., Anstey, K. J., & Luszcz, M. A. (2010). Patterns of longitudinal change in older adults' self-rated health: the effect of the point of reference. *Health Psychol*, *29*(2), 143-152. https://doi.org/10.1037/a0017652

Scheffler, I. E. (2008). *Mitochondria*. Wiley-Liss.

Schneider, J., Malinowski, P., Watson, P. M., & Lattimore, P. (2019). The role of mindfulness in physical activity: a systematic review. *Obes Rev*, *20*(3), 448-463. https://doi.org/10.1111/obr.12795

Schoeller, D. A., Taylor, P. B., & Shay, K. (1995). Analytic requirements for the doubly labeled water method. *Obes Res*, *3 Suppl 1*, 15-20. https://doi.org/10.1002/j.1550-8528.1995.tb00003.x

Schuch, F., Vancampfort, D., Firth, J., Rosenbaum, S., Ward, P., Reichert, T., Bagatini, N. C., Bgeginski, R., & Stubbs, B. (2017). Physical activity and sedentary behavior in people with major depressive disorder: A systematic review and meta-analysis. *J Affect Disord*, *210*, 139-150. https://doi.org/10.1016/j.jad.2016.10.050

Sharma, P., & Sampath, H. (2019). Mitochondrial DNA Integrity: Role in Health and Disease. *Cells*, *8*(2). https://doi.org/10.3390/cells8020100

Sharma, N., Pasala, M. S., & Prakash, A. (2019). Mitochondrial DNA: Epigenetics and environment. *Environ Mol Mutagen*, *60*(8), 668-682. https://doi.org/10.1002/em.22319

Schuch, F. B., Vancampfort, D., Firth, J., Rosenbaum, S., Ward, P. B., Silva, E. S., Hallgren, M., Ponce De Leon, A., Dunn, A. L., Deslandes, A. C., Fleck, M. P., Carvalho, A. F., & Stubbs, B. (2018). Physical Activity and Incident Depression: A Meta-Analysis of Prospective Cohort Studies. *Am J Psychiatry*, *175*(7), 631-648. https://doi.org/10.1176/appi.ajp.2018.17111194

Smiley, A., Ramos, W., Elliott, L., & Wolter, S. (2020). Comparing the Trail Users with Trail Non-Users on Physical Activity, Sleep, Mood and Well-Being Index. *International journal of environmental research and public health*, *17*(17), 6225. https://doi.org/10.3390/ijerph17176225

Sodergren, M., Sundquist, J., Johansson, S. E., & Sundquist, K. (2008). Physical activity, exercise, and self-rated health: a population-based study from Sweden. *BMC Public Health*, *8*, 352. https://doi.org/10.1186/1471-2458-8-352

Sojcher, R., Gould Fogerite, S., & Perlman, A. (2012). Evidence and potential mechanisms for mindfulness practices and energy psychology for obesity and binge-eating disorder. *Explore (NY)*, *8*(5), 271-276. https://doi.org/10.1016/j.explore.2012.06.003

Somers, V. K., White, D. P., Amin, R., Abraham, W. T., Costa, F., Culebras, A., Daniels, S., Floras, J. S., Hunt, C. E., Olson, L. J., Pickering, T. G., Russell, R., Woo, M., Young, T., American Heart Association Council for High Blood Pressure Research Professional Education Committee, C. o. C. C., American Heart Association Stroke, C., American Heart Association Council on Cardiovascular, N., & American College of Cardiology, F. (2008). Sleep apnea and cardiovascular disease: an American Heart Association/american College Of Cardiology Foundation Scientific Statement from the American Heart Association Council for High Blood Pressure Research Professional Education Committee, Council on Clinical Cardiology, Stroke Council, and Council On Cardiovascular Nursing. In collaboration with the National Heart, Lung, and Blood Institute National Center on Sleep Disorders Research (National Institutes of Health). *Circulation*, *118*(10), 1080-1111. https://doi.org/10.1161/CIRCULATIONAHA.107.189375

Steffen, L. M., Folsom, A. R., Cushman, M., Jacobs, D. R., & Rosamond, W. D. (2007). Greater fish, fruit, and vegetable intakes are related to lower incidence of venous thromboembolism: the Longitudinal Investigation of Thromboembolism Etiology. *Circulation*, *115*(2), 188-195. https://doi.org/10.1161/CIRCULATIONAHA.106.641688

Sundquist, J., & Johansson, S. E. (1997). Self-reported poor health and low educational level predictors for mortality: a population based follow up study of 39,156 people in Sweden. *Journal of epidemiology and community health*, *51*(1), 35-40. https://doi.org/10.1136/jech.51.1.35

Sundquist, J., Lilja, A., Palmer, K., Memon, A. A., Wang, X., Johansson, L. M., & Sundquist, K. (2015). Mindfulness group therapy in primary care patients with depression, anxiety and stress and adjustment disorders: randomised controlled trial. *Br J Psychiatry*, *206*(2), 128-135. https://doi.org/10.1192/bjp.bp.114.150243

Sundquist, J., Palmér, K., Memon, A. A., Wang, X., Johansson, L. M., & Sundquist, K. (2019). Long-term improvements after mindfulness-based group therapy of depression, anxiety and stress and adjustment disorders: A randomized controlled trial. *Early Interv Psychiatry*, *13*(4), 943-952. https://doi.org/10.1111/eip.12715

Svetkey, L. P., Pollak, K. I., Yancy, W. S., Jr., Dolor, R. J., Batch, B. C., Samsa, G., Matchar, D. B., & Lin, P. H. (2009). Hypertension improvement project: randomized trial of quality improvement for physicians and lifestyle modification for patients. *Hypertension*, *54*(6), 1226-1233.https://doi.org/10.1161/HYPERTENSIONAHA.109.134874

Sundquist K, Eriksson U, Kawakami N, Skog L, Ohlsson H, Arvidsson D. (2011). Neighborhood walkability, physical activity, and walking behavior: the Swedish Neighborhood and Physical Activity (SNAP) study. Soc Sci Med. 72(8):1266-73. doi: 10.1016/j.socscimed.2011.03.004. Epub 2011 Mar 21

Swedish National Institute of Public Health (Folkhälsoinstitutet) (2010). *Physical activity in the prevention and treatment of disease (swedish title: fyss, fysisk aktivitet i sjukdomsprevention och sjukdomsbehandling)*. [Book]. Stockholm: 2010

Södergren, M., Sundquist, J., Johansson, S.-E., & Sundquist, K. (2008). Physical activity, exercise, and self-rated health: a population-based study from Sweden. *BMC Public Health*, *8*, 352-352. https://doi.org/10.1186/1471-2458-8-352

Takahashi, P. Y., Jenkins, G. D., Welkie, B. P., McDonnell, S. K., Evans, J. M., Cerhan, J. R., Olson, J. E., Thibodeau, S. N., Cicek, M. S., & Ryu, E. (2018). Association of mitochondrial DNA copy number with self-rated health status. *Appl Clin Genet*, *11*, 121-127. https://doi.org/10.2147/TACG.S167640

Tranquillo, J., & Stecker, M. (2016). Using intrinsic and extrinsic motivation in continuing professional education. *Surgical neurology international*, *7*(Suppl 7), S197-S199. https://doi.org/10.4103/2152-7806.179231

Troiano, R. P., Berrigan, D., Dodd, K. W., Masse, L. C., Tilert, T., & McDowell, M. (2008). Physical activity in the United States measured by accelerometer. *Med Sci Sports Exerc*, *40*(1), 181-188. https://doi.org/10.1249/mss.0b013e31815a51b3

Tsafou, K.-E., Lacroix, J. P., van Ee, R., Vinkers, C. D., & De Ridder, D. T. (2016). The relation of trait and state mindfulness with satisfaction and physical activity: A cross-sectional study in 305 Dutch participants. *Journal Of Health Psychology*.

Tsafou, K. E., De Ridder, D. T., van Ee, R., & Lacroix, J. P. (2016). Mindfulness and satisfaction in physical activity: A cross-sectional study in the Dutch population. *J Health Psychol*, *21*(9), 1817-1827. https://doi.org/10.1177/1359105314567207

Tuomilehto, J., Lindstrom, J., Eriksson, J. G., Valle, T. T., Hamalainen, H., Ilanne-Parikka, P., Keinanen-Kiukaanniemi, S., Laakso, M., Louheranta, A., Rastas, M., Salminen, V., Uusitupa, M., & Finnish Diabetes Prevention Study, G. (2001). Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med*, *344*(18), 1343-1350. https://doi.org/10.1056/NEJM200105033441801

Ulmer, C. S., Stetson, B. A., & Salmon, P. G. (2010). Mindfulness and acceptance are associated with exercise maintenance in YMCA exercisers. *Behav Res Ther*, *48*(8), 805-809. https://doi.org/10.1016/j.brat.2010.04.009

van der Linde, R. M., Mavaddat, N., Luben, R., Brayne, C., Simmons, R. K., Khaw, K. T., & Kinmonth, A. L. (2013). Self-rated health and cardiovascular disease incidence: results from a longitudinal population-based cohort in Norfolk, UK. *PLoS One*, *8*(6), e65290. https://doi.org/10.1371/journal.pone.0065290

van Stralen, K. J., Doggen, C. J., Lumley, T., Cushman, M., Folsom, A. R., Psaty, B. M., Siscovick, D., Rosendaal, F. R., & Heckbert, S. R. (2008). The relationship between exercise and risk of venous thrombosis in elderly people. *J Am Geriatr Soc*, *56*(3), 517-522. https://doi.org/10.1111/j.1532-5415.2007.01588.x

Varraso, R., Kabrhel, C., Goldhaber, S. Z., Rimm, E. B., & Camargo, C. A. (2012). Prospective study of diet and venous thromboembolism in US women and men. *Am J Epidemiol*, *175*(2), 114-126. https://doi.org/10.1093/aje/kwr377

Veerman, J. L., Healy, G. N., Cobiac, L. J., Vos, T., Winkler, E. A., Owen, N., & Dunstan, D. W. (2012). Television viewing time and reduced life expectancy: a life table analysis. *Br J Sports Med*, *46*(13), 927-930. https://doi.org/10.1136/bjsports-2011-085662

von Wurmb-Schwark, N., Ringleb, A., Schwark, T., Broese, T., Weirich, S., Schlaefke, D., Wegener, R., & Oehmichen, M. (2008). The effect of chronic alcohol consumption on mitochondrial DNA mutagenesis in human blood. *Mutat Res*, *637*(1-2), 73-79. https://doi.org/10.1016/j.mrfmmm.2007.07.003

Vyas, C. M., Ogata, S., Reynolds, C. F., Mischoulon, D., Chang, G., Cook, N. R., Manson, J. E., Crous-Bou, M., De Vivo, I., & Okereke, O. I. (2020). Lifestyle and behavioral factors and mitochondrial DNA copy number in a diverse cohort of mid-life and older adults. *PLoS One*, *15*(8), e0237235. https://doi.org/10.1371/journal.pone.0237235

Waller, G., Janlert, U., Norberg, M., Lundqvist, R., & Forssen, A. (2015). Self-rated health and standard risk factors for myocardial infarction: a cohort study. *BMJ Open*, *5*(2), e006589. https://doi.org/10.1136/bmjopen-2014-006589

Walseth, L. T., Abildsnes, E., & Schei, E. (2011). Patients' experiences with lifestyle counselling in general practice: A qualitative study. *Scandinavian Journal of Primary Health Care*, *29*(2), 99-103. https://doi.org/10.3109/02813432.2011.553995

Warburton, D. E. R., & Bredin, S. S. D. (2017). Health benefits of physical activity: a systematic review of current systematic reviews. *Curr Opin Cardiol*, *32*(5), 541-556. https://doi.org/10.1097/hco.0000000000000437

Warburton, D. E. R., Nicol, C. W., & Bredin, S. S. D. (2006). Health benefits of physical activity: the evidence. *CMAJ: Canadian Medical Association journal = journal de l'Association medicale canadienne*, *174*(6), 801-809.

Wattanakit, K., Lutsey, P. L., Bell, E. J., Gornik, H., Cushman, M., Heckbert, S. R., Rosamond, W. D., & Folsom, A. R. (2012). Association between cardiovascular disease risk factors and occurrence of venous thromboembolism. A time-dependent analysis. *Thromb Haemost*, *108*(3), 508-515. https://doi.org/10.1160/th11-10-0726

Whittaker, R., McRobbie, H., Bullen, C., Rodgers, A., Gu, Y., & Dobson, R. (2019). Mobile phone text messaging and app-based interventions for smoking cessation. *The Cochrane database of systematic reviews*, *10*(10), CD006611-CD006611. https://doi.org/10.1002/14651858.CD006611.pub5

Wilbur, J., & Shian, B. (2012). Diagnosis of deep venous thrombosis and pulmonary embolism. *Am Fam Physician*, *86*(10), 913-919.

Williams, C. M., Nathan, N., & Wolfenden, L. (2014). Physical activity promotion in primary care has a sustained influence on activity levels of sedentary adults. *Br J Sports Med*, *48*(13), 1069-1070. https://doi.org/10.1136/bjsports-2013-093187

Wolinsky, F. D., Miller, T. R., Malmstrom, T. K., Miller, J. P., Schootman, M., Andresen, E. M., & Miller, D. K. (2008). Self-rated health: Changes, trajectories, and their antecedents among African Americans. *Journal of Aging and Health*, *20*(2), 143-158. https://doi.org/10.1177/0898264307310449

World Health Organization. (2009). *Mortality and burden of disease attributable to selected major risks* (978 92 4 156387 1). W. H. O. WHO Press, 20 Avenue Appia, 1211 Geneva 27, Switzerland. https://apps.who.int/iris/handle/10665/44203. Accessed 29 Oct. 2020

World Health Organization. (2011). W. press. http://www.who.int/dietphysicalactivity/publications/9789241599979/en/

World Health Organization. (2017). *'Best buys' and other recommended interventions for theprevention and control of noncommunicable diseases*. https://www.who.int/publications/i/item/WHO-NMH-NVI-17.9

World Health Organization. (2020). *WHO GUIDELINES ON PHYSICAL ACTIVITY AND SEDENTARY BEHAVIOUR*. World Health Organization, Geneva 2020. Licence: CC BY-NC-SA 3.0 IGO.

Yue, P., Jing, S., Liu, L., Ma, F., Zhang, Y., Wang, C., Duan, H., Zhou, K., Hua, Y., Wu, G., & Li, Y. (2018). Association between mitochondrial DNA copy number and cardiovascular disease: Current evidence based on a systematic review and meta-analysis. *PLoS One*, *13*(11), e0206003. https://doi.org/10.1371/journal.pone.0206003

Yusuf, S., Hawken, S., Ounpuu, S., Dans, T., Avezum, A., Lanas, F., McQueen, M., Budaj, A., Pais, P., Varigos, J., Lisheng, L., & Investigators, I. S. (2004). Effect of

potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet*, *364*(9438), 937-952. https://doi.org/10.1016/S0140-6736(04)17018-9

Zajacova, A., & Woo, H. (2016). Examination of Age Variations in the Predictive Validity of Self-Rated Health. *The Journals of Gerontology: Series B*, *71*(3), 551-557. https://doi.org/10.1093/geronb/gbv050

Zanesco, A., & Antunes, E. (2007). Effects of exercise training on the cardiovascular system: pharmacological approaches. *Pharmacol Ther*, *114*(3), 307-317. https://doi.org/10.1016/j.pharmthera.2007.03.010

Zeidan, F., Adler-Neal, A. L., Wells, R. E., Stagnaro, E., May, L. M., Eisenach, J. C., McHaffie, J. G., & Coghill, R. C. (2016). Mindfulness-Meditation-Based Pain Relief Is Not Mediated by Endogenous Opioids. *The Journal of Neuroscience*, *36*(11), 3391. https://doi.org/10.1523/JNEUROSCI.4328-15.2016

Zeidan, F., Baumgartner, J. N., & Coghill, R. C. (2019). The neural mechanisms of mindfulness-based pain relief: a functional magnetic resonance imaging-based review and primer. *Pain Rep*, *4*(4), e759. https://doi.org/10.1097/PR9.0000000000000759

Zoellner, J., Thomson, J. L., Landry, A. S., Anderson-Lewis, C., Connell, C., Molaison, E. F., & Yadrick, K. (2014). Improvements in blood pressure among undiagnosed hypertensive participants in a community-based lifestyle intervention, Mississippi, 2010. *Preventing Chronic Disease: Public Health Research, Practice, and Policy*, *11*.

Zou, D., Wennman, H., Ekblom, Ö., Grote, L., Arvidsson, D., Blomberg, A., Torén, K., Bergström, G., Börjesson, M., & Hedner, J. (2019). Insomnia and cardiorespiratory fitness in a middle-aged population: the SCAPIS pilot study. *Sleep Breath*, *23*(1), 319-326. https://doi.org/10.1007/s11325-018-1765-9

Zöller, B., Li, X. J., Ohlsson, H., Ji, J. G., Sundquist, J., & Sundquist, K. (2015). Family history of venous thromboembolism as a risk factor and genetic research tool. *Thrombosis and Haemostasis*, *114*(5), 890-900. https://doi.org/10.1160/Th15-04-0306

Zöller, B., Ohlsson, H., Sundquist, J., & Sundquist, K. (2013). Familial risk of venous thromboembolism in first-, second- and third-degree relatives: a nationwide family study in Sweden. *Thrombosis and Haemostasis*, *109*(3), 458-463. https://doi.org/10.1160/Th12-10-0743

Zöller, B., Ohlsson, H., Sundquist, J., & Sundquist, K. (2014). Family history of venous thromboembolism (VTE) and risk of recurrent hospitalization for VTE: a nationwide family study in Sweden. *Journal of Thrombosis and Haemostasis*, *12*(3), 306-312. https://doi.org/10.1111/jth.12499

Zöller, B., Svensson, P. J., Dahlbäck, B., Lind-Hallden, C., Hallden, C., & Elf, J. (2020). Genetic risk factors for venous thromboembolism. *Expert Rev Hematol*, *13*(9), 971-981. https://doi.org/10.1080/17474086.2020.1804354

Paper I

Patients' experience of a nurse-led lifestyle clinic at a Swedish health centre

Peter Nymberg MSc, RN (District Nurse)[1] and **Eva Drevenhorn** PhD, RN (Senior Lecturer)[2]

[1]Husensjö Health Centre, Helsingborg, Sweden and [2]Department of Health Sciences, Faculty of Medicine, University of Lund, Lund, Sweden

Scand J Caring Sci; 2016; 30; 349–355

Patients' experience of a nurse-led lifestyle clinic at a Swedish health centre

Background: In Sweden, 56% of the population aged 16–84 have an unhealthy lifestyle. The primary health care (PHC) has been instructed to offer citizens health promotion and disease-preventive actions. Very few studies have been conducted about how individuals experience interventions from the PHC intended to help them to change lifestyle.
Aim: The purpose of the study was to explore patients' experiences of visiting a nurse-led lifestyle clinic.
Methods: Patients (n = 137), who participated in a screening test at a lifestyle clinic, were invited to focus group interviews. Of these, 14 patients agreed to participate. The data were analysed using content analysis.
Results: The patients felt that the visit to the lifestyle clinic gave insight into their habits and diminished their

fear of not being healthy. Primary health care was seen as a safe provider in this matter. Disappointment was occasioned by the unfulfilled expectations of blood tests, lack of follow-up visit and inconsistencies of approach during the visit to the lifestyle clinic. Personal chemistry was perceived to be crucial for how the encounter with the public health nurse evolved.
Conclusion: Lifestyle clinics can give patients opportunity to change lifestyle and also to confirm the good habits. It may also be important to have follow-up visits to give the patients' support when changing lifestyle. Nurses counselling patients about lifestyle changes need to have recurrent training in Motivational Interviewing.

Keywords: lifestyle, prevention, counselling, patients' experience, nurse-led clinic, public health nurse, primary health care, focus groups, content analysis.

Submitted 21 February 2015, Accepted 12 May 2015

Introduction

According to the Swedish National Institute of Public Health (1), 56 per cent of the Swedish population aged 16–84 years have unhealthy habits such as a low intake of fruits and vegetables, a sedentary lifestyle, daily tobacco use, a high alcohol intake, risky gambling behaviour and use of cannabis. Obesity was reported in 14 per cent of the Swedish population. The primary health care (PHC) in Sweden has been designated the assignment (2) of preventing illness from different perspectives, both from the perspective of helping the individual to remain healthy and from a purely economic perspective. The guidelines regarding the financial compensation system state that PHC should be active in providing citizens with health promotion and disease prevention. The guidelines include both primary prevention, with health counselling

for healthy groups and groups at risk, and secondary prevention for those already diagnosed with an illness. Primary health nurses (PHN) in Sweden have a special academic education (3) to work with health promotion in a holistic manner including a psychosocial approach.

During the past few years, a number of intervention studies have been carried out with the aim of investigating how a changed lifestyle affects the incidence of chronic disease. Most of the studies have shown improvements regarding a lower incidence of diabetes (4–6), hypertension (7–10) and obesity (11–13). The studies have shown that patients can get healthier in the experimental setting, but have not examined the patients' views of how to discuss their health problems. Duaso and Cheung (14) investigated patients' recall and perception of lifestyle counselling given by Registered Nurses in a general practice. The study showed that it is important for PHC to work with lifestyle issues because a number of health risks can be detected and patients can receive guidance to a healthier life. Poskiparta, Kasila and Kiuru (15) argue that it is necessary to have methods that facilitate the discussion of changes of health

Correspondence to:
Peter Nymberg, Vårdcentralen Husensjö, Skaragatan 102, SE-253 63 Helsingborg, Sweden.
E-mail: peter.nymberg@skane.se

behaviour with patients, and to be able to do this successfully, communication training is required for the staff involved. This was exemplified in a study (16) with patients treated in a patient-centred way by trained nurses at nurse-led hypertension clinics in primary health care. In telephone interviews, the patients expressed more satisfaction with the counselling than patients in the control group did. These studies show that working with lifestyle changes with patients at risk of diseases is important, and this work should be performed from a patient-centred perspective to be successful.

Persson and Friberg conducted a study (17), which aimed to illuminate patients' experiences of health conversations, and found that the patients preferred a patient-centred approach and wanted to be seen as individuals. The way in which the health conversation influenced the patients depended heavily on the patients' previous experiences which Kärner et al. (18) likewise pointed out when investigating how patients' experienced constraining and facilitating factors related to their lifestyle changes. Hardly any studies, however, have focused on patients' experiences of visiting a lifestyle clinic to discuss their health. Therefore, this study was conducted with the aim of contributing with further knowledge about patients' views of being counselled about lifestyle factors at a lifestyle clinic.

Aim

The purpose was to explore patients' experiences of visiting a nurse-led lifestyle clinic.

Methods

Context

At the beginning of 2010, a lifestyle clinic was started at a PHC centre in a prosperous neighbourhood in the south of Sweden to meet the accreditation requirements for an active health promotion. This service was free of charge for the PHC centre patients. The purpose of the lifestyle clinic was to find individuals who were at risk of obesity, hypertension, diabetes, chronic obstructive pulmonary disease (COPD) or mental illness and to prevent illness and promote health among these patients. Visits were offered to patients who were 40, 50 or 60 years of age who did not have a diagnosis of chronic disease. There were also opportunities for other patients to make an appointment, and some patients were recommended to visit the lifestyle clinic by the staff of the PHC centre. All questionnaires were developed by PHNs, physicians and a welfare officer at the PHC centre and were tested step by step.

During the visit to the lifestyle clinic, patients were screened regarding unhealthy habits in the areas of diet, exercise, tobacco and alcohol, but also from a psychosocial perspective. Together with the invitation, patients received a short questionnaire which they could complete at home and bring to the clinic. This short questionnaire concerned lifestyle habits, heredity, levels of motivation for change and whether or not the patient had any symptoms of diseases caused by an unhealthy lifestyle. At the lifestyle clinic, the patients were asked to do all the measurements by themselves with some help from the public health nurse (PHN). The measurements included height, weight, blood pressure, blood glucose, waist circumference and body mass index (BMI). Smokers also did the breath test COPD-6 (FEV %). When measurements were made, the patients filled out a form regarding their self-perceived health, what they wanted to change and what kind of help they expected to be given. Their answers were discussed with the PHN, along with the measured values, in order to find out what was suitable to change, which was then documented. The counselling was based on Motivational Interviewing (MI) (19). If worries about mental unhealth were present, the patient filled out a form to rate their mental health status. Patients who showed abnormal values regarding the different parameters were passed on to other professionals at the health centre according to a developed flow chart.

Participants The inclusion of patients in the study started with an invitation to every fifth patient consecutively of those who visited the lifestyle clinic but, but since many refused to participate, all of the patients (n = 137) received a letter requesting them to participate in focus group interviews. Fourteen patients agreed to participate (13 women and 1 man). Of these, 10 had been invited and 4 had visited the lifestyle clinic of their own accord. The interviewed patients were 50.5 (md) (40–84) years of age.

Data collection

Data were collected through focus group interviews in which the moderator steered the conversation within the aim of the study (20). Four interviews were conducted with a total of 14 respondents (4, 3, 3 and 4 respondents at each interview). The interviews took place approximately one month apart, according to when the invited respondents reported an interest in participating. Each interview started with an open question, and then follow-up questions were put in when necessary to keep up the conversation. The focus group interviews lasted between 30 and 60 minute and were conducted in a neutral conference room. The interviews were recorded and notes were taken by the moderator (PN) during the interviews. In order to find any flaws that might exist in the interview techniques and to test the technical equipment, a test interview with a group of six colleagues was conducted.

The reason for using focus group interviews was to capture the different experience of the respondents (21).

Focus group interviews (22, 23) can be described as an interaction between the moderator and the respondents for the purpose of data collection. The idea of focus groups is that the group process may help to develop and clarify the key points of the topic of discussion.

Analysis

Material was analysed using content analysis (24). Interviews were transcribed verbatim including, for example pauses, laughter and sighs. The interviews and the field notes were read through several times in order to get to know the material, what is called naive reading. After this reading, both similarities and differences in the informants' stories were seen and noted in the margins. All text relating to the purpose of the study was extracted and brought together, and these texts were divided into meaning units that were condensed. The condensed meaning units were abstracted and labelled with a code. Codes were subclassified in order to obtain a broad category that explained the content and responded to the purpose. Both authors subclassified the codes and gathered them into categories. During the analysis, similarities and differences in subcategories and categories were discussed.

Ethics

The study was approved by the Health Sciences Ethics Committee (VEN 30-11). Information about the voluntariness of participation in the study was given before each interview, and confidentiality was assured. Discussion of one's experiences of visiting a lifestyle clinic can give a bad conscience, but can also serve as a reminder to the participants of the need continue to pursue a healthy lifestyle. Of this reason, the moderator of the focus groups was anxious to let all participants of the group to take part in the discussion to not let any person become dominant. Preparations were made to take care of any need that might arise, for physical examination by a physician or psychosocial care by a psychologist in accordance with the local routines at the PHC centre.

Results

Analysis resulted in two categories: sense of security and unfulfilled expectations. These categories are used as headlines in the presentation of the results with the subcategories as subheadings (Table 1). To verify the analysis, the result is presented with quotations.

Sense of security

Seen as being on an equal level. Some patients felt that the way any particular meeting would turn out depended on the individual PHN they met. It was perceived as positive

Table 1 Categories in bold with subcategories

Sense of security	*Unfulfilled expectations*
Seen as being on an equal level	Disappointment
Control of health	Missing being seen as an individual
The importance of the responsible authority	Physical examination

when the PHN was the same age as they, themselves, were which meant that patients could ask about the nurse's experience of different phenomena.

> I could ask her (PHN) when did you get hot flashes and how did that feel? Because she knew, she was about my age more or less and could, I felt very close to being able to ask questions.(Respondent No. 3)

However, there were those who felt that age was irrelevant and thought that it was instead the person's competence that determined whether the meeting would be good or bad. Communication in a direct and straightforward manner without any unnecessary euphemisms was perceived as positive and encouraged patients to understand the effects of poor habits. Through the visit to the lifestyle clinic, and the counselling, many different insights were revealed about how the patients actually lived or what they needed to change.

Control of health. Fear of not being healthy and not relying upon their own sense of being healthy was the main reason patients visited the lifestyle clinic.

> It was just about finding out about my health, I know I'm fine, but if I get it in writing or if someone can tell me that I'm living in the right way(Respondent No. 5)

There was also an element of uncertainty about what it was that comprised a healthy way of life. Although the patients had the actual knowledge, they wanted it to be confirmed by the visit to the lifestyle clinic. The patients wanted a healthcare professional to take responsibility for the correctness of their perception of being healthy and to continue to monitor their health status over time.

The importance of the responsible authority. Respondents felt that the PHC was a reliable actor which gave the expectation of good quality of care in contrast to that of the occupational health care.

> the way that at least I feel is that you want confidentiality with regard to your employer, I don't want to tell everything to my employer. After all, you're at a disadvantage. So, that's why I think that it will be better for me to go to lifestyle counselling that's given under the authority of Region Skåne. I

think I will be able to feel more relaxed about being open than I would in a situation at work.(Respondent No. 7)

The patients had expectations of better adherence to confidentiality in the management of care by PHC than in occupational healthcare or company health services where they felt there was a greater risk that their troubles of a private nature might come to the employer's knowledge and that this could be used in a negative way against them at the workplace.

Unfulfilled expectations

Disappointment. Patients felt that the invitation to the clinic omitted some information about what would be included in the visit and how the lifestyle clinic was structured. A major area of disappointment was that the PHN was not updated with the patients' past medical history, which the patients perceived strange. The nature of the work at the clinic was also experienced too physically focused with the emphasis placed on the body's constitution and functions. This caused disappointment about not being able to discuss other dimensions.

it was just about the body, like weighing and measuring and taking some small blood samples.(Respondent No. 3)

The patients felt that the visit to the clinic was very short, even though they did not expect all their problems to be solved during this first visit. However, since there were no planned follow-up visits, much of the disappointment the patients felt was due to their expectations of a motivational follow-up that did not take place.

making a sort of base inventory, how are you today? Then take some basic tests, this is our starting point, and then from there give a stimulus, this is something you need to think about, then you bring people together (in a follow-up) who have the same basis to work on.(Respondent No. 10)

The follow-up was expected to contain motivational aspects for changing lifestyle and to be supported by telephone or, even better, within problem-specific groups, where the group members could give support to each other.

The patients wanted to be prepared for the visit by completing all the questionnaires before the visit so they could get the most out of the counselling. The reason for this was partly because it would provide a greater opportunity for the PHN to assist them in a better way. The patients saw it as wasted time filling out one of the forms on the spot while the PHN just sat beside them watching. This meant that the situation was perceived as stressful and the responses to the form were often oversimplified. On the other hand, there were those who wanted to complete the questionnaire, 'Your health profile', during the actual visit.

It can be good that you haven't seen them before, the questions, I mean; it'll be more spontaneous I think if you fill it in on the spot. At home you think, what's their ulterior motive with this? That's how you think when you've got more time.(Respondent No. 6)

The reason was that the questions were easy to respond to and if they had filled them out at home that might have brought up many unnecessary questions and suspicions of any possible ulterior motives behind the various questions.

Missing being seen as an individual. Patients expected to be intellectually stimulated to make changes in their lifestyle, not to be told exactly what changes to make. They were disappointed about not being helped to get an overall picture of their lifestyle.

but I felt when I took up things that I had problems with, then she (PHN) began talking about the problems she had and I just mmmhmmm (humming) I'm not interested in that, I mean it felt very odd to me.(Respondent No. 4)

Patients' also expressed disappointment over being given bad advice instead of being encouraged to gain their own insight. This gave them a feeling of a lack of good counselling techniques and an impression that the lifestyle counselling was unprofessionally performed. Some perceived the straightforward approach on purpose as to bring them to insight, as sarcasm.

she told me to empty my fridge, but you need to have something in the fridge! But then you must have things that are good for the body and not a whole lot of sweets and stuff.(Respondent No. 8)

Patients experienced that they did not receive enough assistance in putting their knowledge into practice. When the PHN made comparisons between her own experiences and the patients' concerns, the patients felt that they were not being taken seriously. This, still more, increased their feeling of being unprofessionally treated at the lifestyle clinic.

Physical examination. The patients expected a thorough traditional physical health examination using objective measurements such as height, weight, blood pressure, lung function tests, as well as extensive blood tests to obtain baseline values.

I think I'd expected more blood tests as well, it was something like, OK was it only blood sugar.(Respondent No. 3)

The most frequently missed test that was mentioned was cholesterol. The reason was that this test was strongly associated with lifestyle and could be influenced by changes in one's lifestyle. The patients had knowledge about how high cholesterol affects the incidence of cardiovascular diseases, which created anxiety due to their

not knowing what value they had themselves. Further-more, some uncertainty was brought into the visit by the self-measurement of blood pressure with an automatic blood pressure cuff.

> then it brought on more worry, that was maybe unjustified, because the measurement technique wasn't optimal(Respondent No. 7)

The patients did not understand the purpose of the nurse sitting beside watching them doing the measure-ment instead of doing it herself, as is usually done at vis-its in health care. Furthermore, when the results differed between the two measurements performed, the patients' uncertainty increased.

Discussion

It emerged from the focus group interviews about patients' experiences visiting a lifestyle clinic that they gained a sense of security. This sense came partly from being confirmed in arriving at new insights or that the way they were living was healthy. Disappointment was felt when the patients had other expectations of visiting the clinic than what was provided.

The interviewed patients highlighted the importance of personal chemistry with the PHN during the health con-versation, but a patient-centred approach might have resulted into a more successful encounter (16–18). According to the patients, the PHN in our study used an arsenal of different strategies in an effort to help the patients with their struggling for a healthier way of liv-ing. The PHN may have used inappropriate strategies towards some of the patients; in some patients, it went well but others were upset. This shows the importance of working in a patient-centred way where everyone can benefit from it (25). Patient-centred counselling is obvi-ously an important working model (16–18, 26) for health conversations if they are to have any impact on the patient. Lack of training can be one barrier to patient-centred lifestyle counselling as shown in a study with GPs and nurses (26). Frequent counselling exercises would not just get a more professional impression, but also ensure greater adherence to treatment among the patients (27). Another way to get adherence to given advice could be follow-up visits which also was what the patients expected. This could have resulted in confidence between the PHN and the patient being built up (28). On the other hand, patients who visited the life style clinic and had abnormal weight, blood pressure, blood sugar or had any other health problem detected were either brought back to a follow-up visit or got an appointment with a GP. Why those patients, who were healthy and objectively did not have any need for a follow-up visit, were disappointed is not clear. But according to Persson and Friberg's findings (17), the visit may nevertheless have affected them but not to the extent that they felt the need of any major lifestyle change. However, the patients received a second opinion about their health and felt reassured when they realised they were healthy and not at risk of diseases related to their way of living.

Another aspect highlighted in the interviews was the degree of integrity, as the respondents compared preven-tive work organised by occupational health service and the county council. In this comparison, they had the opinion that the county council could offer a higher degree of integrity. According to the company health ser-vices' professional association in Sweden (29), occupa-tional health service is to be primarily based on the work environment. In the second place, they should act with a desire to optimise the health of the employees so they can stay in production. In contrast, patients experienced PHC as a secure and independent actor in this context to take care of their health check-ups.

Previous experiences may have influenced the patients in a way that led to high expectations which did not match the clinic's intention. This is something Persson and Friberg (17) and Kärner et al. (18) pointed out as an important factor to take into account. The patients expe-rienced a fixation with their physical condition at the clinic, but, at the same time, they would also have pre-ferred a more comprehensive health assessment. One reason for this could possibly be that confidence had not been built up between the nurse and the patient, which might result in greater difficulties in talking about more sensitive things in the patients' lives (9).

Measurements were important for the patients and it is important that they are conducted in an evidence-based way. This is especially important for blood pressure mea-surement, as there are many sources of errors (30). This means that it would have been better to perform the mea-surements manually and to utilise the expertise the PHN has about blood pressure measurement so as to avoid false values. Furthermore, this would have made the patients more comfortable as they were familiar with having their blood pressure manually measured by healthcare person-nel. Another very important aspect is that blood pressure measurements should be performed in the same way, regardless of who is performing the measurement (31), especially when follow-up monitoring is performed.

Methodological considerations

The low response to the invitation to participate in the focus group interviews is a major limitation of this study. Preferably, to make it easier to engage more participants, the interviews should have been performed continuously soon after the patients' visit the lifestyle clinic. Small focus groups (23) are preferable to big ones, because they are easier to handle. However, whether or not three respondents could be classified as a focus group is open to contestation. According to Krueger and Casey (22),

the lower limit of mini focus groups is four respondents. The reason for the low number in two of the groups was that some respondents did not show up but, to show respect for those who did, the interviews were conducted anyway.

To ensure credibility and dependability, the analysis was performed manually in a systematic manner. The co-author was familiar with the material and performed analysis in addition to the first author. The results were compared and discussed between the authors until consensus was reached. This way of working strengthens the results in terms of credibility and confirmability and also ensures that the results would be transferable to a different lifestyle clinic in a similar context (32).

Conclusions

Lifestyle clinics can both give patients opportunity to change their current unhealthy lifestyle and confirm the good habits. Identifying patients' individual needs by using a screening form prior to the visit to a lifestyle clinic might be appropriate. It may also be important to have follow-up visits to provide the patients support when changing lifestyle. Nurses counselling patients about lifestyle changes need to have frequently recurring training in Motivational Interviewing to be able to provide a patient-centred holistic approach including somatic, psychological and social aspects. There is a need for further studies focusing on health benefits with a focus on patients' experiences of lifestyle clinics.

Author contributions

Peter Nymberg and Eva Drevenhorn contributed to the design of the study, analysis of the data and wrote the manuscript; Peter Nymberg involved in data collection.

Ethical approval

The Health Sciences Ethics Committee at the Department of Health Sciences, Lund University, has given an advisory report (VEN 30-11).

Funding

None.

References

1 FHI. Levnadsvanor, lägesrapport 2010. (Lifestyle, state of the art report 2010). Statens folkhälsointitut (Swedish National Institute of Public Health), 2010 Contract No.: A. 2010, 13.

2 Region Skåne. Förutsättningar för ackreditering och avtal för vårdenhet i Hälsoval Skåne gällande 2010 (Requirements for accreditation and agreements for patient care In the Choice of Health in Skåne for 2010), 2010.

3 Swenurse. Kompetensbeskrivning, Legitimerad sjuksköterska med specialistsjuksköterskeexamen Distriktssköterska (Description of competence for registered nurse with graduate diploma in specialist nursing-district nurse), 2008. http://www.swenurse.se/Documents/Komptensbeskrivningar/KompbeskrDistriktwebb.pdf (last accessed 18 December 2014).

4 Pan XR, Li GW, Hu YH, Wang JX, Yang WY, An ZX, Hu ZX, Lin J, Xiao JZ, Cao HB, Liu PA, Jiang XG, Wang JP, Zheng H, Zhang H, Bennet PH, Howard BV. Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance. The Da Qing IGT and Diabetes Study. *Diabetes Care* 1997; 20: 537–44.

5 Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, Nathan DM; Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 2002; 346: 393–403.

6 Sakane N, Sato J, Tsushita S, Tsujii S, Kotani K, Tominaga M, Kawazu S, Sato Y, Usui T, Kamae I, Yoshida T, Kiyohara Y, Sato S, Tsuzaki K, Takahashi K, Kuzuya H; Japan Diabetes Prevention Program (JDPP) Research Group. Effect of baseline HbA1C level on the development of diabetes by lifestyle intervention in primary healthcare settings: insights from subanalysis of the Japan Diabetes Prevention Program. *BMJ Open Diabetes Res Care* 2014; 2: e000003.

7 Zanesco A, Antunes E. Effects of exercise training on the cardiovascular system: pharmacological approaches. *Pharmacol Ther* 2007; 114: 307–17.

8 Svetkey LP, Pollak KI, Yancy WS Jr, Dolor RJ, Batch BC, Samsa G, Matchar DB, Lin PH. Hypertension improvement project: randomized trial of quality improvement for physicians and lifestyle modification for patients. *Hypertension* 2009; 54: 1226–33.

9 Eriksson KM, Westborg CJ, Eliason MC. A randomized trial of lifestyle intervention in primary healthcare for the modification of cardiovascular risk factors. *Scand J Public Health* 2006; 34: 453–61.

10 Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, McQueen M, Budaj A, Pais P, Varigos J, Liheng L; INTERHEART Study Investigators. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case–control study. *Lancet* 2004; 364: 937–52.

11 Hinderliter AL, Sherwood A, Craighead LW, Watkins L, Babyak MA, Blumenthal JA. The long term effects of lifestyle change on blood pressure: one-year follow-up of the ENCORE study. *Am J Hypertens* 2014; 27: 734–41.

12 Goodpaster BH, Delany JP, Otto AD, Kuller L, Vockley J, South-Paul JE, Thomas SB, Brown J, McTigue K, Hames KC, Lang W, Jakicic JM. Effects of diet and physical activity interventions on weight loss and cardiometabolic risk factors in severely

obese adults: a randomized trial. *JAMA* 2010; 304: 1795–802.

13 Fitzpatrick SL, Coughlin JW, Appel LJ, Tyson C, Stevens VJ, Jerome GJ, Dalcin A, Brantley PJ, Hill-Briggs F. Application of latent class analysis to identify behavioral lifestyle interventions in overweight and obese adults. *Int J Behav Med* 2014. DOI 10.1007/s12529-014-9446-y.

14 Duaso MJ, Cheung P. Health promotion and lifestyle advice in a general practice: what do patients think? *J Adv Nurs* 2002; 39: 472–9.

15 Poskiparta M, Kasila K, Kiuru P. Dietary and physical activity counselling on Type 2 diabetes and impaired glucose tolerance by physicians and nurses in primary healthcare in Finland. *Scand J Prim Health Care* 2006; 24: 206–10.

16 Drevenhorn E, Bengtsson A, Kjellgren KI. Patients' view on hypertension care after consultation training to nurses. *Eur J Cardiovasc Nurs* 2008; 7: S56.

17 Persson M, Friberg F. The dramatic encounter: experiences of taking part in a health conversation. *J Clin Nurs* 2009; 18: 520–8.

18 Kärner A, Tingström P, Abrandt-Dahlgren M, Bergdahl B. Incentives for lifestyle changes in patients with coronary heart disease. *J Adv Nurs* 2005; 51: 261–75.

19 Miller WR. Motivational interviewing: research, practice, and puzzles. *Addict Behav* 1996; 21: 835–42.

20 Parahoo K. *Nursing Research: Principles, Process and Issues*, 2 edn. 2006, Palgrave Macmillan, Houndsmills, Basingstoke, xii, 481 sider.

21 Kvale S, Brinkmann S. *INTERVIEWS: Learningthe Craft of Qualitative Reaserch Interviewing*. 2 edn. 2009, SAGEpublications, London.

22 Krueger RA, Casey MA. *Focus Groups: A Practical Guide for Applied Research*, 4th edn. 2009, SAGE, Los Angeles, xviii, 219.

23 Cote-Arsenault D, Morrison-Beedy D. Practical advice for planning and conducting focus groups. *Nurs Res* 1999; 48: 280–3.

24 Graneheim UH, Lundman B. Qualitative content analysis in nursing research: concepts, procedures and measures to achieve trustworthiness. *Nurse Educ Today* 2004; 24: 105–12.

25 Hörnsten Å, Lindahl K, Persson K, Edvardsson K. Strategies in health-promoting dialogues–primary healthcare nurses' perspectives – a qualitative study. *Scand J Caring Sci* 2014; 28: 235–44.

26 Lambe B, Collins C. A qualitative study of lifestyle counselling in general practice in Ireland. *Fam Pract* 2010; 27: 219–23.

27 Drevenhorn E, Bengtson A, Nilsson PM, Nyberg P, Kjellgren KI. Consultation training of nurses for cardiovascular prevention – a randomized study of 2 years duration. *Blood Press* 2012; 21: 293–9. Epub 2012/05/02.

28 Walseth LT, Abildsnes E, Schei E. Patients' experiences with lifestyle counselling in general practice: a qualitative study. *Scand J Prim Health Care* 2011; 29: 99–103.

29 Sveriges Företagshälsor. Sveriges Företagshälsor (Sweden's occupational health services). 2012 [cited 2012 22/6]; Sweden Företagshälsor is the occupational health.

30 Drevenhorn E, Håkansson A, Petersson K. Blood pressure measurement – an observational study. *J Clin Nurs*, 2001; 10: 189–94.

31 SBU. Måttligt förhöjt blodtryck: en systematisk litteraturöversikt: uppdatering av SBU-rapporten Måttligt förhöjt blodtryck (*Moderate hypertension:a systematic review: an update of the SBU-report Moderate hypertension*) (2004), nr 170/1. Statens beredning för medicinsk utvärdering (SBU) National Council on Technology Assessment, Stockholm. 2007, 199.

32 Burnard P. A method of analysing interview transcripts in qualitative research. *Nurse Educ Today* 1991; 11: 461–6.

Paper II

Trials

STUDY PROTOCOL

Open Access

CrossMark

Pilot study on increased adherence to physical activity on prescription (PAP) through mindfulness: study protocol

Peter Nymberg[1*] , Eva Ekvall Hansson[2], Emelie Stenman[1], Susanna Calling[1], Kristina Sundquist[1], Jan Sundquist[1] and Bengt Zöller[1]

Abstract

Background: In the Swedish population aged between 50 and 64 years only 7.1% reach the recommended level of physical activity. Physical activity on prescription (PAP) has been used in Sweden since the beginning of the twenty-first century with moderate adherence of approximately 50%. Mindfulness seems to affect motivation to and satisfaction with physical activity. The aim is to test the feasibility of a study in routine care; i.e. to test if mindfulness can improve adherence to PAP, measured by changes in physical activity.

Methods/design: We will include 90 sedentary individuals, aged 40–65 years, from primary health care centres in Sweden. Individuals will be randomised to only PAP, mindfulness and PAP or mindfulness only. The PAP group will be based on patients' preferences. The mindfulness groups will meet once a week for 8 weeks and practise 20 min of individual training per day. There will not be any motivational interview or physical activity on prescription in the group assigned to only mindfulness.

The participants will complete the Five Facet Mindfulness Questionnaire, the Insomnia Severity Index and also answer questions concerning their lifestyle. Physical activity will be measured by ACTi Graph GT1X activity monitor at baseline and after 3 and 6 months. Patients with a severe psychological disease, unstable angina or a recent myocardial infarction will be excluded. The main outcome will be adherence to PAP in an ordinary primary health care setting. In this pilot study, we will also evaluate measures such as the recruitment rate, number of dropouts and adherence to mindfulness practice.

Discussion: This study is the first to explore the effect of mindfulness on adherence to PAP and test the feasibility of the study design.

Trial registration: ClinicalTrials.gov, NCT02869854. Registered on 26 August 2016.

Keywords: Physical activity, Motivation, Health care, Lifestyle change

Background

A lifestyle with an adequate amount of physical activity can decrease the risk of cardiovascular illness [1, 2] and improve perceived quality of life [3]. Although people in northern Europe are physically active [4], they report more sedentary time than their southern European counterparts [5]. A study concerning sedentary behaviour among 50- to 64-year-old Swedes showed that only 7.1% of the 948 participants fulfilled the World Health Organization (WHO) recommendations for physical activity [6]. In Sweden, the health care service recommends the use of physical activity on prescription (PAP) as a complementary treatment to motivate patients to increase their activity level; the treatment addresses both primary and secondary prevention of sickness. The written prescription can be a proposal for an activity or an extensive solution with a supportive structure, depending on the patient's needs and level of motivation. PAP is associated with up to a 60% increase in activity levels, but, unfortunately, the

* Correspondence: peter.nymberg@med.lu.se
[1]Lund University/Region Skåne, Centre for Primary Health Care Research, Jan Waldenströmsgata 35, Skåne University Hospital Malmö, University Hospital, SE-205 02 Malmö, Sweden
Full list of author information is available at the end of the article

increase is not sustainable over time [7, 8]. A systematic review estimated that one must treat 12 sedentary adults with a physical activity promotion intervention in order to make one of them achieve the recommended physical activity level at 1 year follow-up [9]. In addition, PAP seems to be most effective in individuals who are already slightly active. Satisfaction plays a crucial role in changing a behaviour; this has been observed in smoking cessation [10], weight loss [11] and physical activity [12]. Satisfaction is increased both by the awareness in a specific positive situation and by the reduction of negative thoughts, e.g. about physical activity [13]. To experience increased satisfaction with physical activity, it seems necessary to be aware of the present; something which may be facilitated by practising mindfulness [14]. All people have varying capacities to attend to and to be aware of the present moment, which is called dispositional mindfulness, and it is an intrinsic but a modifiable trait [15]. Mindfulness can be exerted as sitting meditation but also as an approach to everyday life [16]. The practice of mindfulness can increase recognition of mental experiences in the present moment by self-regulation of attention—meaning that it is preserved on immediate experience. It might also enable individual traits such as increased curiosity, openness and acceptance because of the orientation toward one's experiences in the present moment [17]. Being mindful in a specific situation and satisfaction are suggested to be consecutive mediators for the path between possessing a dispositional tendency to be mindful and physical activity [14]. This might explain why self-reported mindfulness seems to mediate the relationship between intrinsic motivation and the physical activity level [18]. In other words, practising mindfulness can make it easier to experience satisfaction with physical activity and, in this way, support the change from a physically inactive behaviour to a physically active one. Conversely, trials have shown that regular exercise can also lead to increased dispositional mindfulness [19]. Thus, mindfulness may have a crucial role in motivation by reinforcing satisfaction with physical activity. However, the matter of causality is still unclear.

Methods/design
Aim
The aim of this pilot study is to test the feasibility of the main study in regular care. The overall aim of the main study is to examine whether a mindfulness programme can increase the adherence to PAP in an ordinary primary health care setting. To achieve this, we will compare three different intervention groups: PAP, mindfulness and a combination of PAP and mindfulness. A secondary aim is to evaluate differences between the three intervention groups regarding changes in health-related parameters related to physical activity,

such as blood pressure, weight, lipid profile, biomarkers, gene and protein expression, self-rated health, insomnia and mindfulness.

Setting
The pilot study involves three primary health care centres in the county of Skåne (Scania) in southern Sweden. In total, there are approximately 164 primary health care centres in the county. Scania has approximately 1.2 million residents, 410,000 of whom are aged between 40 to 65 years old.

Participants
The main inclusion criterion for participants is that they are insufficiently physically active individuals aged between 40 to 65 years. The criteria of physical activity are defined according to the WHO guidelines regarding physical activity recommendations, where the lower limits are set to < 150 min per week of moderate intensity or < 75 min per week of high intensity.

Exclusion criteria are dementia, serious mental disorder, newly diagnosed untreated unstable angina pectoris or myocardial infarction within 6 weeks prior to study entry. Individuals with a physical disability which decreases their ability to perform physical activity will be excluded as well as individuals who cannot master the Swedish language in speech and writing.

Interventions
Intervention A comprises PAP only, which is treatment as usual in physically inactive patients [7, 8].

Intervention B comprises PAP and mindfulness. This involves treatment as usual with the addition of a 2-h-long mindfulness group session once a week for 8 weeks, as well as 20 min of daily practice. The mindfulness course is based on both mindfulness-based stress reduction (MBSR) and mindfulness-based cognitive therapy (MBCT) and includes meditative exercises. The patients will receive instructions concerning the daily practice with meditative exercises in the web-based programme. The instructions include breathing technique and body scan [20].

Intervention C comprises the same mindfulness course as intervention B, but without PAP.

A flowchart describing the study design is presented in Fig. 1.

The randomisation will be stratified by the patients' age and sex, and there will be three age groups: 40–49, 50–59 and 60–65 years. The randomisation will be done using the minimisation method with a random element [21] and the statistical program STATA version 14.1.

Procedure
Placards will be placed in the participating primary care centres to raise interest among the patients to participate

Fig. 1 Study design
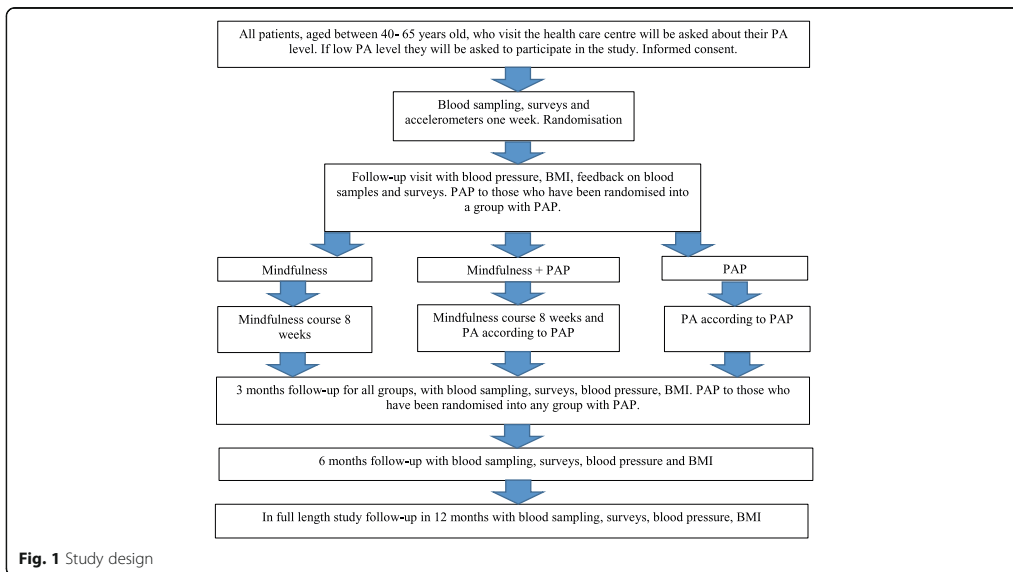
in the study. All patients within the 40–65 age group, regardless of the reason for their visit, will be asked about their physical activity level. Patients who regard themselves as insufficiently physically active (according to WHO's recommendation) will be asked to participate in the study. Eligible patients will be contacted by a nurse to be informed about the study and give their written consent if they wish to participate further. Patients who are willing to participate will be asked to come for fasting blood sampling and will receive accelerometers, which will be attached to their hip during the next 7 days apart from when bathing and sleeping at night. Mindfulness will be measured by the Five Facet Mindfulness Questionnaire (FFMQ) [22], and insomnia will be measured with the Insomnia Severity Index (ISI) [23]. The survey about lifestyle habits includes short questions about alcohol, food, physical activity and eating habits. All the surveys will be in Swedish. The patients will fill out the questionnaires during the period prior to their follow-up visit after approximately a week. During the time between blood sampling and the follow-up visit, patients will be randomised to one of the three intervention groups. The patients will be informed about the randomisation at their follow-up visit. At this visit, the blood pressure (in sitting position after 5 minutes, in the right arm) and body mass index (BMI) will be measured. The patients will also get feedback on the fasting blood tests at the initial visit, triglycerides, cholesterol and blood sugar. There will be feedback on the questionnaires and a discussion concerning lifestyle improvements, if there are

any. In the case of abnormal findings in blood samples, blood pressure or extensive alcohol consumption, an appointment will be arranged with the patient's general practitioner. In cases concerning a need to discuss diet, a meeting will be arranged with a dietician. The patients who are randomised into any of the groups with PAP will also receive a motivational interview and written PAP, which will be based on patient preferences according to the choice of physical activity. There will not be any motivational interview or PAP in the group randomised to only mindfulness,

In this pilot study, the mindfulness groups will include a mix of participants from interventions A and B. In a full-scale study setting there will be separated groups. To increase the number of participants, the courses will be scheduled after normal working hours. The courses will start late in the afternoon and commence as soon as there are 10 participants. The mindfulness course will be led by a trained instructor, and meetings will be held once a week for 8 weeks at the primary health care centre. Participants will also have access to a web-based mindfulness training programme together with an individual login. The web-based training programme can be used with a computer, tablet or mobile phone, regardless of which operating system is used. The web-based course includes a total of 21 h and 36 min of training in eight different levels. The participants will be urged to practise mindfulness with the web-based training programme on a daily basis for approximately 20 min at a time, except on the day of the group meeting. The adherence to the web-based

training programme will be measured by minutes spent practising on the web-based programme and with advancement in level.

Three months after the first visit, all the patients will be invited by letter to return for a new set of blood samples and measurements with accelerometer, BMI, blood pressure and surveys. If they do not appear, they will receive a phone call to schedule an appointment time. The patients who received PAP at the first visit will get another prescription in this session with motivational interviewing and written instructions.

After another 3 months (6 months from the commencement of the study), the same measurements, questionnaires and blood samples will be performed as for the two prior visits. At this visit, the patients in the group randomised to only mindfulness will get PAP if needed, as this is standard treatment in inactive patients and so far the most effective way to promote physical activity.

Measures

The schedule study procedures along the study time points are presented in Fig. 2.

Primary outcome

The primary outcome is the change in minutes of activity, both self-reported and measured by accelerometers (expressed in metabolic equivalent of task (MET) minutes), and compared between the groups.

Secondary outcomes

The secondary outcomes are:

1. Changed levels in blood pressure, weight, lipids, biomarkers and gene and protein expression.
2. Changed perceived self-rated health, measured with a five-step scale: very poor, poor, fair, good or very good.
3. Changes in insomnia problem as measured by ISI [23], which assesses the severity of maintaining sleep as well as sleep onset with seven items. The satisfaction with sleep patterns, implication of daily functioning and degree of distress caused by sleep problems are also monitored.
4. Changes in mindfulness measured with FFMQ [22]. This questionnaire consists of 29 statements with the following five facets: non-reactivity to inner experience, observing, acting with awareness,

		STUDY PERIOD											
TIMEPOINT weeks	Enrol ment	0	1	2	3	4	5	6	7	8	3 months followup	6 months followup
ENROLMENT:													
Eligibility screen	X												
Informed consent	X												
Baseline assessment	X											X	X
Follow up visit with feedback		X										X	X
Allocation	X												
INTERVENTIONS:													
PAP												X	X
Mindfulness+ PAP												X	X
Mindfulness												X	X
ASSESSMENTS:													
Accelerometer	X											X	x
FFMQ	X											X	X
ISI	X											X	X
Self-rated health	X											X	X
Life style Habits Questionnaire	X											X	X
Blood Pressure	X											X	X
BMI	X											X	X
Blood samples	X											X	X

FFMQ-The Five Facets of Mindfulness Questionnaire. ISI- Insomnia Severity Index. Self-rated Health a scale with five options from very poor to very good. Life style habits questionnaire, short questions about physically activity level, food, smoking, alcohol consumption. BMI-Body Mass Index. Blood samples- lipids, biomarkers, gene and protein expression.

Fig. 2 SPIRIT figure: schedule of forms and procedures per study time point

describing, non-judging of experience. The questionnaire uses a 1–5 scale ranging from never/rarely true to very often/always true.

Feasibility criteria for the pilot study

Several measures for a successful pilot study, i.e. feasibility criteria, will be monitored:

1. Recruitment rate: A recruitment rate of 30% will be considered successful. For comparison, a previous study of exercise training by King et al. had a recruitment rate of only 11% [24].
2. Dropout rate: A dropout rate of maximum 30% will be considered acceptable, which is determined according to the power calculation for the main study.
3. Attendance rate: Another criterion for success is if more than 70% of those randomised to the mindfulness group attend six meetings (75%) or more during the 8-week-long course. The rationale for this cut-off point is that a higher proportion of attendance is assumed to give a higher effect of the training [20].
4. Attendance rate: Another attendance criterion for success is if 70% of patients randomised to mindfulness practice mindfulness for at least 20 min with the web-based application at least 5 days a week [25].

If all the feasibility criteria stated above are fulfilled, the main study can be conducted without further changes in the protocol. If the criteria are not fulfilled, the protocol needs adjustment, and if the criteria are fulfilled to less than 70%, it will not be able to carry on with the main study in its current form.

Laboratory values

Study-specific blood samples, drawn after an overnight fast, will be taken at baseline and at both the 3 and 6 months follow-ups. This will be done to analyse eventual changes in lipid profile and plasma glucose. The blood samples will be analysed at the Department of Clinical Chemistry at Helsingborg Hospital. Blood samples will be collected for long-term storage for future analysis of biomarkers, gene and protein expression.

Adverse events

Patients will be required to answer questions about adverse advents during the follow-up visits. All side effects will be reported, both positive and negative, and independent of possible relation to the intervention.

Statistical and power calculation

This pilot study will be the basis of an upcoming power calculation for a full study. The statistical analyses and results will be delivered approximately 1 year after the study has commenced; i.e. when all the results are sampled from the 90 patients. The number of patients equal to 90 is approximately 10% of a power calculation to a full-scale study.

Preliminary sample size of the full intervention study, with follow-up, is based on a 1:1 relationship between two of the groups and estimated to $N = 320$ in the intervention group (mindfulness + PAP) and $N = 320$ in the control group (PAP only) by group based on a power analysis with 5% significance level and 80% strength. The expected dropout rate is set to 30%. The calculation is based on other studies on compliance to prescribed physical activity outcome measure, where 50% of the subjects followed the recommendation of physical activity by PAP [26]. We expect an increased adherence of 25%, from 50% to 62.5%, in the mindfulness + PAP group at 12 months follow-up.

Discussion

Physically inactive patients belong to a group who are at great risk of developing different diseases, as reported in previous research [27]. Although many studies have been performed with the aim of finding interventions about getting physically inactive people to become physically active, very few of these studies have been implemented in primary care with sustainability. The implementation of PAP in Sweden is one such intervention that has had success over time. The adherence of about 50% [7] can be explained by the previous data, which showed that it required 12 inactive individuals treated with an intervention like PAP to make one of them increase their physical activity level and maintain it for a year [9]. Thus, it is necessary to try other tools to increase people's physical activity levels. Patients trust their health care centre to take care of primary prevention, which for most patients includes both screening for diseases and help with behavioural problems such as increased physical activity and smoking cessation [28, 29]. As satisfaction plays a crucial role in behavioural changes, it may make a difference to try to make it easier for patients to feel satisfaction by taking a mindfulness course. In this way, combined with motivational interviewing and PAP, greater number of individuals may be motivated to become physically active. This is especially pertinent when connections have been seen between mindfulness and performing physical activity [14]. Mindfulness is already an accepted treatment in Swedish primary health care, where there now exist mindfulness group sessions with patients who suffer from insomnia, stress, anxiety and depression [20]. Since mindfulness group sessions are an

already-accepted treatment, it is easy to broaden their use to inactive individuals regardless of other problems. The combination of physical activity and mindfulness may also provide a greater effect in those with insomnia, depression and anxiety, for which physical activity also has a positive effect.

To conduct the described study, we must be aware of some obstacles. The first is the challenge to engage physically inactive patients to be a part of a study regarding activity. If a person does not have the motivation to take a 30-min brisk walk 5 days per week, we hypothesise that it could be difficult for that person to join a study aiming to increase the activity level significantly. It is possible that the patients who agree to participate are those with a physical activity level just below WHO's recommendation. It may also be possible that patients will underestimate their physical activity level, with the aim to match the inclusion criteria for the chance to be randomised to one of the mindfulness groups. Even if we try to get the groups to have equal numbers of the same sex, we will likely get the same distribution, with about 60–70% women, as in other studies [30] aiming to increase physical activity levels. We cannot affect this, and we do not know if it is a problem. However, we must take it into consideration when presenting the results. It is also a challenge to include patients quickly enough into the study. Dropouts can increase if it takes a long time between patients getting randomised until the mindfulness group can be started. Since the course is free of charge for the patients and starts in the late afternoon, we hypothesise that this will prevent dropouts. However, the fact that the course is free of charge can also have the opposite effect; i.e. it may not have any value for the patient, who may find it easier to skip group sessions. To evaluate the pilot study, we measure the time spent training with the web-based training programme, but we are also aware that the participants can practise mindfulness without being logged in to the web-based training programme, which can lead to measurement bias. In the concept with PAP there are follow-ups included, which may counteract dropouts. We will also call the patients who do not keep appointments in order to further encourage them to stay in the study.

The reason for using three different groups, instead of two, is to control if only mindfulness itself leads to increased physical activity in this setting. In this way, the study will be a triangulation; the three different treatments will be compared with and tested against each other regarding both physical activity levels and changes in FFMQ to see tendencies—if physical activity increases mindfulness or if it is the other way around. There is a risk, when we have both PAP + mindfulness and only mindfulness in the same group session, that the participants will speak to each other and contribute to an influence to increased physical activity in those who are randomised to only mindfulness. This is an issue to have in mind when analysing the material. However, even if the study participants discuss physical activity with each other, those with only mindfulness will not get counselling based on motivational interviewing or a prescription on physical activity. We therefore believe this limits the increase in physical activity in the mindfulness group due to influence from individuals randomised to PAP+ mindfulness. We are aware of the risk, and in a full-scale study there will be, as previously described, separate groups. Moreover, we will be able to compare intervention groups A and B without any carryover effect assessing whether mindfulness in combination with PAP has any additional benefits compared with PAP alone. It can also be a challenge to get participants to return for the follow-ups at 3 and 6 months. Participants who do not appear at the 3 months follow-up after two reminders will be contacted again 6 months from inclusion, if they do not express a will to not participate anymore. The dropout rate is estimated to be approximately 30% in the full study. We hope to have a lower dropout rate and aim to get enough material for an adequate power calculation. We hope to shed some light on the idea that mindfulness interventions can reinforce satisfaction to physical activity and give an increased adherence to PAP in inactive primary health care patients.

Trial status

The pilot study commenced enrolment on 1 September 2016, and by 21 August 2018 we had recruited 88 participants. The plan is to enrol 90 patients. A total of 54 participants have passed the 6 months follow-up, and there are 12 confirmed dropouts.

Additional file

Additional file 1: SPIRIT 2013 checklist: recommended items to address in a clinical trial protocol and related documents. (PDF 116 kb)

Ethics approval and consent to participate
All parts of the study will be conducted according to the principles of the 1964 Helsinki Declaration, and the study has been approved by the Regional Ethical Review Board in Lund (registration number 2016/404). The study is registered at ClinicalTrials.gov, registration number NCT02869854. Written informed consent will be obtained from all patients entering the study before inclusion. We intend to extend the pilot study if it shows positive results. In this case, we will apply for new ethical approval. The study adheres to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines, and the SPIRIT checklist is provided as Additional file 1. The results will be reported following the Consolidated Standards of Reporting Trials (CONSORT) guidelines.

Competing interests
The authors declare that they have no competing interests.

Publisher's Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Author details
[1]Lund University/Region Skåne, Centre for Primary Health Care Research, Jan Waldenströmsgata 35, Skåne University Hospital Malmö, University Hospital, SE-205 02 Malmö, Sweden. [2]Department of Health Sciences, Division of Physiotherapy, Lund University, Baravägen 3, SE-221 00 Lund, Sweden.

References
1. Ding D, Lawson KD, Kolbe-Alexander TL, Finkelstein EA, Katzmarzyk PT, van Mechelen W, Pratt M. The economic burden of physical inactivity: a global analysis of major non-communicable diseases. Lancet. 2016;388(10051):1311–24.
2. Reis RS, Salvo D, Ogilvie D, Lambert EV, Goenka S, Brownson RC. Scaling up physical activity interventions worldwide: stepping up to larger and smarter approaches to get people moving. Lancet. 2016;388(10051):1337–48.
3. Maher JP, Doerksen SE, Elavsky S, Hyde AL, Pincus AL, Ram N, Conroy DE. A daily analysis of physical activity and satisfaction with life in emerging adults. Health Psychol. 2013;32(6):647–56.
4. Gerovasili V, Agaku IT, Vardavas CI, Filippidis FT. Levels of physical activity among adults 18–64 years old in 28 European countries. Prev Med. 2015;81:87–91.
5. Loyen A, Van Hecke L, Verloigne M, Hendriksen I, Lakerveld J, Steene-Johannessen J, Vuillemin A, Koster A, Donnelly A, Ekelund U, et al. Variation in population levels of physical activity in European adults according to cross-European studies: a systematic literature review within DEDIPAC. Int J Behav Nutr Phys Act. 2016;13:72.
6. 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.
7. Leijon ME, Bendtsen P, Nilsen P, Festin K, Stahle A. Does a physical activity referral scheme improve the physical activity among routine primary health care patients? Scand J Med Sci Sports. 2009;19(5):627–36.
8. Morgan O. Approaches to increase physical activity: reviewing the evidence for exercise-referral schemes. Public Health. 2005;119(5):361–70.
9. Orrow G, Kinmonth AL, Sanderson S, Sutton S. Effectiveness of physical activity promotion based in primary care: systematic review and meta-analysis of randomised controlled trials. BMJ. 2012;344:e1389.
10. Hertel AW, Finch EA, Kelly KM, King C, Lando H, Linde JA, Jeffery RW, Rothman AJ. The impact of expectations and satisfaction on the initiation and maintenance of smoking cessation: an experimental test. Health Psychol. 2008;27(3 Suppl):S197–206.
11. Baldwin AS, Rothman AJ, Jeffery RW. Satisfaction with weight loss: examining the longitudinal covariation between people's weight-loss-related outcomes and experiences and their satisfaction. Ann Behav Med. 2009;38(3):213–24.
12. Williams DM, Lewis BA, Dunsiger S, Whiteley JA, Papandonatos GD, Napolitano MA, Bock BC, Ciccolo JT, Marcus BH. Comparing psychosocial predictors of physical activity adoption and maintenance. Ann Behav Med. 2008;36(2):186–94.
13. Baldwin AS, Baldwin SA, Loehr VG, Kangas JL, Frierson GM. Elucidating satisfaction with physical activity: an examination of the day-to-day associations between experiences with physical activity and satisfaction during physical activity initiation. Psychol Health. 2013;28(12):1424–41.
14. Tsafou KE, De Ridder DT, van Ee R, Lacroix JP. Mindfulness and satisfaction in physical activity: a cross-sectional study in the Dutch population. J Health Psychol. 2016;21(9):1817–27.
15. Brown KW, Ryan RM. The benefits of being present: mindfulness and its role in psychological well-being. J Pers Soc Psychol. 2003;84(4):822–48.
16. Kabat-Zinn J. Wherever you go, there you are: mindfulness meditation for everyday life. London: Piatkus; 1994.
17. Bishop SR, Lau M, Shapiro S, Carlson L, Anderson ND, Carmody J, Segal ZV, Abbey S, Speca M, Velting D, et al. Mindfulness: a proposed operational definition. Clin Psychol Sci Pract. 2004;11(3):230–41.
18. Ruffault A, Bernier M, Juge N, Fournier JF. Mindfulness may moderate the relationship between intrinsic motivation and physical activity: a cross-sectional study. Mindfulness. 2016;7(2):445–52.
19. Mothes H, Klaperski S, Seelig H, Schmidt S, Fuchs R. Regular aerobic exercise increases dispositional mindfulness in men: a randomized controlled trial. Ment Health and Phys Act. 2014;7:111–9.
20. Sundquist J, Lilja A, Palmer K, Memon AA, Wang X, Johansson LM, Sundquist K. Mindfulness group therapy in primary care patients with depression, anxiety and stress and adjustment disorders: randomised controlled trial. Br J Psychiatry. 2015;206(2):128–35.
21. Pocock SJ, Simon R. Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. Biometrics. 1975;31(1):103–15.
22. Lilja JL, Frodi-Lundgren A, Hanse JJ, Josefsson T, Lundh LG, Skold C, Hansen E, Broberg AG. Five Facets Mindfulness Questionnaire—reliability and factor structure: a Swedish version. Cogn Behav Ther. 2011;40(4):291–303.
23. Bastien CH, Vallieres A, Morin CM. Validation of the Insomnia Severity Index as an outcome measure for insomnia research. Sleep Med. 2001;2(4):297–307.
24. King AC, Haskell WL, Taylor CB, Kraemer HC, DeBusk RF. Group- vs home-based exercise training in ealthy older men and women. A community-based clinical trial. Jama. 1991;266(11):1535–1542.
25. Gluck TM, Maercker A. A randomized controlled pilot study of a brief web-based mindfulness training. BMC Psychiatry. 2011;11:175.
26. Leijon ME, Bendtsen P, Stahle A, Ekberg K, Festin K, Nilsen P. Factors associated with patients self-reported adherence to prescribed physical activity in routine primary health care. BMC Fam Pract. 2010;11:38.
27. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, McQueen M, Budaj A, Pais P, Varigos J, 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.
28. Nymberg P, Drevenhorn E. Patients' experience of a nurse-led lifestyle clinic at a Swedish health centre. Scand J Caring Sci. 2016;30(2):349–55.
29. Leijon ME, Stark-Ekman D, Nilsen P, Ekberg K, Walter L, Stahle A, Bendtsen P. Is there a demand for physical activity interventions provided by the health care sector? Findings from a population survey. BMC Public Health. 2010;10:34.
30. Leijon ME, Bendtsen P, Nilsen P, Ekberg K, Stahle A. Physical activity referrals in Swedish primary health care - prescriber and patient characteristics, reasons for prescriptions, and prescribed activities. BMC Health Serv Res. 2008;8:201.

Paper III

RESEARCH   **Open Access**

Effect of mindfulness on physical activity in primary healthcare patients: a randomised controlled trial pilot study

Peter Nymberg[1,2]* , Susanna Calling[1,2], Emelie Stenman[1,2], Karolina Palmér[1], Eva Ekvall Hansson[3], Kristina Sundquist[1,2], Jan Sundquist[1,2] and Bengt Zöller[1,2]

Abstract: Increased physical activity can have health benefits among inactive individuals. In Sweden, the healthcare system uses physical activity on prescription (PAP) to motivate patients to increase their physical activity level. Mindfulness may further heighten the internal motivation to engage in physical activity. However, previous research has not demonstrated clear evidence of such an association.

Aim: Examine the feasibility of the study design as a preparation for a full-scale study, and examine the differences, between three interventions, in change over time in physical activity levels and in related variables.

Method: Comparison between three different interventions in an ordinary primary health care setting: PAP, mindfulness, and a combination of PAP and mindfulness. Physical activity was measured with self-report and ACTi Graph GT1X activity monitor. Statistical analysis was performed with a mixed-effect model to account for repeated observations and estimate differences both within groups and between groups at 3- and 6-months follow-up.

Results: Between September 2016 and December 2018, a total of 88 participants were randomised into three groups. The total dropout rate was 20.4%, the attendance rate to the mindfulness courses (52% > 6 times) and the web-based mindfulness training (8% > 800 min) was low according to the stated feasibility criteria. Eleven participants were excluded from analysis due to low activity monitor wear time. Neither the activity monitor data nor self-reported physical activity showed any significant differences between the groups.

Conclusion: The study design needs adjustment for the mindfulness intervention design before a fully scaled study can be conducted. A combination of PAP and mindfulness may increase physical activity and self-rated health more than PAP or mindfulness alone.

Trial registration: ClinicalTrials.gov, registration number NCT02869854. Regional Ethical Review Board in Lund registration number 2016/404.

Key messages regarding feasibility

- What uncertainties existed regarding the feasibility? An association between being mindful and physical activity level has been suggested. However, it is still unknown whether it is mindfulness that leads to

increased physical activity or vice versa. Physical activity on prescription (PAP) is an established method for promoting physical activity and we wanted to examine the feasibility of comparing sedentary primary care patients that were randomized into PAP, mindfulness training or a combination of both. Feasibility was estimated by measuring adherence, recruitment rate and number of dropouts. The results will be used to design a

---

* Correspondence: peter.nymberg@med.lu.se
[1]Center for Primary Health Care Research, Region Skåne, Lund, Sweden
[2]Department of Clinical Sciences, Malmö Lund University, Lund, Sweden
Full list of author information is available at the end of the article

larger scale randomized controlled study with a proper power calculation.

- What are the key findings?
  Of 136 eligible patients, a total of 88 volunteered to participate thus resulting in a recruitment rate of 64.7%. Only 52% of the patients, which were randomized to only mindfulness or the combination group, attended the mindfulness course, and only 8% did 800 min or more of the associated web-based training. Besides the low dropout rate of 20.4%, there was loss to follow-up regarding accelerometer data. There was a tendency towards an increased effect of PAP on physical activity level when mindfulness training was added.

- What are the implications of the feasibility findings for design of the main study?
  The mindfulness intervention needs to be remoulded to improve compliance in a larger-scale study. The type of accelerometers used (hip/wrist worn) also need to be considered to minimize the loss of objective physical activity data to follow-up.

Introduction

A lifestyle with an adequate amount of physical activity can decrease the risk of both somatic and mental illness [1–4]. Although people in northern Europe are generally physically active [5], they report more sedentary time than their southern European counterparts [6]. A study regarding sedentary behaviour, among 50- to 64-year-old Swedish adults, showed that only 7.1% of the 948 participants fulfilled the World Health Organization's (WHO) recommendation for physical activity [7]. Making individuals change their physical activity behaviour is an ongoing challenge. A systematic review estimated that 12 sedentary adults need to be treated with a physical activity promotion intervention in order to make one of them achieve the recommended physical activity level at one year follow-up [8]. In Sweden, the health care services recommend the use of physical activity on prescription (PAP) as a complementary treatment to motivate patients to increase their physical activity level; the treatment addresses both primary and secondary prevention of illness. The written prescription in the Swedish PAP model can be a proposal for an activity or an extensive solution with a supportive structure depending on the patient's needs and level of motivation. The Swedish PAP model has been associated with up to 60% increased activity levels, but the effect has not shown sustainability over time [9–11]. In some of the studies complemented with pedometers, the most common way to report the effect of PAP has been by self-reported measures [11]. To the authors' knowledge, only one study has used activity monitors to measure the

effect of the Swedish PAP model [12] and it failed to show significantly increased levels of moderate to vigorous physical activity (MVPA).

Research has demonstrated that satisfaction can play a crucial role in changing a behaviour such as physical activity [13], smoking cessation [14] or weight loss [15]. It has been suggested that satisfaction can be increased both by the awareness in a specific positive situation and by the reduction of negative thoughts, e.g. about physical activity [16]; something which may be facilitated by practising mindfulness [17]. All people have a varying intrinsic, albeit modifiable, trait to be aware of the present moment—dispositional mindfulness [18]. Mindfulness can be exerted as sitting meditation but also as an approach to everyday life [19]. The practice of mindfulness might give the individual an orientation toward one's experiences in the present moment [20]. Being mindful in a specific situation and, in addition, satisfaction are suggested to be consecutive mediators for the path between possessing a dispositional tendency to be mindful and physical activity [17]. This might explain why self-reported mindfulness seems to mediate the relationship between intrinsic motivation and the physical activity level [21]. In addition, mindfulness has been shown to increase pain tolerance [22, 23]. In other words, practising mindfulness can make it easier to experience satisfaction and mitigate discomfort connected with physical activity and, in this way, support the change from a physically inactive to a physically active behaviour. Recent research has shown a lower decrease—if mindfulness was being practised—in physical activity due to seasonal decline compared with a control group [24]. A review, which was conducted to investigate the role of mindfulness in physical behaviour changes, revealed that mindfulness interventions influenced the physical activity outcomes in a positive direction in a majority of the 40 included studies [25]. Mindfulness-based interventions were suggested to be successful if they targeted psychological factors related to increased physical activity, such as self-efficacy and acceptance. Even if mindfulness correlates with factors that can influence the increase of physical activity, it has been shown that regular exercise can lead to an increased dispositional mindfulness [26]. Thus, mindfulness may have an important role to play concerning motivation by reinforcing satisfaction with physical activity [25].

Aim

To examine the feasibility of the study design as a preparation for a full-scale study.

The intervention outcome was differences of change in physical activity level over time between three groups: PAP, mindfulness and a combination containing both

PAP and mindfulness, in a population with insufficient self-reported levels of physical activity.

Methods/design
Participants
This was a pilot-study preparing for a larger-scale randomised trial. For detailed information about the study, we refer to the published study-protocol [27]. Men and women, which could speak fluent Swedish and were aged between 40 and 65 years, visiting their primary healthcare clinic for any reason were asked to rate their physical activity level. Those with a self-rated physical activity level below the WHO recommendations were asked to participate in the study. We excluded from the study (within 6 weeks before study entry) those with dementia, severe mental disorder, unstable untreated angina pectoris or myocardial infarction. The criteria of physical activity were defined according to the WHO guidelines, in which the lower limits for sufficient activity are set to 150 min per week of moderate intensity or 75 min per week of high intensity exercise.

Setting
The pilot study involved three primary health care centres, recruited on voluntary basis, in the county of Scania in southern Sweden. In total, there are approximately 164 primary health care centres in the county. Scania has approximately 1.2 million residents and about 400, 000 of these are aged between 40 and 65 years old.

Outcome measures
Feasibility criteria for a successful design

1. Recruitment rate more than 30% [28].
2. Dropout rate of less than 30%.
3. Compliance to the mindfulness course: ≥ 70% of those randomised to any of the groups containing mindfulness should participate in at least 75% of the mindfulness meetings [29].
4. Web-based practice for at least 20 min 5 days per week (800 min) by 70% of patients randomised to any group containing mindfulness [30].

Intervention outcome
All measurements and questionnaires were collected at baseline, after 3 months and after 6 months.

The primary intervention outcome was changed level of physical activity, self-reported and measured by ACTi Graph GT1X activity monitors. We used the same definitions and methods to handle the activity monitor data as in previously published research regarding physical activity [7, 12]. Activity monitor data were divided into sedentary, light physical activity (LIPA) and moderate to vigorous physical activity (MVPA). The participants were instructed to wear the activity monitor every day for a week before randomisation, at 3 months and at 6 months follow-up. Wear time was defined by subtracting non-wear time from 24 h. Non-wear time was defined as at least 60 consecutive minutes with no movement (0 counts per minute), with allowance for maximum 2 min of counts between 0 and 100 [7, 31]. We considered ≥ 600 min wear time per day for at least 4 days to be valid compliance [7, 12]. Due to a small sample size, we did not demand four consecutive days with valid wear time, and we did not differ between weekdays and weekends. Average was expressed as total counts divided by wear time in minutes per day (counts per minute) and averaged over worn days. Registrations below 100 counts per minute were determined as being sedentary [7, 12, 32]. 100–2019 counts per minute were considered as LIPA and > 2020 counts per minute as MVPA [7, 12]. The results are presented as percentage sedentary, LIPA or MVPA per valid day and averaged over the number of valid days [12] self-reported daily activity (e.g. gardening, slow walks, biking) was measured by an eight-step scale (0 = 0 min/week, 7 ≥ 300 min/week), and self-reported leisure time activity (e.g. running, football) was measured by a seven-step scale (0 = 0 min/week, 6 ≥ 200 min/week).

Secondary intervention outcomes

1. Change in self-rated health (SRH) between baseline and follow-up, measured with a five-step scale (1–5): very poor, poor, fair, good or very good.
2. Change in blood pressure, weight or serum lipids between baseline and follow-up.
3. Change in insomnia problems as measured with insomnia severity index (ISI) [33] between baseline and follow-up.
4. Change in mindfulness measured with five facets of mindfulness questionnaire (FFMQ) [34] between baseline and follow-up.

Interventions
Participants in the PAP group were prescribed Swedish PAP [9, 35], which is the recommended treatment for physically inactive patients and adjusted to each patient's individual preferences. The participants in the mindfulness group received a two-hour long mindfulness group session once a week for 8 weeks and were instructed to practise mindfulness for 20 min every day. The mindfulness course [29] was based on both Mindfulness-Based Stress Reduction (MBSR) and Mindfulness-Based Cognitive Therapy (MBCT) and included meditative exercises. The patients received instructions concerning the daily mindfulness practice with meditative exercises via a web-based program [29]. The instructions included breathing technique and body scan. The combination

Nymberg *et al. Pilot and Feasibility Studies*   (2021) 7:70

Page 4 of 14

Table 1 Patient characteristics for all participants at baseline, 3 months and 6 months

Randomisation group	PAP	Mindfulness	Combination
Baseline *n* (%)			
Women	22 (76)	22 (73)	20 (69)
Men	7 (24)	8 (27)	9 (31)
3 months			
Women	18 (72)	19 (79)	17 (65)
Men	4 (18)	5 (21)	9 (35)
6 months			
Women	17 (77)	19 (79)	15 (63)
Men	5 (23)	5 (21)	9 (37)
Age median (range)			
Baseline	54 (42–65)	53 (41–65)	54 (43–64)
Percent of time in sedentary time[a] mean (SD, range)			
Baseline	66.2 (6.7, 78.2–50.2)	65.5 (9.2, 80.3–43.7)	66.7 (8.8, 80.0–47.2)
3 months follow-up	66.7 (6.7, 78.3–56.3)	65.5 (7.5, 78.9–51.3)	67.5 (8.1, 81.2–51.3)
6 months follow-up	65.0 (6.8, 73.6–50.0)	65.9 (9.4,81.0–36.2)	64.0 (9.1,78.4–45.6)
Percent of time in LIPA[a] mean (SD, range)			
Baseline	30.9 (6.2, 45.5–20.9)	31.7 (8.2, 50.0–19.0)	30.3 (8.0, 49.2–18.8)
3 months follow-up	31.0 (6.0, 42.6–21.5)	31.8 (6.9, 47.8–19.9)	28.6 (7.1,44.5–16.3)
6 months follow-up	32.0 (5.8, 43.8–23.1)	31.6 (9.0, 58.4–17.0)	32.8 (8.9, 50.7–18.6)
Percent of time in MVPA[a] median (SD, range)			
Baseline	2.6 (0.18, 6.3–0.5)	2.3 (0.02, 9.1–0.1)	2.4 (0.02, 9.0–0.2)
3 months follow-up	2.4 (0.14, 5.0–0.2)	1.9. (0.02, 12.7–0.3)	3.4 (0.03, 11.1–0.1)
6 months follow-up	2.6 (0.02, 6.2–0.4)	1.9 (0.02, 9.0–0.2)	2.7 (0.02, 9.2–0.3)
Weight kg median (range)			
Baseline	92.0 (67–121)	86.8 (57–132)	81.5 (62–146)
3 months follow-up	*87.9 (67–111)*	81.2 (56–135)	83 (62–143)
6 months follow-up	*91.3 (59–110)*	83.0 (60–139)	80.2 (60–145)
BMI kg/m^2 median (range)			
Baseline	31.4 (21–43)	29.9 (22–44)	28.5 (21–40)
3 months follow-up	30.0 (21–42)	28.6 (22–43)	28.2 (21–39)
6 months follow-up	29.4 (21–42)	28.6 (23–44)	27.9 (23–39)
Total cholesterol mmol/L mean (SD, range)			
Baseline	5.20 (1.05, 7.7–2.9)	5.63 (0.87, 7.3–4.1)	5.41 (1.04, 7.4–3.4)
3 months follow-up	4.99 (1.02, 6.9–3.3)	5.35 (0.96, 7.1–3.8)	5.12 (1.00, 7–3.1)
6 months follow-up	5.08 (1.23, 7.1–3)	5.72 (1.09, 7.7–3.6)	5.08 (1.19, 7.6–2.9)
Low-density cholesterol mmol/L mean (SD, range)			
Baseline	3.43 (1.04, 5.9–1.3)	3.80 (0.92, 5.7–2)	3.66 (0.94, 5.5–2)
3 months follow-up	3.15 (0.97, 5.1–1.7)	3.51 (1.02, 5.8–2)	3.52 (1.01, 5.3–1.7)
6 months follow-up	3.26 (1.14, 5.3–1.5)	3.83 (1.04, 5.9–1.9)	3.57 (1.15, 6.3–1.6)
High-density cholesterol mmol/L median (SD, range)			
Baseline	1.5 (0.54, 3.1–0.9)	1.4 (0.52, 2.9–0.5)	1.5 (0.36, 2.4–1.0)
3 months follow-up	1.5 (0.56, 2.7–0.9)	1.5 (0.60, 2.8–0.4)	1.5 (0.32, 2.1–0.9)
6 months follow-up	1.5 (0.55, 2.7–0.9)	1.4 (0.64, 2.9–0.4)	1.4 (0.27, 2.3–0.9)

Table 1 Patient characteristics for all participants at baseline, 3 months and 6 months *(Continued)*

Randomisation group	PAP	Mindfulness	Combination
Triglycerides mmol/L median (SD, range)			
Baseline	1.2 (0.97, 5.1–0.4)	1.6 (1.14, 5.2–0.5)	1.4 (0.70, 3.2–0.7)
3 months follow-up	1.25 (0.68, 3–0.5)	1.4 (1.13,4.9–0.8)	1.5 (0.62, 3.2–0.7)
6 months follow-up	1.3 (0.87, 4.1–0.4)	1.65(1.18, 5.8–0.5)	1.4 (0.60,3.2–0.7)
Systolic blood pressure mmHg median (range)			
Baseline	130 (110–160)	120 (80–160)	130 (100–155)
3 months follow-up	127 (100–150)	122 (104–165)	120 (106–145)
6 months follow-up	126 (90–160)	129 (102–150)	131 (108–160)
Diastolic blood pressure mmHg median (range)			
Baseline	80 (64–100)	80 (60–100)	80 (60–90)
3 months follow-up	80 (60–90)	80 (68–99)	78(60–90)
6 months follow-up	80 (60–100)	80 (60–100)	80 (60–100)
Leisure-time activity[b] (min = 0, max = 6) median (range)			
Baseline	1 (1–5)	2 (1–3)	2 (1–4)
3 months follow-up	3 (1–6)	2 (1–3)	3 (1–6)
6 months follow-up	3 (1–6)	2 (1–6)	3 (1–6)
Daily activity[b](min = 0, max = 7) median (range)			
Baseline	3 (1–7)	3 (1–6)	4 (1–5)
3 months follow-up	5 (2–7)	3 (1–7)	5 (1–6)
6 months follow-up	5 (3–7)	4 (1–7)	5 (1–7)
ISI[b] (min = 0, max = 28) median (range)			
Baseline	8 (0–24)	11 (0–27)	10 (0–21)
3 months follow-up	7 (0–20)	11 (0–27)	9 (0–27)
6 months follow-up	6 (0–18)	13 (0–25)	9 (0–18)
FFMQ[b] (min = 29, max = 145) mean (SD)			
Baseline	105.5 (80–129)	105.6 (82–128)	100.6 (89–114)
3 months follow-up	107.6 (90–125)	103.5 (81–129)	103.8 (92–117)
6 months follow-up	106.8 (85–132)	102.5 (83–127)	102.8 (87–116)
SRH[b] (min = 1 max = 5) median (range)			
Baseline	3 (1–4)	3 (2–5)	3 (2–5)
3 months follow-up	3 (1–4)	3 (2–5)	4 (2–5)
6 months follow-up	4 (1–4)	4 (2–5)	4 (2–5)

[a]Percentage of sedentary time and time in different intensity of physical activity per valid day and averaged over the number of valid days, activity monitor measured

[b]Self-reported measurements. Data are presented as mean values and standard deviation (SD) for normally distributed variables, and as median and range for variables with skewed distribution and variables based on nominal scales. *LIPA* light physical activity, *MVPA* moderate to vigorous physical activity, *ISI* insomnia severity index, *FFMQ* five facets of mindfulness questionnaire, *SRH* self-rated health

group comprised both PAP and mindfulness, meaning an individually adjusted PAP combined with an addition of the same mindfulness course as in the mindfulness group.

Statistics

Power calculation
Sample size of a full-scale intervention study with a follow-up time at 12 months was calculated on a 1:1 relationship between two groups (PAP and combination), and estimated to $n = 375$ in each group, based on a power analysis with 5% significant-level and a power of 80%. Drop out was expected to be 30%. The calculation was based on other studies with self-reported compliance to PAP as an outcome measure, where 50% of the participants followed the recommendation on physical activity from the PAP. We estimated an increase from

50% to 62.5% of self-reported adherence to PAP [36]. The pilot-study sample size is based on the assumed patient flow and due to a limited project budget [37]. In this pilot study, we aimed to include approximately 30 participants in each arm, which is in concordance to a general flat rule, using a minimum of 30 participants to be able for estimating a parameter [38].

Randomisation

The randomisation to the three intervention groups (PAP, combination, mindfulness) was stratified by the patients' age and sex, with a total of three age groups: 40–49, 50–59 and 60–65 years. The randomisation was done by a minimisation method with a random element, as minimisation variables in the randomisation we used age and sex to get the groups as equal as possible [39]. The randomisation was done in the statistical programme STATA version 15 (StataCorp, College Station, TX).

Statistical methods

The intervention effect on changes in outcome measures was examined by analysing average group differences (PAP, combination, mindfulness) in baseline score and change in each outcome between baseline and 3 and 6 months follow-up using a linear mixed-effects model. Each model included the time variable and group as indicator variables, and an interaction between time and group to estimate treatment differences in change over time, adjusted for baseline measures and taking the correlation between repeated measurements into account. We did not adjust for the minimisation variables in the analysis. Statistical analyses were done using STATA version 15 (StataCorp, College Station, TX).

Results

Recruitment

For the period 1st of September 2016 until the 31st of December 2018, a total of 136 eligible patients were asked to participate in the study and 88 were included. The median age among the participants in the PAP-group was 54 years; in the combination-group, it was 54 years and in the mindfulness-group it was 53 years (Table 1). Among those who declined participation, the average age was 56 years (29 women and 19 men) (Fig. 1).

Fulfilment of feasibility criteria

We monitored several feasibility criteria to evaluate the suitability of the study design [27]. If all the feasibility criteria were fulfilled, the main study was considered possible to conduct without further changes in the protocol. If the criteria were not fulfilled, the protocol was considered to need adjustment, and if the criteria were fulfilled to less than 70% it was considered not

possible to carry on with a full-scale study in the current form.

A recruitment rate of 30% was considered to be successful; 88 (64.7%) of all the 136 patients eligible for the study, who were asked to participate, accepted.

A dropout rate of less than 30% was considered successful: during the study, there were a total of 20.4% (5 men, 13 women) dropouts with an average age of 52.

A successful attendance rate to the mindfulness course was set to ≥ 70%, of those randomised to any of the groups containing mindfulness should participate in at least 75% of the mindfulness meetings. There were 52% (n = 15 in the mindfulness group, n = 16 in the combination) who attended six times or more to the meetings.

Seventy percent of patients randomised to any group containing mindfulness should practise mindfulness for at least 20 min with the web-based application at least 5 days a week (a total of 800 min or more). The mean time spent in web-based training, during the study, was 184.69 min with a standard deviation of 330.93 min (minimum 0 and max 1300 min). Only 8% (seven persons) did 800 min or more (n = 4 in the mindfulness group, n = 3 in the combination).

Secondary outcome

The patients were randomised into the three groups, PAP (n = 29), combination (n = 29), or mindfulness (n = 30). In the PAP-group, there were 24.1% (2 men, 5 women) dropouts with an average age of 53 years. In the mindfulness group, there were 20% (3 men, 3 women) dropouts with an average age of 50 years. The combination group had 17.2% (5 women) of dropouts with an average age of 53 years (Fig. 1). Two dropouts were due to illness, five persons did not show up at follow-ups even after two reminders. Six individuals did not want to continue without giving any reason, four people cited lack of time and one person moved and could not continue participating in the study (Fig. 1). After exclusion of those with fewer than four valid activity monitor wear days, n = 26 in the PAP-, n = 26 in the combination- and n = 25 in the mindfulness group remained. The wear time with activity monitors differed between 0 and 12 days. There were no significant baseline differences between the dropouts and the remaining participants (see Additional file 1). There were over 80% of the participants at each time-point who wore the accelerometer for 4 days or more (see Additional file 2)

In the sensitivity analyses, we analysed the data in several different ways, both with one valid activity monitor day (see Additional file 3), and four valid activity monitor days (Table 2), with similar results.
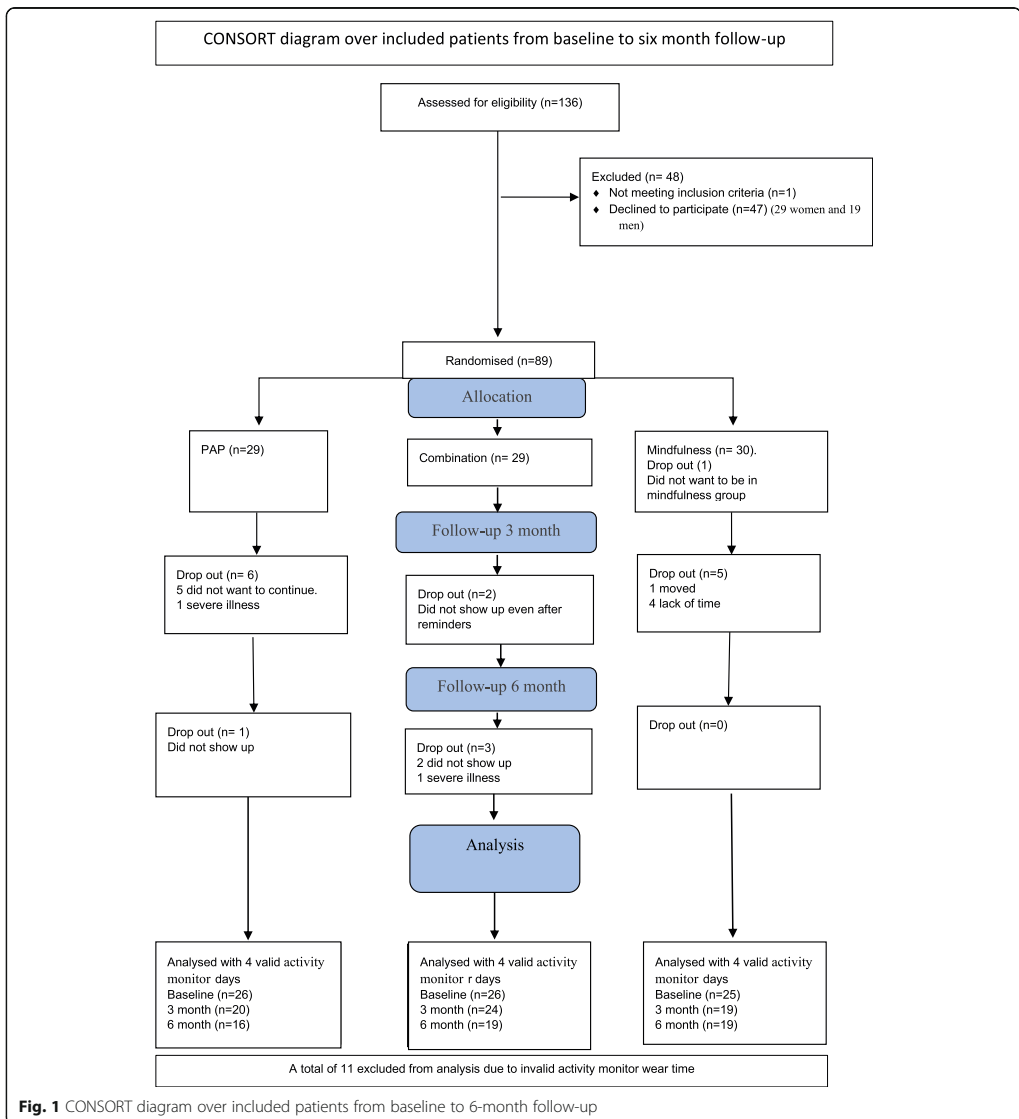
Fig. 1 CONSORT diagram over included patients from baseline to 6-month follow-up

Intervention outcomes

Differences in change between intervention groups

Regarding group differences in alteration over time, percentage sedentary time showed only small and non-significant indications of differences between the three groups (95% CI – 1.74 ; 0.22; Table 2; Fig. 2). The same signals of suggested alteration were seen in differences regarding change in mean percentage of time in LIPA

(95% CI – 0.35; 1.47; Table 2; Fig. 3) between the three groups. There was only a minor alteration in mean percentage of time in MVPA, and no differences in change between the three groups (95% CI – 0.19; 0.48; Table 2; Fig. 4).

Self-reported leisure time activity increased in all groups but did not show any overall difference in change (95% CI – 0.03; 0.49) between the groups (Table 2; Fig. 5). The

Table 2 Intercept (adjusted baseline value) and changes from baseline to 3 and 6 months in the three groups using mixed-effect models. Individuals with at least 4 valid days (600 min activity monitor wear time per day)

Outcome	Adjusted baseline value	Change from baseline to 3 months	Change from baseline to 6 months	Overall mean difference between groups over time[d] (95% CI)
Sedentary [a] (percentage)				− 0.75 (− 1.74 ; 0.22)
PAP	66.3	0.5	0.2	
Mindfulness	65.8	1.1	1.4	
Combination	66.4	− 0.2	− 2.8	
LIPA [a] (percentage)				0.56 (− 0.35 ; 1.47)
PAP	30.9	0.01	0.03	
Mindfulness	31.7	− 1.1	− 1.3	
Combination	30.5	− 0.9	2.4	
MVPA[a] (percentage)				0.15 (− 0.19 ; 0.48)
PAP	2.9	− 0.5	− 0.2	
Mindfulness	2.5	− 0.1	− 0.1	
Combination	3.1	1.0	0.2	
Leisure time activity (1–6) [b]				0.23 (− 0.03; 0.49)
PAP	1.67	1.11	1.18	
Mindfulness	1.88	− 0.05	0.59	
Combination	1.81	1.62	2.00	
Daily activity (1–7) [b]				1.93 (− 0.22; 0.26)
PAP	3.40	1.21	1.09	
Mindfulness	3.63	0.39	0.77	
Combination	3.42	1.16	1.14	
Weight (kg)				0.18 (− 0.32; 0.68)
PAP	90.9	− 1.8	− 2.4	
Mindfulness	85.3	− 0. 13	− 0.6	
Combination	84.8	− 0.74	− 1.6	
SRH[c] (1–5)				0.8 (− 0.06; 0.21)
PAP	3.2	0.2	0.2	
Mindfulness	3.3	0.3	0.3	
Combination	3.3	0.4	0.5	

[a]Percentage of mean time measured by activity monitor, *LIPA* light physical activity, *MVPA* moderate to vigorous physical activity
[b]Self-reported measurements: leisure time activity on a scale from 0 = 0 min per week, 6 ≥ 120 min/week Daily activity on a scale 0 = 0 min per week, 7 ≥ 300 min per week
[c]Self-rated health
[d]interaction between all three groups and timepoints

same pattern was seen in self-reported daily activity, with no difference in change between groups over time (95% CI − 0.22; 0.26; Table 2; Fig. 6).

Secondary intervention outcomes
The analysis did not show any indications of large differences in change between groups regarding SRH (Table 2; Fig. 7), ISI (see Additional file 4) or FFMQ (see Additional file 4. The indicated alteration of blood pressure (see Additional file 4), weight (Table 2; figure see Additional file 5), BMI (see Additional file 4 for table, see Additional file 6 for figure) and blood lipids (see Additional file 4) did

not suggest any statistically significant differences in change over time between the three groups.

Discussion
Main findings of the study
Feasibility
Since only two of the four feasibility criteria were fulfilled, major changes in the mindfulness intervention design should be considered before we can conduct a full study. Even if the drop-out rate was acceptable, according to the feasibility criteria, a sample size calculation to a full study must consider the loss to follow-up.
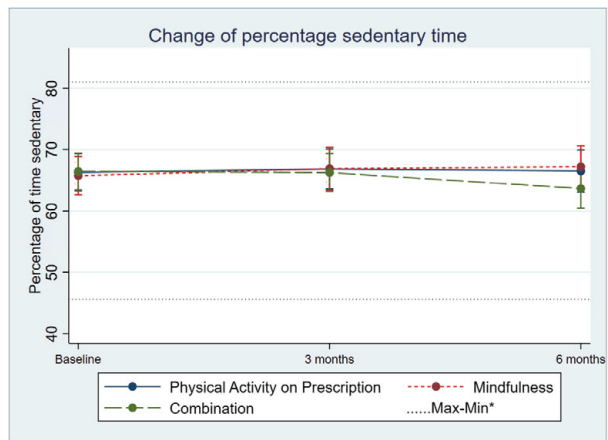
Fig. 2 Change in percentage sedentary in 1 the three groups over time. Differences between and within the groups are estimated by a mixed-effect model. *Maximum and minimum value of all observations

In the present pilot-study, there were 11 participants excluded from analysis due to low activity monitor wear time. In an attempt to increase the adherence to wear the activity monitor, participants should perhaps get the opportunity to choose the type of activity monitor, i.e. worn by the hip or by the wrist. However, using activity monitors measuring from different places of the body (wrist or hip) may affect the ability to conduct a correct analysis of the measurements. In a modified study, comparing the three groups (PAP, mindfulness and combination), we may need to adjust what time of day the mindfulness courses are arranged, and perhaps adjust the length of time for the daily exercise. Spending 20 min per day doing mindfulness may be hard to fit into one's ordinary schedule and even more difficult to combine with increased physical activity.

Intervention outcome

The main intervention outcome was to compare differences in change over time of physical activity level
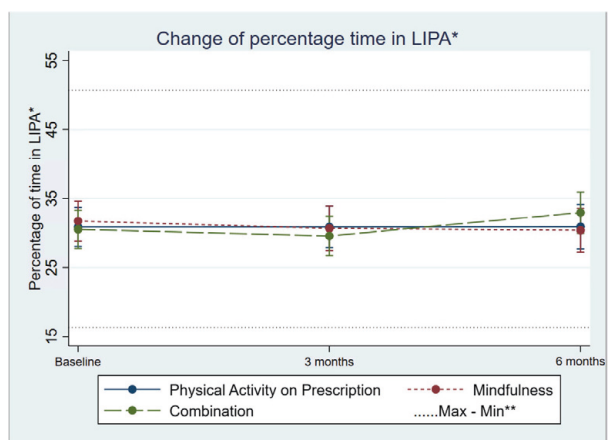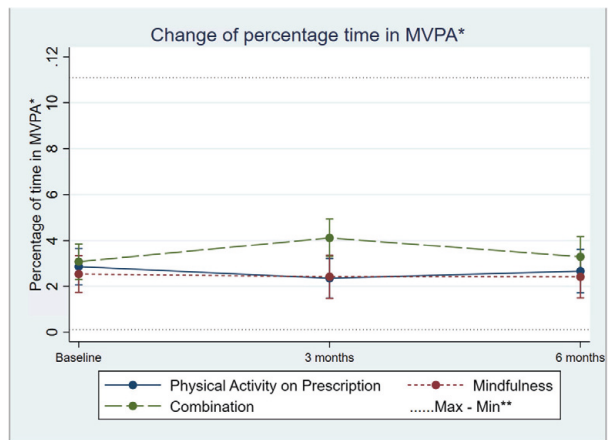

Fig. 3 Change in percentage light physical activity (LIPA), in the three groups over time. Differences between and within the groups are estimated by a mixed-effect model. **Maximum and minimum value of all observations

Fig. 4 Change in percentage moderate to vigorous physical activity (MVPA), in the three groups over time. Differences between and within the groups are estimated by a mixed-effect model. *Moderate to vigorus physical activity. **Maximum and minimum value of all observations

between three groups: PAP, mindfulness and a combination containing both PAP and mindfulness. The results showed no differences between the groups regarding activity monitor measurements. Neither were there any differences in change of self-reported activity. We did not find any indications that mindfulness alone increased the percentage of time in physical activity, according to the data from the activity monitors. The combination seemed to increase LIPA, self-reported physical activity and SRH more than the other

interventions in within-group comparisons, even if there was no difference in change between the groups.

Even if PAP and the combination seemed to increase self-reported physical activity more than mindfulness alone, the changes were small. The 2.4 percentage points increase of LIPA at 6 months compared with baseline in the combination group represented about 15 min more per day on average, based on a count with an activity monitor wear time of 600 min per day. Nevertheless, the small decrease in sedentary behaviour and increase in
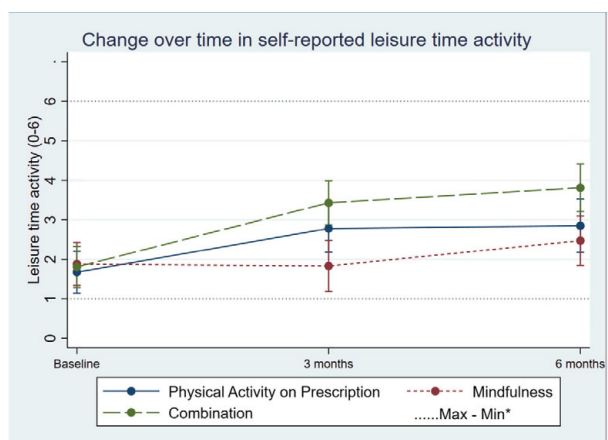

Fig. 5 Change in units of self-reported leisuretime activity in the three groups over time. Differences between and within the groups are estimated by a mixed-effect model. *Maximum and minimum value of all observations
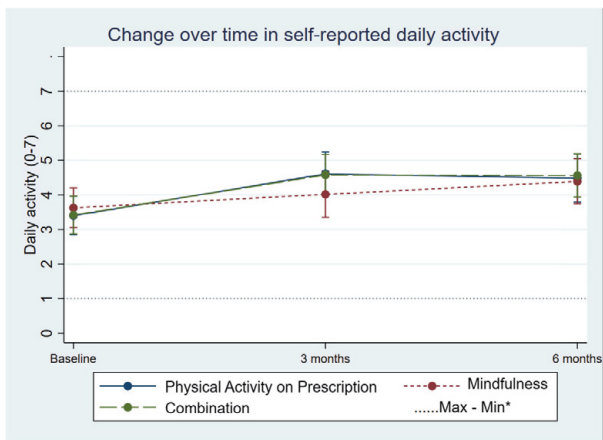
Fig. 6 Change in units of self reported daily activity in the three groups over time. Differences between and within the groups are estimated by a mixed-effect model. *Maximum and minimum value of all observations

physical activity during the short follow-up can be seen as a positive outcome. With a longer follow-up, we may have seen a bigger change, considering that it is a major life challenge to change from being mostly sedentary to being more active. On the other hand, previous research has indicated that the self-reported effect of PAP is most pronounced during the first 3 months [36].

The discrepancy between the activity monitoring and the self-reported activity seen in the present study may be explained by low physical activity in the week when

measured with an activity monitor, and thus not representative for the physical activity in an average week for the patient. However, it is a known fact that the self-reported activity level increases more over time compared to objective measurements, especially with repeated measurements [31, 40]. PAP is, at present, in the Swedish healthcare system, the only accessible tool for motivating inactive people to increase their overall activity level. PAP has indeed shown effectiveness according to Onerup et al. [11], but the findings in our study could
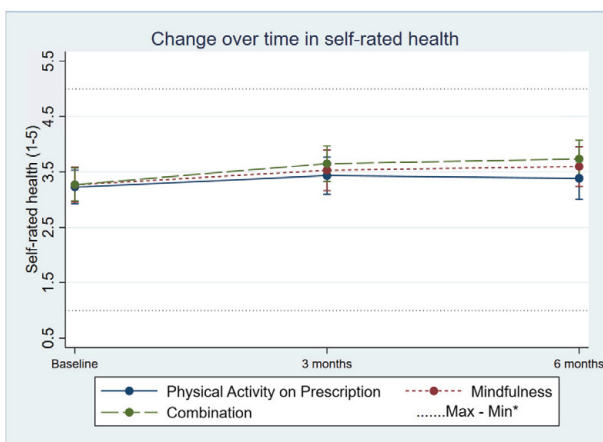

Fig. 7 Change in units of self-rated health in the three groups over time. Differences between and within the groups are estimated by a mixed-effect model. *Maximum and minimum value of all observations

not confirm this effect with activity monitors. Our results are consistent with a previous study [12], which failed to detect any significantly increased MVPA among patients who received PAP. Since using PAP in healthcare is time-consuming, it is important to examine if the method is effective. Therefore, larger controlled trials with PAP and activity monitors are needed in order to evaluate the effect. To obtain the participants' true activity pattern, it is important to complete self-reported activity with activity monitors, perhaps over several weeks.

A noteworthy finding is the increase in units of SRH within all groups (Table 2; Fig. 7), which can depend on the same fact as other self-reported values that increase with repeated measurements [31, 40]. Both mindfulness [18, 41] and physical activity [42, 43] have been associated with increased levels of SRH; thus, this may be an explanation of the increased SHR in all groups.

We invited all patients, who reported themselves as physically inactive regardless of diagnosis, thus representing a usual cohort of patients in a Swedish primary health care clinic. It is possible that the results might have been different if we included a more specified group of patients. Hence, our results suggest that mindfulness may have a motivating effect. However, the small tendencies need to be confirmed by a larger study.

Strengths

This is one of the first randomised trials with the Swedish PAP model and mindfulness aiming at a broad primary health care population with objective measurements of physical activity. According to the baseline activity monitor data, we managed to capture the most sedentary patients with a low percentage of physical activity, which was the aim. The high recruitment rate and low dropout rate indicates that patients are interested in participating in these types of studies, and thus a marker for the possibility to obtain enough participants in a bigger study with the same aim as the present study.

Limitations

This pilot study is underpowered compared with the planned full study, which can be the reason that we failed to show significant differences between the groups regarding the activity monitor measured results. The limitation with the ACTi Graph GT1X activity monitor is that it only measures cardiorespiratory training and not other physical activities such as weightlifting, biking and swimming. Low compliance in wearing the activity monitor also compromised the reliability of the results (Table 2).

Conclusions

The study design needs adjustment for the mindfulness intervention design before a fully scaled study can be conducted. The combination of PAP and mindfulness may increase physical activity and SRH more than PAP or mindfulness alone.

Abbreviations

PAP: Physical activity on prescription; WHO: World Health Organization; ISI: Insomnia Severity Index; FFMQ: Five Facets of Mindfulness Questionnaire; LIPA: Light physical activity; MVPA: Moderate to vigorous physical activityMBSRMindfulness-Based Stress Reduction; MBCT: Mindfulness-Based Cognitive Therapy

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s40814-021-00810-6.

Additional file 1. Table presenting differences in baseline values between dropouts and those who continued.

Additional file 2. Table presenting number of days with activity monitor wear time of 600 minutes or more per day.

Additional file 3. Intercept (adjusted baseline value) and changes from baseline to 3 and 6 months in the three groups using mixed effect models. Containing individuals with at least 1 valid day (600 minutes activity monitor wear time per day).

Additional file 4. Intercept (adjusted baseline value) and changes from baseline to 3 and 6 months in the three groups using mixed effect models. Containing analysis of BMI, total cholesterol, low-density cholesterol, high-density cholesterol, triglycerides, diastolic- and systolic blood pressure, insomnia severity scale and five facets of mindfulness questionnaire. Individuals with at least 4 valid days (600 minutes activity monitor wear time per day).

Additional file 5. Change in kilograms in the three groups over time. Differences between and within the groups are estimated by a mixed effect model.

Additional file 6. Change in BMI (kg/m^2) in the three groups over time. Differences between and within the groups are estimated by a mixed effect model.

Declarations

Ethics approval and consent to participate
All parts of the study were conducted according to the principles of the 1964 Helsinki Declaration and the study was approved by the Regional Ethical Review Board in Lund (registration number 2016/404). The study is registered at ClinicalTrials.gov, registration number NCT02869854, registration date 17 August 2016, https://clinicaltrials.gov/ct2/show/NCT02869854. Written informed consent was obtained from all patients entering the study before inclusion.

Consent for publication
Not applicable

Competing interests
The authors declare that they have no competing interests.

Author details
[1]Center for Primary Health Care Research, Region Skåne, Lund, Sweden. [2]Department of Clinical Sciences, Malmö Lund University, Lund, Sweden. [3]Department of Health Sciences/Physiotherapy, Lund University, Lund, Sweden.

References
1. 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.
2. Maher JP, Doerksen SE, Elavsky S, Hyde AL, Pincus AL, Ram N, et al. A daily analysis of physical activity and satisfaction with life in emerging adults. Health Psychol. 2013;32(6):647–56.
3. Penedo FJ, Dahn JR. Exercise and well-being: a review of mental and physical health benefits associated with physical activity. Curr Opin Psychiatry. 2005;18(2):189–93.
4. Zschucke E, Gaudlitz K, Strohle A. Exercise and physical activity in mental disorders: clinical and experimental evidence. J Prev Med Public Health. 2013;46(Suppl 1):S12–21.
5. Gerovasili V, Agaku IT, Vardavas CI, Filippidis FT. Levels of physical activity among adults 18-64 years old in 28 European countries. Prev Med. 2015;81: 87–91.
6. Loyen A, Van Hecke L, Verloigne M, Hendriksen I, Lakerveld J, Steene-Johannessen J, et al. Variation in population levels of physical activity in European adults according to cross-European studies: a systematic literature review within DEDIPAC. Int J Behav Nutr Phys Act. 2016;13:72.
7. 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.
8. Orrow G, Kinmonth AL, Sanderson S, Sutton S. Effectiveness of physical activity promotion based in primary care: systematic review and meta-analysis of randomised controlled trials. BMJ. 2012;344:e1389.
9. Leijon ME, Bendtsen P, Nilsen P, Festin K, Stahle A. Does a physical activity referral scheme improve the physical activity among routine primary health care patients? Scand J Med Sci Sports. 2009;19(5):627–36.
10. Morgan O. Approaches to increase physical activity: reviewing the evidence for exercise-referral schemes. Public Health. 2005;119(5):361–70.
11. Onerup A, Arvidsson D, Blomqvist A, Daxberg EL, Jivegard L, Jonsdottir IH, et al. Physical activity on prescription in accordance with the Swedish model increases physical activity: a systematic review. Br J Sports Med. 2019; 53(6):383–8. https://doi.org/10.1136/bjsports-2018-099598. Epub 2018 Nov 9.
12. Moren C, Welmer AK, Hagstromer M, Karlsson E, Sommerfeld DK. The Effects of "Physical Activity on Prescription" in Persons With Transient Ischemic Attack: A Randomized Controlled Study. J Neurol Phys Ther. 2016;40(3):176–83.
13. Williams DM, Lewis BA, Dunsiger S, Whiteley JA, Papandonatos GD, Napolitano MA, et al. Comparing psychosocial predictors of physical activity adoption and maintenance. Ann Behav Med. 2008;36(2):186–94.
14. Hertel AW, Finch EA, Kelly KM, King C, Lando H, Linde JA, et al. The impact of expectations and satisfaction on the initiation and maintenance of smoking cessation: an experimental test. Health Psychol. 2008;27(3 Suppl): S197–206.
15. Baldwin AS, Rothman AJ, Jeffery RW. Satisfaction with weight loss: examining the longitudinal covariation between people's weight-loss-related outcomes and experiences and their satisfaction. Ann Behav Med. 2009;38(3):213–24.
16. Baldwin AS, Baldwin SA, Loehr VG, Kangas JL, Frierson GM. Elucidating satisfaction with physical activity: an examination of the day-to-day associations between experiences with physical activity and satisfaction during physical activity initiation. Psychol Health. 2013;28(12):1424–41.
17. Tsafou KE, De Ridder DT, van Ee R, Lacroix JP. Mindfulness and satisfaction in physical activity: A cross-sectional study in the Dutch population. J Health Psychol. 2016;21(9):1817–27.
18. Brown KW, Ryan RM. The benefits of being present: mindfulness and its role in psychological well-being. J Pers Soc Psychol. 2003;84(4):822–48.
19. Kabat-Zinn J. Wherever you go, there you are : mindfulness meditation for everyday life. London: Piatkus; 1994. p. xix. 1 , 281
20. Bishop SR, Lau M, Shapiro S, Carlson L, Anderson ND, Carmody J, et al. Mindfulness: A proposed operational definition. Clin Psychol Sci Pract. 2004; 11(3):230–41.
21. Ruffault A, Bernier M, Juge N, Fournier JF. Mindfulness May Moderate the Relationship Between Intrinsic Motivation and Physical Activity: A Cross-Sectional Study. Mindfulness. 2016;7(2):445–52.
22. Zeidan F, Baumgartner JN, Coghill RC. The neural mechanisms of mindfulness-based pain relief: a functional magnetic resonance imaging-based review and primer. Pain Rep. 2019;4(4):e759.
23. Mohammed WA, Pappous A, Sharma D. Effect of Mindfulness Based Stress Reduction (MBSR) in Increasing Pain Tolerance and Improving the Mental Health of Injured Athletes. Front Psychol. 2018;9:722.
24. Meyer JD, Torres ER, Grabow ML, Zgierska AE, Teng HY, Coe CL, et al. Benefits of 8-wk Mindfulness-based Stress Reduction or Aerobic Training on Seasonal Declines in Physical Activity. Med Sci Sports Exerc. 2018;50(9): 1850–8.
25. Schneider J, Malinowski P, Watson PM, Lattimore P. The role of mindfulness in physical activity: a systematic review. Obes Rev. 2019;20(3):448–63.
26. Mothes H, Klaperski S, Seelig H, Schmidt S, Fuchs R. Regular aerobic exercise increases dispositional mindfulness in men: a randomized controlled trial. Mental Health Phys Activity. 2014;7:111–9.
27. Nymberg P, Ekvall Hansson E, Stenman E, Calling S, Sundquist K, Sundquist J, et al. Pilot study on increased adherence to physical activity on prescription (PAP) through mindfulness: study protocol. Trials. 2018;19(1):563.
28. King AC, Haskell WL, Taylor CB, Kraemer HC, DeBusk RF. Group- vs home-based exercise training in healthy older men and women. A community-based clinical trial. Jama. 1991;266(11):1535–42.
29. Sundquist J, Lilja A, Palmer K, Memon AA, Wang X, Johansson LM, et al. Mindfulness group therapy in primary care patients with depression, anxiety and stress and adjustment disorders: randomised controlled trial. Br J Psychiatry. 2015;206(2):128–35.
30. Gluck TM, Maercker A. A randomized controlled pilot study of a brief web-based mindfulness training. BMC psychiatry. 2011;11:175.
31. Troiano RP, Berrigan D, Dodd KW, Masse LC, Tilert T, McDowell M. Physical activity in the United States measured by accelerometer. Med Sci Sports Exerc. 2008;40(1):181–8.
32. Matthews CE, Chen KY, Freedson PS, Buchowski MS, Beech BM, Pate RR, et al. Amount of time spent in sedentary behaviors in the United States, 2003-2004. Am J Epidemiol. 2008;167(7):875–81.
33. Dragioti E, Wiklund T, Alföldi P, Gerdle B. The Swedish version of the Insomnia Severity Index: Factor structure analysis and psychometric properties in chronic pain patients. Scand J Pain. 2016;9:22–7.
34. Lilja JL, Frodi-Lundgren A, Hanse JJ, Josefsson T, Lundh LG, Skold C, et al. Five Facets Mindfulness Questionnaire--reliability and factor structure: a Swedish version. Cogn Behav Ther. 2011;40(4):291–303.
35. folkhälsoinstitut S. FAR®: individanpassad skriftlig ordination av fysisk aktivitet. Öatersund: Statens folkhälsoinstitut; 2011.
36. Leijon ME, Bendtsen P, Stahle A, Ekberg K, Festin K, Nilsen P. Factors associated with patients self-reported adherence to prescribed physical activity in routine primary health care. BMC Fam Pract. 2010;11:38.

37.   Leon AC, Davis LL, Kraemer HC. The role and interpretation of pilot studies in clinical research. J Psychiatr Res. 2011;45(5):626–9.
38.   Browne RH. On the use of a pilot sample for sample size determination. Stat Med. 1995;14(17):1933–40.
39.   Pocock SJ, Simon R. Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. Biometrics. 1975;31(1):103–15.
40.   Forsen L, Loland NW, Vuillemin A, Chinapaw MJ, van Poppel MN, Mokkink LB, et al. Self-administered physical activity questionnaires for the elderly: a systematic review of measurement properties. Sports Med. 2010;40(7):601–23.
41.   Auty KM, Cope A, Liebling A. A systematic review and meta-analysis of yoga and mindfulness meditation in prison: effects on psychological well-being and behavioural functioning. Int J Offender Ther Comp Criminol. 2017;61(6): 689–710.
42.   Jepsen R, Dogisso TW, Dysvik E, Andersen JR, Natvig GK. A cross-sectional study of self-reported general health, lifestyle factors, and disease: the Hordaland Health Study. PeerJ. 2014;2:e609.
43.   Sodergren M, Sundquist J, Johansson SE, Sundquist K. Physical activity, exercise and self-rated health: a population-based study from Sweden. BMC Public Health. 2008;8:352.

Publisher's Note

Paper IV

Self-rated health and venous thromboembolism among middle-aged women: a population-based cohort study

Peter Nymberg[1] · Emelie Stenman[1] · Susanna Calling[1] · Jan Sundquist[1] · Kristina Sundquist[1] · Bengt Zöller[1]

Abstract

Venous thromboembolism (VTE) is one of the most common types of cardiovascular diseases (CVDs) and is associated with increased mortality-risk. Poor-self rated health (SHR) has been associated with elevated inflammatory markers and CVDs. However, little is known about as a predictor of incident VTE. To examine the association between self-rated health, lifestyle and incident VTE among middle-aged women. 6917 women aged 50–64 years, followed for 20 years in the Women's Health In the Lund Area (WHILA) study. After exclusion of those who medicated with anticoagulants, were living in nursing homes or suffered from cancer, stroke, VTE or CHD before baseline, a cohort of 5626 women remained. Cox regression was used to analyse the relationship between self-rated health and time to VTE, censored for any of the previous mentioned diseases during follow-up. Data were collected by questionnaires, physical examinations and Swedish registers. In total, 220 women were affected by VTE corresponding to an incidence rate of 3.9 per 1000 person-years. Adjustment for self-rated health did not significantly predict incident VTE, and neither did any of the lifestyle-related habits (e.g. physical activity and dietary habits including alcohol consumption), besides smoking. This study supports previous results with varicose veins and waist circumference as strong predictors of VTE. Poor self-rated health does not seem to be a valid predictor of VTE. Among lifestyle-related parameters, smoking was significantly associated with risk of VTE. We could also confirm the effect of the other already known risk factors.

Keywords Venous thromboembolism · Varicose veins · Prevention · Self-rated health · Women

Highlights

- Poor self-rated health does not seem to be useful as a predictor of VTE.
- Varicose veins, smoking and waist circumference showed a association with risk of incident VTE.
- Other lifestyle associated behaviors do not seem to have any strong effect on risk of incident VTE.
- Prevention in those with varicose veins can be important.

✉ Peter Nymberg
peter.nymberg@med.lu.se

1   Region Skåne, Center for Primary Health Care Research, Jan Waldenströms gata 35, Skåne University Hospital Malmö, University Hospital, Lund University, Jan Waldenströms gata 35, 205 02 Malmö, Sweden

Introduction

The incidence of venous thromboembolism (VTE) exceeds 1 per 1000 persons-years. More than 200,000 new cases of VTE occur in the United States each year, with a corresponding mortality rate of about 30% within 30 days [1]. Among the survivors, 30% develop recurrent VTE [1] and there is an increased mortality risk up to 8 years after the first thrombosis, [1, 2]. Provoked VTE occurs in relation to identifiable risk factors, such as pregnancy, bone fractures, or surgery [1, 3]. Unprovoked VTE shares some known risk factors with other cardiovascular diseases (CVDs) such as obesity, smoking [4–7] and sleep-apnoea [8–10]. Other risk factors for VTE include high body height [11] and varicose veins [1, 12–15]. Varicose veins and VTE has been suggested to share familial susceptibility [16] and a genetic component of the familial clustering has been found for VTE, which makes heredity a potent risk factor [17, 18] The risk of VTE also increases with age, especially among men aged > 50 years [19, 20].

Poor self-rated health (SRH) has been associated with elevated serum inflammatory markers [21] and has also been shown to be a predictor of depression [22], stroke [23] and other CVDs [24], diabetes [25], lung-cancer [26] and all-cause mortality [27, 28]. Thus, SRH is usually considered a valid and efficient measure of mental and physical health, especially in women [29], although there is still a need to identify the validity limits of SRH for prediction of illness and mortality [30].

A previous study investigating associations between the first VTE-episode and work-related disability showed a reduced risk for VTE when adjusted for good SRH. The authors discussed a possible association between low SRH and an elevated risk of incident VTE [31].

To the authors' knowledge, there are no previously published studies regarding the longitudinal association between SRH and incident VTE later in life among middle aged women. If such an association exists, it can be useful to include in risk assessment for incident VTE. In addition, as women often are more affected by poor SRH, they are particularly suitable for a study of a possible longitudinal association with VTE. SRH is also better at predicting somatic diseases in women than in men [29].

The main aim of this cohort study was to examine the association between baseline SRH in middle-aged women (50–64 years) and incident VTE. The second aim was to analyze the association between lifestyle habits, i.e. physical activity, diet, smoking, alcohol consumption and VTE.

Method

Study population

The Women's Health In the Lund Area (WHILA) is a prospective cohort study in southern Sweden. Sample characteristics, data collection and clinical definitions for WHILA have been described previously [32]. Briefly, the study invited all women (n = 10,766) living in any of the five municipalities around the city of Lund by December 1995, and who were born between December 1935 and December 1945, to a screening procedure that took place from December 1995 until February 2000. A total of 6917 women consented to participate in the study, of which 6916 had complete datasets. The study population was identified through a population registry that comprised all inhabitants. A health-screening program included laboratory examinations, blood samples and a basic baseline questionnaire that was mailed along with the invitation and collected in conjunction with the first examination. The baseline questionnaire included 104 questions concerning education, household, working status, perimenopausal status, medical history, drug

treatment, personal and family history of diabetes or cardiovascular disease (myocardial infarction, stroke, deep venous thrombosis or hypertension in parents or siblings with an event before the age of 60 years). It also contained questions about habits like smoking, alcohol consumption, physical activity, general dietary habits, quality of life, as well as subjective physical and mental symptoms. This questionnaire was a composite of several pre-existing and validated questionnaires.

Measurements and definitions

Information about diseases and medication was obtained from the Swedish Hospital Discharge Register, the Hospital Outpatient Register and the Swedish Cancer Register in addition to self-reported data from WHILA study baseline questionnaires and measurements. The definition of VTE includes the following ICD-codes; ICD-7; 463-466, 583.00 334.40, 334,50 682, 684. ICD-8 321, 450-453, 671 (not 671,00) 673,9. ICD-9; 437G, 451-453, 415B, 416 W, 671C, D, E, F, X, 673C, 639G. ICD-10; I26, I636, I676, I80-82, O222-225, O229, O870-873, O879, O882, O082, O087. We excluded from our analyses participants with stroke (ICD-7; 331, 332, 334.09. ICD-8; 430-434, 436. ICD-9; 430-434, 436. ICD-10; I60-I64 (not I63.6).) or CVD (ICD-7; 420. ICD-8; 410-414. ICD-9; 410-414. ICD-10; I20-I25.), cancer (ICD-7; 140–209) or VTE before baseline, both self-reported and by register. In addition, we excluded women who were living in nursing homes or similar at baseline or medicated with warfarin, dicumarol, or antithrombin (ATC-code; B01AA03, B01AA01, and B01AB02). After exclusion, 5626 women remained (Table 1).

SRH was assessed only at baseline from a single question, in which the participants were asked to rate their perceived health in a 7-graded Likert scale from "Very poor" to "Excellent, could not be better" (1 = very poor, 7 = Excellent). In this study, we classified alternative 1–4 as poor SRH and 5–7 as good SRH. Weight and height were rounded off to the nearest 0.1 kg and 0.5 cm. Body mass index (BMI) was calculated as weight in kilograms divided by height in

Table 1 Number of exclusions and reason for exclusion both by register and self-reported

Total included	6916
No. of living in nursing homes or similar	190
No. of prevalent VTE diagnoses	321
No. of prevalent CHD	104
No. of prevalent stroke	79
No. of prevalent cancer	716
No. of anticoagulant (not ASA)	30
Remaining after exclusion	5626

The same person can occur in several groups

meters squared (kg/m^2). BMI was considered as underweight if BMI was < 18.5, normal weight if BMI = 18.5–24.9, overweight if BMI = 25.0–29.9, obese class I if BMI = 30.0–34.9, obese class II if BMI = 35.0–39.9 and obese class III if BMI was > 39.9. BMI class II and class III were put together due to small groups. Subjects were categorized as current smokers (i.e. those who smoked regularly or occasionally) or non-smokers (i.e. former smokers and never smokers). Low physical activity, i.e. less than 30 min vigorous activity 5 days a week [33] was defined as the lower tertile among the answering alternatives (i.e. very low and low) (Table 2).

Diet was defined by questions about intake of fat, sugar, fruit or dietary fiber. If high intake of sugar or fat or low intake of dietary fiber or fruit were reported, we considered the diet as less healthy [32]. If low intake of sugar and fat and high intake of fruit and dietary fiber was reported, we considered the diet as healthy. Education was categorized into three classes; comprehensive school (9 years), upper secondary school (12 years), and university degree. In the multivariate models model, we used waist circumference instead of BMI; this was due to previous studies showing waist circumference as a valid predictor for VTE [34].

Statistical analysis

P-values were calculated with two-sided Student's t test for continuous variables and with χ^2-test for dichotomized variables. Cox proportional hazards regression was used to analyze the relationship between SRH and time to VTE. Hazard ratios (HR) with 95% confidence intervals (CI) were calculated. Those who were diagnosed with hypertension or varicose veins after baseline were censored, as well as those who were affected by stroke, CHD or cancer diagnosis before the VTE during the follow-up time. In the multivariate model, only confounding variables that showed a significantly increased incident VTE-risk in the univariate test were included. In the first model, we adjusted for age. In the second model, we added physical activity, smoking, and waist circumference. In the third model, we completed with varicose veins and hypertension. The proportional hazard assumption was tested with Schoenfeld residuals [35, 36]. Analyses were performed in STATA 14.1.

To test the robustness of the results, we investigated the cohort in different ways, at first without excluding prevalent disease (VTE, CHD, stroke, cancer) before baseline. At the next step, we excluded all the patients both prevalent (VTE, CHD, stroke, cancer) and censured incident (CHD, stroke cancer) before VTE. We got almost the same result regardless of which we excluded, there were only small differences in hazard ratios and levels of significance. When the proportional hazard assumption test was significant in the two first models thus meaning the effect were not constant and changed over the follow-up time. We investigated the material by breaking it up into shorter time span of 5 years (0–5, 5–10, 10–15, 15–20). All the different time spans showed proportionality except for the time span 0-5 years. When excluding only the 0–5 year to get broader time span, there was proportionality in all models between 5 and 20 years follow up.

Results

During a follow-up time of 20.4 years, a total of 220 women were affected by VTE. The sum of the follow-up time was 85,645.836 years corresponding to a VTE incidence rate of 3.9 (95% CI 2.26–2.94) per 1000 person-years. There appeared to be statistically significant differences between women that were affected by incident VTE versus women that were not affected, i.e. differences in weight, height, waist-hip ratio, smoking, high and low activity level, dietary fiber, overall diet, SRH and varicose veins.

Women with incident VTE were on average taller, heavier and had a greater waist-hip ratio than those without incident VTE. There was a higher percentage of smokers and women with a low physical active level in the group with incident VTE. Regarding diet, there were only significant differences between the groups in dietary fiber intake and overall diet. Among women with incident VTE, a higher percentage had a low intake of dietary fiber and a less healthy overall diet. In the incident VTE-group there was also a greater number with varicose veins. The SRH differed significantly between the groups with a higher percentage rating their health as poor in the incident VTE

Table 2 Definition of activity groups

Very-high	Hard training several times per week
High	> 3 h of running, skiing swimming
Middle-high	1–2 h/week with running, swimming, gymnastics, 4 h light physical activity/week and total responsibility of household tasks
Middle	Light activity 2–4 h/week walking, gardening dancing. Head of responsibility of household tasks
Low	Mostly sitting, light household work or gardening but not head of responsibility of the tasks
Very low	Hardly any physical activity at all

Table 3 Univariate Cox regression with those variables which differed with a statistical significance in the baseline characteristics

	Hazard ratio	95% CI	p	n	Failures
Age	1.05	1.00–1.10	.033	5626	220
Marital				5606	220
Unmarried	1.22	.75–1.99	.42		
Married	Ref				
Divorced	.99	.68–1.44	.961		
Widowed	1.10	.60–2.03	.757		
Education				5523	214
7–9 years	1.42	.99–2.00	.052		
10–12 years	Ref				
> 12 years	1.18	.86–1.63	.294		
Physical activity				5539	216
Very low	2.27	.92–5.59	.075		
Low	1.56	.88–2.74	.125		
Middle	Ref				
Middle-high	1.02	.76–1.35	.914		
High	.76	.33–1.73	.508		
Very high	6.34E−16	0	1.000		
Activity high/low	1.70	1.07–2.74	.026	5539	216
Current smoker	1.43	1.04–1.96	.028	5533	216
Former smoker	.92	.65–1.32	.656		
(Ref non-smoker)					
Height	1.03	1.00–1.06	.013	5482	213
Waist circumference	1.03	1.02–1.04	0	5041	198
Alcohol				5398	211
0g/w	1.26	.93–1.70	.135		
0–12g/w	Ref				
> 12g/w < 130g/w	.77	.48–1.22	.265		
Sugar				5580	216
Daily	1.70	.97–3.01	.066		
Sometimes	Ref				
Avoids	1.05	.78–1.42	.748		
Fat in food				5353	205
Much	1.46	.89–2.40	.132		
Careful with	Ref				
Avoids	1.11	.82–1.49	.509		
Fiber				5547	215
Low intake	1.16	.42–3.13	.771		
Regularly	Ref				
Much	.77	.58–1.03	.078		
Fruit				5594	219
Rarely	1	.76–1.32	.985		
Regularly	Ref				
Much	.76	.24–2.41	.644		
Portion size				5240	198
Big	.81	.45–1.46	.481		
Regular	Ref				
Small	.95	.70–1.30	.753		
Diet	1.38	.94–2.00	.095	5612	220
Family history				5477	216
Yes	1.38	.93–2.06	.112		
No	Ref				

Table 3 (continued)

	Hazard ratio	95% CI	p	n	Failures
Don't know	1.11	.68–1.83	.675		
Acetylsalicylic	1.52	.38–6.12	.554	5626	221
Diabetes	.62	.28–1.41	.261	5577	221
Hypertension	1.17	.67–2.05	.581	5626	220
Varicose veins	2.7	1.47–4.95	.001	5626	220
Self-rated health				5529	216
1. Very poor	2.78	.99–7.80	.051		
2.	.71	.25–1.99	.516		
3.	1.15	.66–2.01	.628		
4.	Ref				
5.	.83	.55–1.25	.374		
6.	.7	.47–1.05	.087		
7. Excellent	.54	.34–.85	.008		
Poor self-rated health	1.51	1.13–2.03	.005	5529	216

Self-rated health was dichotomized into the variable Poor self-rated health, with group 1–4 as poor self-rated health and 5–7 as good self-rated health

group and this was even more obvious when categorizing into poor or good SRH.

An unadjusted Cox regression analysis was conducted (Table 3) with the aim to investigate if there were any significant associations between the variables that fell out with significance in the former analysis and incident VTE.

Despite a relatively small difference in mean age between the groups at baseline, there was an increased risk for incident VTE for every year older at baseline (HR 1.05, 95% CI 1.00–1.10, p = 0.033). Cox regression analysis of SRH did not show any significant association with VTE-risk except for a decreased risk for those who rated their health as excellent (HR 0.54, CI 0.34–0.85, p = 0.008). When dichotomizing SRH into poor and good respectively, there was an increased risk for those who rated their health as poor (hazard ratio 1.51, CI 1.13–2.03, p = 0.005). When we dichotomized the variable physical activity, there was an increased incident VTE-risk for the low group (HR 1.70, CI 1.07–2.74, p = 0.026). Smoking at baseline was associated with a 43% increased risk of incident VTE (HR 1.43, CI 1.04–1.96, p = 0.028), smokers who had quit smoking at least one month before inclusion had a non-significant decreased risk of incident VTE (0.92, 0.65–1.32, p = 656). Waist circumference and varicose veins were associated with an increased risk as well (HR 1.03, CI 1.02–1.04, p = 0.000 and HR 2.70, CI 2.47–4.95, p = 0.001 respectively). Knowledge about family history of VTE (parents or siblings) was not associated with increased incident VTE-risk (HR 1.38, CI 0.93–2.06, p = 0.112). There was a non-significant trend towards an association between unhealthy diet and risk of incident VTE (HR 1.38, CI 0.44–2.00, p = 0.095). There was no significant association between hypertension before baseline and incident VTE (HR1.17, CI. 0.67–2.05, p = 0.581).

When the Cox regression results were adjusted for age (Table 4), model 1 showed a 51% increased risk for incident VTE if SRH was poor (HR 1.51, CI 1.12-2.02 p = 0.006). When we adjusted for lifestyle-related variables; physical activity, smoking, former smoking and waist circumference in model 2, the association between poor SRH and increased risk of incident VTE decreased to 16% and was not significant (HR 1.16, CI 0.84–1.61 p = 0.370). Even if low physical activity was associated with a significantly increased risk of incident VTE in the unadjusted model, this association was reduced and not significant when adjusting for other variables (HR 1.19, CI 0.62–2.04, p = 0.526). In model 3, adjusting for varicose veins and hypertension, the association between SRH and risk of incident VTE increased to 18% (HR 1.18, CI 0.85–1.65 p = 0.315). Even though the increased risk of age remained, it was not statistically significant in any of the models. In model 3, only the well-known risk factors had significant effect; smoking (HR 1.44, CI 1.02–2.03, p = 0.037), waist circumference (HR 1.03, CI 1.02–1.04, p = 0.000) and varicose veins (HR 2.60 CI 1.40–4.80, p = 0.002). When testing the proportional hazards assumptions for model 1, the global test was significant (p = 0.0390), which means that the hazards were not proportional over time. The second and third model showed proportional hazards (p = 0.1290, p = 0.1872) in the global test.

Discussion

This is, to our knowledge, the first study that examines SRH as a predictor of incident VTE among middle-aged women in a well-defined cohort. In the multivariate model 3, there was a tendency towards an association between poor SRH and risk

Table 4 Multivariate Cox regression with the confounding variables that showed a significantly increased incident VTE-risk in the univariate test (Table 3)

Total (n)	5529	4806	4806
Failures (n)	216	188	188
Self-rated health (poor/good)	1.51	1.16	1.18
CI	1.12–2.02	.84–1.61	.85–1.65
p	.006	.37	.315
Age	1.05	1.03	1.03
CI	1.00–1.09	.98–1.08	.98–1.08
p	.048	.193	.200
Physical activity (low/high)		1.19	.88
CI		.69–2.04	.65–1.19
p		.526	.421
Current smoker*		1.44	1.44
CI		1.02–2.03	1.02–2.03
p		.037	.037
Former smoker*		.89	.90
CI		.61–1.30	.62–1.32
p		.549	.588
Waist circumference		1.03	1.03
CI		1.02–1.04	1.02–1.04
p		0	0
Varicose veins (yes/no)			2.6
CI			1.40–4.80
p			.002
Hypertension (yes/no)			1.12
CI			.63–1.98
p			.696
Proportional hazard assumption test	0.039	0.1290	0.1872

1st model adjusted by age and SRH. 2nd model adjusted by model 1, dichotomized level of physical activity, smoking former smoker and waist circumference. Third model is adjusted by model 2, varicose veins and hypertension

*Reference is non-smoker

of incident VTE, but it was not statistically significant. Our results confirmed, however, an association with the already known risk factors varicose veins, smoking and waist circumference [4, 11, 12, 34].

Braekkan et al. suggested that good SRH could attenuate the risk of VTE among people with a permanent work-related disability. They discussed the possibility that poor SRH may be affected by other diseases that in turn may increase the risk of VTE [31]. If poor SRH was a good predictor of incident VTE, we ought to have observed a significant association in this cohort comprising only women. However, we did not observe any significant association. The reason for this assumption is that SRH has been suggested to be better at predicting different diseases in women than in men [29]. What is notable, however, is that when we excluded those who got affected with VTE between baseline

and 5 years follow up, the risk for VTE among those with poor SRH was increased even in the fully adjusted model (HR 1.38, CI 0.96–1.99, p = 0.086). This shows that there may be a significant association during long time follow-up, but we were unable to capture it in this study. Regarding the association between varicose veins and VTE, Chang et al. [15] pointed out, that it is unknown whether this association is causal or represents a common set of risk factors. Considering the strong association, it can be argued for the need of preventive actions in people with varicose veins. This is especially pertinent since about 40% of adults are affected by varicose veins, and even a higher share among those who are obese and women with more than two pregnancies [37].

Low physical activity, i.e. less than 30 min vigorous activity 5 days a week [33], was significantly associated with increased risk of incident VTE in the unadjusted model, but not in the multivariate model 3 (Table 4). This may have been due to lack of power. There were no significant associations between self-reported intake of healthy or unhealthy food, alcohol, portion size and risk of incident VTE, which is consistent with previous studies among women, even if there have been suggested associations between unhealthy food, activity level and overweight/obesity [38, 39]. We neither noticed any significant associations between hypertension and risk for VTE, or differences between those who got affected with incident VTE and those who did not, regarding hypertension. Healthy food and a proper amount of physical activity do not seem to prevent VTE, but a healthy way of living may help to prevent a large waist circumference, which turned out to be associated with incident VTE in our study.

Why SRH is associated with arterial CVDs [24] but not with VTE in the present study may have several explanations. It is possible that the study participants changed their way of living after baseline measurements including questionnaires if they became more aware of their negative habits and changed them [40, 41]. Another explanation could be that many risk factors are different between VTE and arterial diseases [7], although some risk factors are shared. It is thus possible that SRH is a risk factor for arterial diseases but not for VTE. SRH may also be a weak risk factor for VTE and that a larger study might find a significant association with SRH, albeit weaker than for arterial disease. Finally, it is possible that SRH does not represent an additional risk factor for VTE once the other risk factors have been taken into account.

Strengths

This study is comprised of a well-defined cohort and it contained both self-reported and anthropometric values combined with information from registers. We censored participants who were affected by cancer or any cardiovascular

disease before the first VTE occurrence during follow-up and diagnosed hypertension and varicose veins after baseline in order to decrease the risk of influences on VTE-risk and poor SRH.

Limitations

A limitation is that SRH was only measured at baseline as SRH may change over time. However, a study by Sargent-Cox et al. reported that SRH in women remained relatively stable compared with increasing age, whereas men´s ratings tended to become more negative [42]. The study was performed in middle-aged women living in a certain area, which limits the generalizability to a wider context, e.g. to men and women in other ages than those enrolled. Due to a limited number of VTE events, we could not compare the occurrence of the different VTE-forms deep vein thrombosis (DVT) and pulmonary embolism (PE) between the groups. For the same reason, we could not perform any sub-analysis with provoked and unprovoked VTE.

Conclusions

 Poor self-rated health does not seem to be useful as a predictor of VTE. Lifestyle associated behaviors such as diet, alcohol consumption and physical activity or hypertension do not seem to have any strong effect on risk of incident VTE either. On the other hand, we could confirm the effect of already known risk factors; varicose veins, smoking and waist circumference. Varicose veins showed a strong association with risk of incident VTE, which suggests that it may be important to work preventively in people with varicose veins, for prevention of future VTE or other complications.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The WHILA study was approved by the Regional Ethics Committee at Lund University (LU 174-95) and the Data Registry Inspection in Stockholm. Informed consent was obtained from all participants.

References

1. Heit JA, Silverstein MD, Mohr DN, Petterson TM, Lohse CM, O'Fallon WM, Melton LJ 3rd (2001) The epidemiology of venous thromboembolism in the community. Thromb Haemost 86:452–463

2. Flinterman LE, van Hylckama Vlieg A, Cannegieter SC, Rosendaal FR (2012) Long-term survival in a large cohort of patients with venous thrombosis: incidence and predictors. PLoS Med 9:e1001155

3. Anderson FA, Spencer FA (2003) Risk factors for venous thromboembolism. Circulation 107:I9–I16

4. Holst AG, Jensen G, Prescott E (2010) Risk factors for venous thromboembolism. Circulation 121:1896–1903

5. Chiuve SE, Cook NR, Shay CM, Rexrode KM, Albert CM, Manson JE, Willett WC, Rimm EB (2014) Lifestyle-based prediction model for the prevention of CVD: the Healthy Heart Score. J Am Heart Assoc 3:e000954

6. Prandoni P (2017) Venous and arterial thrombosis: is there a link? Adv Exp Med Biol 906:273–283

7. Gregson J, Kaptoge S, Bolton T, Pennells L, Willeit P, Burgess S, Bell S, Sweeting M, Rimm EB, Kabrhel C et al (2019) Cardiovascular risk factors associated with venous thromboembolism. JAMA Cardiol 4:163–173

8. Lippi G, Mattiuzzi C, Franchini M (2015) Sleep apnea and venous thromboembolism. Thromb Haemost 114:958–963

9. Deflandre E, Degey S, Opsomer N, Brichant J-F, Joris J (2016) Obstructive sleep apnea and smoking as a risk factor for venous thromboembolism events: review of the literature on the common pathophysiological mechanisms. Obes Surg 26(3):640–648

10. Somers VK, White DP, Amin R, Abraham WT, Costa F, Culebras A, Daniels S, Floras JS, Hunt CE, Olson LJ et al (2008) Sleep apnea and cardiovascular disease. Circulation 118(10):1080–1111

11. Zoller B, Ji J, Sundquist J, Sundquist K (2017) Body height and incident risk of venous thromboembolism: a cosibling design. Circ Cardiovasc Genet 10(5):e001651

12. Ahti TM, Mäkivaara LA, Luukkaala T, Hakama M, Laurikka JO (2010) Lifestyle factors and varicose veins: does cross-sectional design result in underestimate of the risk? Phlebology 25(4):201–206

13. Muller-Buhl U, Leutgeb R, Engeser P, Achankeng EN, Szecsenyi J, Laux G (2012) Varicose veins are a risk factor for deep venous thrombosis in general practice patients. VASA Zeitschrift fur Gefasskrankheiten 41(5):360–365

14. Tiwari A, Lester W, Tang TY (2018) Varicose veins and deep venous thrombosis. JAMA 320(5):509–510

15. Chang SL, Huang YL, Lee MC, Hu S, Hsiao YC, Chang SW, Chang CJ, Chen PC (2018) Association of varicose veins with incident venous thromboembolism and peripheral artery disease. JAMA 319(8):807–817

16. Zoller B, Ji J, Sundquist J, Sundquist K (2014) Venous thromboembolism and varicose veins share familial susceptibility: a nationwide family study in Sweden. J Am Heart Assoc 3(4):e000850

17. Zoller B, Ohlsson H, Sundquist J, Sundquist K (2013) Familial risk of venous thromboembolism in first-, second- and third-degree relatives: a nationwide family study in Sweden. Thromb Haemost 109(3):458–463

18. Zoller B, Li X, Ohlsson H, Ji J, Sundquist J, Sundquist K (2015) Family history of venous thromboembolism as a risk factor and genetic research tool. Thromb Haemost 114(5):890–900

19. Roach REJ, Cannegieter SC, Lijfering WM (2014) Differential risks in men and women for first and recurrent venous thrombosis: the role of genes and environment. J Thromb Haemost 12(10):1593–1600

20. Zöller B, Li X, Sundquist J, Sundquist K (2011) Age- and gender-specific familial risks for venous thromboembolism. Circulation 124(9):1012–1020

21. Christian LM, Glaser R, Porter K, Malarkey WB, Beversdorf D, Kiecolt-Glaser JK (2011) Poorer self-rated health is associated with elevated inflammatory markers among older adults. Psychoneuroendocrinology 36(10):1495–1504

22. Badawi G, Page V, Smith KJ, Gariepy G, Malla A, Wang J, Boyer R, Strychar I, Lesage A, Schmitz N (2013) Self-rated health: a predictor for the three year incidence of major depression in individuals with Type II diabetes. J Affect Disord 145(1):100–105

23. Emmelin M, Weinehall L, Stegmayr B, Dahlgren L, Stenlund H, Wall S (2003) Self-rated ill-health strengthens the effect of biomedical risk factors in predicting stroke, especially for men—an incident case referent study. J Hypertens 21(5):887–896

24. van der Linde RM, Mavaddat N, Luben R, Brayne C, Simmons RK, Khaw KT, Kinmonth AL (2013) Self-rated health and cardiovascular disease incidence: results from a longitudinal population-based cohort in Norfolk, UK. PLoS ONE 8(6):e65290–e65290

25. Naess S, Eriksen J, Midthjell K, Tambs K (2005) Subjective well-being before and after the onset of diabetes mellitus: results of the Nord-Trondelag Health Study. J Diabetes Complicat 19(2):88–95

26. Riise HK, Riise T, Natvig GK, Daltveit AK (2014) Poor self-rated health associated with an increased risk of subsequent development of lung cancer. Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation 23(1):145–153

27. Sundquist J, Johansson SE (1997) Self reported poor health and low educational level predictors for mortality: a population based follow up study of 39,156 people in Sweden. J Epidemiol Community Health 51(1):35–40

28. DeSalvo KB, Fan VS, McDonell MB, Fihn SD (2005) Predicting mortality and healthcare utilization with a single question. Health Serv Res 40(4):1234–1246

29. Baćak V, Ólafsdóttir S (2017) Gender and validity of self-rated health in nineteen European countries. Scand J Public Health 45(6):647–653

30. Benyamini Y (2011) Why does self-rated health predict mortality? An update on current knowledge and a research agenda for psychologists. Psychol Health 26(11):1407–1413

31. Braekkan SK, Grosse SD, Okoroh EM, Tsai J, Cannegieter SC, Naess IA, Krokstad S, Hansen JB, Skjeldestad FE (2016) Venous thromboembolism and subsequent permanent work-related disability. J Thromb Haemost 14(10):1978–1987

32. Samsioe G, Lidfeldt J, Nerbrand C, Nilsson P (2010) The women's health in the Lund area (WHILA) study—an overview. Maturitas 65(1):37–45

33. World Health Organization (2011) Global recommendations on physical activity for health. World Health Organization, Geneva

34. Borch KH, Braekkan SK, Mathiesen EB, Njolstad I, Wilsgaard T, Stormer J, Hansen JB (2010) Anthropometric measures of obesity and risk of venous thromboembolism: the Tromso study. Arterioscler Thromb Vasc Biol 30(1):121–127

35. Kirkwood BR, Sterne JAC, Kirkwood BR (2003) Essential medical statistics, 2nd edn. Blackwell Science, Malden

36. Juul S, Frydenberg M (2014) An introduction to Stata for health researchers, 4th edn. Stata Press, College Station

37. Tisi PV (2011) Varicose veins. BMJ Clin Evid 2011:0212

38. Schlesinger S, Neuenschwander M, Schwedhelm C, Hoffmann G, Bechthold A, Boeing H, Schwingshackl L (2019) Food groups and risk of overweight, obesity, and weight gain: a systematic review and dose-response meta-analysis of prospective studies. Adv Nutr 10(2):205–218

39. Kahlmeier S, Wijnhoven TM, Alpiger P, Schweizer C, Breda J, Martin BW (2015) National physical activity recommendations: systematic overview and analysis of the situation in European countries. BMC Public Health 15:133

40. Farnkvist L, Olofsson N, Weinehall L (2008) Did a health dialogue matter? Self-reported cardiovascular disease and diabetes 11 years after health screening. Scand J Prim Health Care 26:135–139

41. Lingfors H, Lindstrom K, Persson LG, Bengtsson C, Lissner L (2003) Lifestyle changes after a health dialogue. Results from the live for life health promotion programme. Scand J Prim Health Care 21:248–252

42. Sargent-Cox KA, Anstey KJ, Luszcz MA (2010) Patterns of longitudinal change in older adults' self-rated health: the effect of the point of reference. Health Psychol 29:143–152

Paper V

Mitochondria-DNA copy-number and incident venous thromboembolism among middle-aged women: a population-based cohort study

Peter Nymberg[1] · Ashfaque A. Memon[1] · Jan Sundquist[1] · Kristina Sundquist[1] · Bengt Zöller[1]

Abstract

Venous thromboembolism (VTE) is the third most common cardiovascular disease. Low amount of mitochondrial DNA copy number (mtDNA-CN) has been associated with arterial cardiovascular disease (CVD) and reflects mitochondrial dysfunctions. However, whether mtDNA-CN is associated with VTE has not been determined. To examine the association between mtDNA-CN and incident VTE among middle-aged women. 6917 women aged 50–64 years, followed for 20 years in the Women's Health In the Lund Area (WHILA) study. DNA samples for mtDNA quantification were available from 2521 women. Quantification of mtDNA-CN was performed using a well-optimized droplet digital PCR method. After exclusions of women with anticoagulant treatment, women living in nursing homes, and women who were diagnosed with cancer, stroke, VTE, or coronary heart disease at baseline, a cohort of 2117 women remained for analysis. Cox regression was used to analyze the relationship between mtDNA-CN and time to VTE (hazard ratio = HR). In total, 87 women were diagnosed with VTE during follow-up, corresponding to an incidence rate of 2.8 per 1000 person-years. Neither crude nor adjusted HR for mtDNA-CN were significantly associated with incident VTE. A sensitivity analysis with inclusion of excluded women did not change the results. MtDNA-CN was not significantly associated with VTE. The present study suggests that mtDNA-CN, reflecting mitochondrial dysfunction, should not be considered a biomarker that plays a major role for developing VTE. However, due to limited study size we may not exclude minor associations.

Abbreviations

VTE	Venous thromboembolism
CVD	Arterial cardiovascular disease
mtDNA-CN	Mitochondrial DNA
PE	Pulmonary embolism
DVT	Deep vein thrombosis
SBP	Systolic blood pressure
DBP	Diastolic blood pressure
WHILA	Women´s Health In the Lund Area study
ddPCR	Optimized droplet digital PCR
SRH	Self-rated health
BMI	Body mass index
HR	Hazards ratio
FH	Family history

✉ Peter Nymberg
peter.nymberg@med.lu.se

1   Center for Primary Health Care Research, Lund University/
    Region Skåne, Skåne University Hospital Malmö, University
    Hospital, Jan Waldenströms gata 35, SE-205 02 Malmö,
    Sweden

Highlights

- This is the first study examining association between mtDNA-CN and incident VTE.
- mtDNA-CN is not associated with incident VTE.
- Low mtDNA-CN is not a major risk factor for VTE among middle-aged women.

Introduction

There are more than 200,000 new cases of venous thromboembolism (VTE) each year in the United States, with a corresponding mortality rate of about 30% within 30 days [1]. Among VTE survivors, 30% develop recurrent VTE [1] and the increased mortality risk lasts up to 8 years after the first VTE event [1, 2]. Arterial cardiovascular diseases (CVD) share several risk factors with VTE such as obesity, cancer, infections, oestrogens [3], smoking, and obstructive sleep apnea syndrome [4–6]. In addition to the shared risk, CVD and VTE predispose for each other, i.e., prevalent

CVD increases the risk of incident VTE [7, 8]. Obesity, with an increased waist circumference, is also a risk factor for metabolic syndrome [9], which increases the risk for varicose veins, VTE, CVD, and diabetes type II [1, 10–14]. According to a systematic review [15] with a meta-analysis of the result from five articles with a total of 8252 cases and 20,904 controls, low amount of mitochondria DNA copy number (mtDNA-CN) is a suggested risk indicator for CVDs. In previous studies, individuals with high BMI and metabolic syndrome have shown a low amount of mtDNA-CN compared with healthy individuals [16, 17]. MtDNA-CN is also suggested to be a biomarker for aging where those with age-related diseases have lower amount of mtDNA-CN [18]. Poor self-rated health has been reported to be associated with lower levels of mtDNA-CN [19]. Poor self-rated health is also a predictor for incident CVD [20]. Lifestyle may also affect the levels of mtDNA-CN; current smoking is associated with lower amount of mtDNA-CN [21] and studies have suggested that high alcohol consumption may affect the levels of mtDNA-CN [22, 23]. In contrast, healthy lifestyle, such as regular physical activity, is associated with higher mtDNA-CN [24, 25]. Physical activity, in accordance with WHO recommendations, lowers risk for both CVD [26] and VTE [27, 28].

Since mtDNA-CN has been associated with CVD, and there are common risk factors that affect the amount of mtDNA-CN shared between both CVD and VTE, we hypothesize that low amount of mtDNA-CN also is associated with an increased VTE risk.

The main aim of this cohort study was to examine the association between baseline mtDNA-CN in middle-aged women (50–64 years) and incident VTE.

Materials and methods

Study population

The Women´s Health In the Lund Area study (WHILA) is a prospective cohort study that was conducted in southern Sweden. Sample characteristics, data collection and clinical definitions for WHILA have been described previously [29, 30]. Briefly, the study invited all women (n = 10,766) living in any of the five municipalities around the city of Lund by December 1995, and who were born between December 1935 and December 1945, to a screening procedure that took place from December 1995 until February 2000. A total of 6917 women consented to participate in the study, of which 6916 had complete datasets. Blood samples for DNA analyses were available at baseline only, and were collected midway through the study and therefore were available only for the last 3062 included women. Out of the 3062 blood sampled women, there were 541 samples with

poor quality DNA as observed during droplet digital PCR analysis of reference gene. Thus, only 2521 women with sufficient quality of DNA were analyzed. These 541 women was excluded from analysis. Women (n = 13) treated with anticoagulants at baseline were also excluded (ATC code; B01AA03, B01AA01, and B01AB02). Women with prevalent VTE (defined below) or any of the following prevalent diagnoses at baseline were excluded: Stroke [ICD-7; 331, 332, 334.09. ICD-8; 430–434, 436. ICD-9; 430–434, 436. ICD-10; I60-I64 (not I63.6)]; Coronary heart disease (CHD) (ICD-7; 420. ICD-8; 410–414. ICD-9; 410–414. ICD-10; I20-I25.); and Cancer (ICD-7; 140–209). In the cohort, there were 22 women with prevalent stroke, 26 women with prevalent CHD, 232 women with prevalent cancer, and 120 women with VTE before baseline (self-reported and/or by register). Moreover, 14 women who were living in nursing homes were excluded. Some of the women had more than one reason for exclusion, which is why the numbers do not add up. After exclusions, a total of 2117 women remained of the 2521 women with sufficient quality DNA. After exclusions of prevalent stroke, prevalent CHD, prevalent cancer and prevalent VTE, 126 women remained with incident VTE. Of these, 39 women with VTE were censored in the cox regression due to incident CHD, stroke, or cancer before VTE during follow-up. Thus, after censoring for 39 incident cases of stroke, CHD, and cancer, we had 87 incident VTE cases in total.

The cohort was identified via the Swedish population registry that comprised all inhabitants in the Lund area. A health-screening program included laboratory examinations, blood samples and a basic baseline questionnaire that was mailed along with the invitation and collected in conjunction with the first examination. The baseline questionnaire included 104 questions concerning education, household, working status, perimenopausal status, medical history, drug treatment, personal and family history of diabetes or cardiovascular disease (myocardial infarction, stroke, deep venous thrombosis or hypertension in parents or siblings with an event before the age of 60 years). It also contained questions about habits like smoking, alcohol consumption, physical activity, general dietary habits, quality of life, as well as subjective physical and mental symptoms. This questionnaire was a composite of several validated questionnaires.

Laboratory measurement of mtDNA-CN

The mtDNA-CN was determined by droplet digital PCR (ddPCR) based method for quantification of absolute copy number of mtDNA in whole blood, as described in detail [31]. Compared to real-time PCR, ddPCR has greater precision and improved reproducibility and provides ultrasensitive and absolute nucleic acid quantification [32]. The used ddPCR method for mtDNA determination has been

well-optimized with intra- and inter-assay coefficient variances as 3.1% and 4.2% respectively [31].

Predictor variables

Self-rated health (SRH) was assessed only at baseline from a single question, in which the participants were asked to rate their perceived health in a 7-graded Likert scale from "Very poor" to "Excellent, could not be better" (1 = very poor, 7 = Excellent). In this study, alternative 1–4 was classified as poor SRH and 5–7 as good SRH. Weight and height were rounded off to the nearest 0.1 kg and 0.5 cm. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared (kg/m^2). Varicose veins were defined by ICD-7; 460, ICD-8; 454, ICD-9; 454, and ICD-10; I83. Women were categorized as current smokers (i.e., those who smoked regularly or occasionally), non-smokers and former smokers. Non-alcohol drinkers were defined as not drinking any alcohol (0 g/week), normal consumption more than 0–12 g/week, and high consumption as over 12 g/week. Low physical activity, i.e., less than 30 min vigorous activity 5 days a week [33] was defined by the three lowest answering alternatives (i.e., very low, low and light activity) (Table 1). Overall diet was defined by questions about intake of fat, sugar, fruit, or dietary fiber. If high intake of sugar or fat or low intake of dietary fiber or fruit were reported, the diet was classified as less healthy [29]. If low intake of sugar and fat and high intake of fruit and dietary fiber was reported, the diet was classified as healthy. Education was categorized into three groups: comprehensive school (9 years), upper secondary school (12 years), and university degree.

Information about diseases and medication was obtained from the Swedish Hospital Discharge Register, the Hospital Outpatient Register and the Swedish Cancer Register in addition to self-reported data from WHILA study baseline questionnaires and measurements.

Outcome variable (VTE)

The definition of VTE includes deep venous thrombosis (DVT), pulmonary embolism (PE), and other VTE types by the following ICD-codes from the Swedish Hospital Discharge Register and the Hospital Outpatient Register:

DVT (deep venous thromboembolism): ICD-7 463, 682. ICD-8 451, 671 (not 671.00). ICD-9 451 (not 451A) 671D 671E. ICD-10 I80 (not I80.0) O22.3, O871. PE (pulmonary embolism): ICD-7 465, 684. ICD-8 451, 671 (not 671.00). ICD-9 415B, 416 W, 639G, 673C. ICD-10 I26, O88.2, O082. Other VTE types: ICD-7 464, 466, 583.00, 334.40, 334.50. ICD-8 321, 452,453. ICD-9 437G, 451A, 452,453,671C, 671F,6171X. ICD-10 I63.6, I676, I800, I81, I82, O222, O225, O229, O870, O873, O879, O087.

Table 1 Comparison between baseline characteristics between those with incident VTE and those without incident VTE

Baseline measures	Incident VTE	No incident VTE	P
Age[*]			0.34
Mean	57.1	56.9	
Std dev	2.8	2.8	
n	126	1991	
mtDNA[*]			0.49
Mean	116.7	118.4	
Std dev	28.9	27.0	
n	126	1991	
SBP (mmHg)[*]			0.84
Mean	132.3	132.0	
Std dev	14.9	17.2	
n	126	1990	
DBP (mmHg)[*]			0.46
Mean	85.7	85.1	
Std dev	8.5	9.0	
n	126	1991	
Height mean[*] (cm)	165.6	165.0	0.20
Std dev	5.6	5.4	
n	122	1948	
Weight[*] (kg)			**0.01**
Mean	70.8	67.9	
Std dev	11.4	10.9	
n	114	1873	
Body mass index			**0.01**
Mean[*]	26.3	25.5	
Std dev	4.0	4.0	
n	126	1991	
Waist (cm)[*]			**0.01**
Mean	84.2	81.5	
Std dev	10.1	10.3	
N	125	1962	
Hip (cm)[*]			**0.02**
Mean	105.8	103.7	
Std dev	7.5	8.0	
N	125	1962	
Waist Hip Ratio			0.11
Mean[*]	0.79	0.78	
Std dev	0.07	0.06	
n	126	1989	
Smoker[**]			0.40
No	73 (59.4%)	1161 (59.5%)	
Current	28 (22.8%)	366 (18.7%)	
Former	22 (17.9%)	426 (21.8%)	
Alcohol[**]			0.54
0 g/w	27 (23.1%)	468 (24.8%)	
> 0–12 g/w	77 (65.8%)	1154 (61.1%)	
> 12 g/w	13 (11.1%)	267 (14.1%)	

Table 1 (continued)

Baseline measures	Incident VTE	No incident VTE	P
Education[**]			0.65
7–9 years	35 (28.0%)	489 (25.0%)	
10–12 years	51 (40.8%)	875 (44.7%)	
>12 years	39 (31.2%)	595 (30.4%)	
Marital[**]			0.90
Married	99 (79.2%)	1538 (77.6%)	
Unmarried	6 (4.8%)	89 (4.5%)	
Divorced	15 (12.0%)	244 (12.3%)	
Widowed	5 (4.0%)	110 (5.6%)	
Low activity[**]	69 (56.1%)	1093 (55.3%)	0.97
High activity	54 (43.9%)	850 (43.7%)	
Sugar[***]			0.74
Daily	8 (6.5%)	60 (3.1%)	
Sometimes	78 (62.9%)	1326 (67.3%)	
Avoids	38 (30.7%)	584 (29.6%)	
Fat in food[***]			0.25
Much	8 (6.7%)	125 (6.7%)	
Careful with	80 (67.2%)	1154 (61.5%)	
Avoids	31 (26.0%)	597 (31.8%)	
Dietary fiber in food[***]			0.29
Low intake	1 (0.8%)	21 (1.1%)	
Regularly	79 (64.8%)	1164 (59.5%)	
High intake	42 (34.4%)	773 (39.5%)	
Fruit[***]			0.38
Much fruit	83 (66.4%)	1229 (62.2%)	
Eats regularly	39 (31.2%)	708 (35.8%)	
Eats rarely	3 (2.4%)	39 (21.97%)	
Overall diet[***]			0.35
Less healthy	16 (12.8%)	202 (10.2%)	
Healthy	109 (87.2%)	1779 (89.8%)	
Self-rated health[***]			0.49
1. Very poor	1 (0.8%)	8 (0.4%)	
2	0 (0.0%)	30 (1.5%)	
3	5 (4.0%)	101 (5.2%)	
4	19 (15.3%)	271 (13.8%)	
5	37 (28.8%)	496 (25.3%)	
6	38 (30.7%)	5589 (30.1%)	
7. Excellent	24 (19.4%)	463 (23.7%)	
Self-rated health group[***]			0.84
Poor	25 (20.2%)	410 (20.1%)	
Good	99 (79.8%)	1548 (79.1%)	
Amount of food[***]			0.60
Big portions	5 (4.4%)	129 (7.0%)	
Regularly	81 (71.7%)	1186 (64.5%)	
Small portions	27 (23.9%)	525 (28.5%)	
Diabetes before baseline[***]			0.59
Yes	1 (0.8%)	27 (1.4%)	
No	124 (99.2%)	1941 (98.6%)	

Table 1 (continued)

Baseline measures	Incident VTE	No incident VTE	P
Hypertension[**]			0.75
Yes	23 (18.4%)	343 (17.3%)	
No	102 (81.6%)	1639 (82%)	
Varicose veins[***]			0.15
Yes	5 (4.0%)	41 (2.1%)	
No	121 (96.0%)	1950 (98.0%)	
Acetylsalicylic treatment[***]			0.99
Yes	1 (0.8%)	16 (0.8%)	
No	125 (99.2%)	1975 (99.2%)	
Knowledge about family history[**]			0.23
Yes	16 (12.9%)	180 (9.3%)	
No	96 (77.4%)	1622 (83.4%)	
Do not know	12 (9.7%)	144 (7.4%)	

Exclusions: Poor quality mtDNA-CN, prevalent VTE, prevalent CHD, prevalent stroke, prevalent cancer, those medicated with anticoagulant, and those living in nursing homes

P-values were calculated with two-sided Student´s t-test[*] for continuous variables, with Chi2-test[**] for normal distributed categorical variables, and with Wilcoxon rank sum test[***] for not normally distributed categorical variables between incident VTE and no incident VTE

Bold numbers indicate P values < 0.05

Physical activity was dichotomized into Low activity (Non, Mostly sitting, and Light activity) and High activity (1–2 h/week, regularly and Very high). Self-rated health was dichotomized into the variable Poor self-rated health, with group 1–4 as poor self-rated health and 5–7 as good self-rated health

Statistical analysis

Levels of mtDNA-CN were used as a dichotomized variable according to median, though mtDNA-CN was also used as a continuous variable in the analysis. In the multivariate models, waist circumference was used instead of BMI; this was due to previous studies showing waist circumference as a valid predictor for VTE [34]. A power analysis revealed that a risk ratio of 1.8 could be detected at a significance level of 5% (two-sided) with a power of 82% in the studied population when using mtDNA-CN as a dichotomous predictor variable (https://www.openepi.com/Power/PowerCohort. htm). P-values were calculated with two-sided Student's t test for continuous variables, with χ^2-test for dichotomized and normal distributed categorical variables, and Wilcoxon rank sum test for not normally distributed categorical variables. Cox proportional hazards regression was used to analyze the relationship between different variables and time to VTE. Hazard ratios (HR) with 95% confidence intervals (CI) were calculated. Women who were affected by stroke, CHD, or cancer diagnosis before the VTE during the follow-up time were censored. Well-known risk factors for increased

VTE-risk were used as confounding variables in the multivariate analysis. At first, in the multivariable model, there was an adjustment for mtDNA-CN and age. In the second model, smoking, waist circumference, physical activity, and varicose veins were added. Among the categorical variables, the same category was used as reference through all analysis. Regarding smoking, "non-smoker" was used as reference, in physical activity the reference was "low physical activity", in varicose veins it was "no varicose veins" reference, and in mtDNA-CN median, under the median (<117) was reference. The mtDNA-CN median and mtDNA-CN as a continuous variable were analyzed separately in the different models by Cox regression using the same adjustments. In the main analysis, we excluded all the patients with prevalent VTE, CHD, stroke, cancer, and women treated with anticoagulants at baseline or living in nursing homes. During follow-up, those with incident CHD, stroke, or cancer before VTE were censored. At the next step, a sensitivity analysis was conducted; the only exclusions in the sensitivity analysis were those with poor quality DNA. All other excluded and censored individuals were included in the sensitivity analysis. P-values <0.05 were considered significant. Analyses were performed in STATA 16.1.

Result

Measurements at baseline were compared between women, with and without incident VTE, during follow-up (Table 1). Women with incident VTE had a significantly higher weight (p=0.01) and BMI (p=0.01) at baseline, and a significantly greater circumference regarding both waist (p=0.01) and hip (p=0.02). There was a greater proportion, among those with incident VTE, who had varicose veins.

Incident VTE and mtDNA-CN

During the follow-up time of 17.9 years, 87 women were diagnosed with VTE. The sum of follow-up time was 31,073.123 years corresponding to a VTE incident rate at 2.8 (95% CI 2.3–3.4) per 1000 person-years. Unadjusted Cox-regression analysis was conducted (Table 2) to determine any associations between possible risk factors and incident VTE. The univariate Cox-regression showed no significant association between increased mtDNA-CN and lower risk for VTE (HR=0.99, 95% CI 0.98–1.00, p=0.13). There was a non-significant decreased risk of VTE with mtDNA-CN over the median (HR=0.76, 95% CI 0.50–1.17, p=0.21) compared with mtDNA-CN under median. Among potential VTE risk factors, statistically significant associations were observed with weight (HR=1.02, 95% CI 1.00–1.04 p=0.01), waist circumference (HR=1.02, 95% CI 1.00–1.04, p=0.01), hip circumference (HR=1.03 95% CI 1.00–1.06 p=0.02), and

varicose veins (HR=2.89, 95% CI 1.17–7.13, p=0.02). A significant association with sugar intake was observed. No significant association was shown with incident VTE and current smokers (HR=1.30, 95% CI 0.78–2.18, p=0.32) or former smokers (HR=0.74, 95% CI 0.41–1.33 p=0.31). Regarding physical activity (HR=0.87, 95% CI 0.56–1.34 p=0.52), there were no significant associations with incident VTE. Likewise, there was not shown any significant associations between incident VTE and self-rated health (HR=1.74, 95% CI 0.24–12.49 p=0.58) (Table 2).

In the second step, a multivariable Cox regression analysis was performed, at first when adjusted for age (Table 3) dichotomized mtDNA-CN over median showed a non-significant decreased risk for VTE (HR=0.76, 95% CI 0.50–1.77 p=0.22) compared to mtDNA-CN under the median (Table 3). With age adjusted Cox regression and mtDNA-CN as a continuous variable, a non-significant decreased risk was shown with increasing mtDNA-CN (HR=0.99, 95% CI 0.98–1.00 p=0.14). The last model 3, adjusted for age, smoking, waist circumference, physical activity, and varicose veins showed mtDNA-CN over the median a non-significant decreased risk of incident VTE (HR=0.89, 95% CI 0.57–1.38 p=0.60) using mtDNA-CN under the median as reference. Using the same adjustments but with mtDNA-CN as a continuous variable showed no effect of neither decreased nor increased risk for incident VTE (HR=1.00, 95% CI 0.99–1.00 p=0.34) (Table 3).

Sensitivity analysis

The only exclusions done in the sensitivity analysis were those with poor quality DNA (541 women). In the sensitivity analyses, a total of 2521 women were remaining and out of these, 142 women were affected with incident VTE during follow-up. Moreover, in the sensitivity analyses, no censoring was performed for women with incident stroke, CHD, or cancer. The sum of follow-up time in the sensitivity analysis was 38,805.318 years corresponding to a VTE incident rate at 3.7 (95% CI 3.1–4.3) per 1000 person-years total analysis time at risk under observation. The result of the univariate sensitivity analysis (Supplementary Table 1) is approximately the same as the univariate main analysis regarding hazard ratios and confidence intervals. The same variables showing significant association in main analysis were significant in the sensitivity analysis, except for knowledge of family history of VTE, which showed an association with incident VTE in the sensitivity analysis (HR=1.67, 95% CI 1.05–2.68, p=0.03) (Supplementary Table 1). Regarding varicose veins, it was the opposite with no significant associations in the sensitivity analysis (Supplementary Table 1). The multivariable sensitive analysis (Table 4) showed the same pattern as the main multivariable analysis. There were

Table 2 Univariate Cox regression with variables associated with VTE

	Hazard ratio	95% CI	p	n	Failures
mtDNA-CN	0.99	0.99–1.00	**0.013**	2117	87
mtDNA-CN median*	0.76	0.50–1.17	0.21	2117	87
Age	1.05	0.97–1.13	0.23	2117	87
Height	1.02	0.99–1.06	0.20	2070	85
Weight	1.02	1.00–1.04	**0.01**	1987	79
BMI	1.18	0.93–1.49	0.18	2117	87
Waist circumference	1.02	1.00–1.04	**0.01**	2087	86
Hip circumference	1.03	1.00–1.05	**0.02**	2087	86
WHR	1.29	0.51–3.15	0.59	2115	87
Diastolic blood pressure	1.01	0.99–1.04	0.30	2117	87
Systolic blood pressure	1.00	0.99–1.02	0.62	2116	87
Education				2084	87
7–9 years	1.39	0.84–2.28	0.20		
10–12 years	Ref				
> 12 years	1.00	0.60–1.67	1.00		
Marital				2106	87
Married	Ref				
Unmarried	1.32	0.53–3.29	0.54		
Divorced	1.07	0.57–2.03	0.83		
Widowed	0.89	0.32–2.44	0.82		
High activity /low activity	0.87	0.56–1.34	0.52	2066	85
Smoking				2076	85
Non smoker	Ref				
Current smoker	1.30	0.78–2.18	0.32		
Former smoker	0.74	0.41–1.33	0.31		
Alcohol				2006	81
0 g/w	0.98	0.59–1.64	0.94		
0–12 g/w	Ref				
> 12 g/w < 130 g/w	0.67	0.32–1.40	0.28		
Sugar				2094	87
Daily	2.87	1.30–6.33	**< 0.01**		
Sometimes	Ref				
Avoids	1.32	0.84–2.08	0.23		
Fat in food				1995	81
Much	1.08	0.47–2.52	0.85		
Careful with	Ref				
Avoids	0.84	0.51–1.38	0.49		
Fiber				2080	84
Low intake	1.23	0.17–8.88	0.84		
Regularly	Ref				
Much	0.96	0.62–1.49	0.85		
Fruit				2101	87
Much fruit	0.96	0.61–1.48	0.84		
Eats regularly	Ref				
Eats rarely	1.16	0.28–4.84	0.84		
Overall diet Less healthy/healthy	1.56	861–2.98	0.14	2106	87
Amount of food				1953	77
Big portions	0.64	0.23–1.77	0.39		
Regularly	Ref				
Small portions	0.64	0.37–1.12	0.12		

Table 2 (continued)

	Hazard ratio	95% CI	p	n	Failures
Acetylsalicylic	1.83	0.25–13.13	0.55	2117	87
Knowledge about FH[**] VTE				2070	86
Yes	1.58	0.86–2.92	0.14		
No	Ref				
Do not know	1.17	0.54–2.55	0.69		
Diabetes	0.89	0.12–6.39	0.91	2093	87
Hypertension	1.30	0.78–2.19	0.32	2107	87
Prevalent varicose veins	2.89	1.17–7.13	**0.02**	2117	87
Self-rated health Poor/good	1.74	0.24–12.49	0.58	2117	87

Exclusions: Poor quality mtDNA-CN, prevalent VTE, prevalent CHD, prevalent stroke, prevalent cancer, those medicated with anticoagulant, and those living in nursing homes. Censored for CVD stroke and cancer before VTE diagnosis during follow-up. Self-rated health was dichotomized into the variable Poor self-rated health, with group 1–4 as poor self-rated health and 5–7 as good self-rated health. Bold numbers indicate statistically significant differences

[*] Reference under median

[**] = family history

Table 3 Cox regression with mtDNA-CN, analyses with median and continuous were done in separate models

Model	1	2	3
Total n	2117	2117	2003
Failures n	87	87	82
mtDNA median[*]			
HR	0.76	0.76	0.89
CI	0.49–1.17	0.50–1.17	0.57–1.38
P	0.21	0.22	0.60
mtDNA (continuous)			
HR	0.99	0.99	1.00
CI	0.98–1.00	0.98–1.00	0.99–1.00
p	0.13	0.14	0.34
	Model 1 mtDNA-CN	Model 2 mtDNA-CN and age	Model 3 mtDNA-CN, age, smoking, waist circumference physical activity and prevalent varicose veins

Exclusions: Poor quality mtDNA-CN, prevalent VTE, prevalent CHD, prevalent stroke, prevalent cancer, those medicated with anticoagulant, and those living in nursing homes. Censored for CVD stroke and cancer before VTE diagnosis during follow-up

[*] Reference is mtDNA-CN under the median

minor differences in hazard ratios and level of significance between the main analysis and the sensitivity analysis.

Discussion

The present first study on mtDNA-CN and future VTE risk found no significant association between mtDNA-CN and incident VTE. Based on our results, we suggest that mtDNA-CN should not be considered a biomarker that plays a major role for developing VTE. VTE and arterial CVD share many risk factors, but some are unique to VTE or CVD [3]. The mtDNA-CN appears to be a factor that is only associated with CVD [15] and not VTE. Thus, mitochondrial dysfunction reflected by low copy number of mtDNA appears not to be of similar importance in VTE as in arterial CVD [15]. Due to limited study size, we may not exclude minor associations. The level of mtDNA-CN is determined by heredity, in addition to the influence on one's lifestyle habits such as physical activity, smoking, and alcohol consumption [21–25, 35]. Poor self-rated health is also associated with low levels of mtDNA-CN [19]. Factors like these, for instance smoking and physical activity, are important for the development of arterial CVD [26]. Nevertheless, we found no significant association between VTE and mtDNA-CN.

Table 4 Sensitivity analysis cox regression with mtDNA-CN, analyses with median and continuous were done in separate models

Model	1	2	3
Total n	2401	2401	2277
Failures n	142	142	136
mtDNA median[*]			
HR	0.87	0.87	0.94
CI	0.63–1.21	0.63–1.22	0.67–1.31
p	0.41	0.42	0.74
mtDNA (continuous)			
HR	1.00	1.00	1.00
CI	0.99–1.00	0.99–1.00	0.99–1.01
p	0.40	0.41	0.66
	Model 1 mtDNA-CN	Model 2 mtDNA-CN and age	Model 3 mtDNA-CN, age, smoking, waist circumference physical activity and prevalent varicose veins

The only exclusions were those with poor quality mtDNA-CN

[*]Reference is mtDNA-CN under the median

An association between incident VTE and dietary habits has previously been reported [36] where a diet with low amount of red meat and high amount of grains and vegetables lowers the risk of incident VTE. Although, in our study, only self-reported daily consumption of sugar showed a significantly increased risk of VTE in this cohort. High sugar intake is a well-known dietary habit that increases the risk of arterial CVD and might also affect VTE risk [37, 38]. However, we think the association with sugar consumption and VTE in the present study is a chance finding. A previous study of the same cohort containing all 6917 women did not show any significant associations between daily sugar consumption, other dietary habits or any significant association between physical activity and incident VTE [30]. In fact, diet remains to be a proven risk factor for VTE [39].

A limitation of the study is the study size. However, well-established risk factors such as anthropometric measures for overweight (weight, BMI, waist circumference, and waist circumference) and varicose veins were all associated with future VTE risk. Even if increasing age is a well-known risk factor for VTE [40, 41], no association between increasing age and incident VTE was found, most likely due to the narrow age span between 50 and 60 years of age at baseline. The method used for measuring physical activity in this study can affect the results, related to the known risk of overestimating the time in physical activity when self-reported [42, 43], which is another limitation of the study regarding physical activity. Another limitation is the inclusion of women only. However, there is no hypothesis suggesting that the importance of mtDNA-CN should be sex dependent. Still, the copy number of mitochondrial DNA has been reported to be lower in males compared with females both in humans [44, 45] and in Drosophila melanogaster [45, 46]. It

will therefore be of interest to investigate whether mtDNA-CN is associated with VTE among males.

A strength of the study is the population-based cohort design with long follow-up time. Using a hospital-based diagnosis of VTE is another strength. The Swedish Hospital register has a general validity between 85 and 95% [46]. VTE has been validated with a 95% positive predictive value [47]. In Sweden, VTE is usually confirmed with objective methods [48–50].

Several common risk factors [3–5] for both VTE and CVDs have been described, and mtDNA-CN has been shown to be a risk indicator of CVDs [15]. Although, mtDNA-CN does not to appear to be a biomarker that is associated with VTE.

Conclusion

MtDNA-CN was not associated with incident VTE among middle-aged women. MtDNA-CN is suggested not to be of major importance for the development of VTE.

Strengths and limitations

This is the first study aiming to investigate the association between mtDNA-CN and incident VTE, which is a strength of this study. Performing the study in a small cohort containing only middle-aged women with a narrow age span is a limitation.

Declarations

Conflict of interest The authors declare that they have no competing interests.

Ethical approval The regional ethical committee at Lund University approved the study (approval nos. 2011/494 and 2015/6) and written informed consent was given by all the participants in the study after full explanation of the purpose and all the protocols were conducted in accordance with the Helsinki Declaration and the Data Registry Inspection in Stockholm. Informed consent was obtained from all participants.

References

1. Heit JA, Silverstein MD, Mohr DN, Petterson TM, Lohse CM, O'Fallon WM et al (2001) The epidemiology of venous thromboembolism in the community. Thromb Haemost 86(1):452–463
2. Flinterman LE, van Hylckama VA, Cannegieter SC, Rosendaal FR (2012) Long-term survival in a large cohort of patients with venous thrombosis: incidence and predictors. PLoS Med 9(1):e1001155. https://doi.org/10.1371/journal.pmed.1001155
3. Lowe GD (2008) Common risk factors for both arterial and venous thrombosis. Br J Haematol 140(5):488–495. https://doi.org/10.1111/j.1365-2141.2007.06973.x
4. Lippi G, Mattiuzzi C, Franchini M (2015) Sleep apnea and venous thromboembolism. A systematic review. Thromb Haemost 114(5):958–963. https://doi.org/10.1160/TH15-03-0188
5. Deflandre E, Degey S, Opsomer N, Brichant JF, Joris J (2016) Obstructive sleep apnea and smoking as a risk factor for venous thromboembolism events: review of the literature on the common

pathophysiological mechanisms. Obes Surg 26(3):640–648. https://doi.org/10.1007/s11695-015-2012-0
6. Somers VK, White DP, Amin R, Abraham WT, Costa F, Culebras A et al (2008) Sleep apnea and cardiovascular disease: an American Heart Association/American College Of Cardiology Foundation Scientific Statement from the American Heart Association Council for High Blood Pressure Research Professional Education Committee, Council on Clinical Cardiology, Stroke Council, and Council On Cardiovascular Nursing. In collaboration with the National Heart, Lung, and Blood Institute National Center on Sleep Disorders Research (National Institutes of Health). Circulation 118(10):1080–1111. https://doi.org/10.1161/CIRCULATIONAHA.107.189375
7. Franchini M, Mannucci PM (2008) Venous and arterial thrombosis: different sides of the same coin? Eur J Intern Med 19(7):476–481. https://doi.org/10.1016/j.ejim.2007.10.019
8. Prandoni P (2017) Venous and arterial thrombosis: is there a link? Adv Exp Med Biol 906:273–283. https://doi.org/10.1007/5584_2016_121
9. Grundy SM, Brewer HB Jr, Cleeman JI, Smith SC Jr, Lenfant C, American Heart A et al (2004) Definition of metabolic syndrome: report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition. Circulation 109(3):433–438. https://doi.org/10.1161/01.CIR.0000111245.75752.C6
10. Ahti TM, Makivaara LA, Luukkaala T, Hakama M, Laurikka JO (2010) Lifestyle factors and varicose veins: does cross-sectional design result in underestimate of the risk? Phlebology 25(4):201–206. https://doi.org/10.1258/phleb.2009.009031
11. Tiwari A, Lester W, Tang TY (2018) Varicose veins and deep venous thrombosis. JAMA 320(5):509–510. https://doi.org/10.1001/jama.2018.7319
12. Chang SL, Chen PC (2018) Varicose veins and deep venous thrombosis-reply. JAMA 320(5):510. https://doi.org/10.1001/jama.2018.7331
13. Zoller B, Ji J, Sundquist J, Sundquist K (2014) Venous thromboembolism and varicose veins share familial susceptibility: a nationwide family study in Sweden. J Am Heart Assoc. https://doi.org/10.1161/JAHA.114.000850
14. Wilson PWF, D'Agostino RB, Parise H, Sullivan L, Meigs JB (2005) Metabolic syndrome as a precursor of cardiovascular disease and type 2 diabetes mellitus. Circulation 112(20):3066–3072. https://doi.org/10.1161/CIRCULATIONAHA.105.539528
15. Yue P, Jing S, Liu L, Ma F, Zhang Y, Wang C et al (2018) Association between mitochondrial DNA copy number and cardiovascular disease: current evidence based on a systematic review and meta-analysis. PLoS ONE 13(11):e0206003. https://doi.org/10.1371/journal.pone.0206003
16. Huang CH, Su SL, Hsieh MC, Cheng WL, Chang CC, Wu HL et al (2011) Depleted leukocyte mitochondrial DNA copy number in metabolic syndrome. J Atheroscler Thromb 18(10):867–873. https://doi.org/10.5551/jat.8698
17. Lee J-Y, Lee D-C, Im J-A, Lee J-W (2014) Mitochondrial DNA copy number in peripheral blood is independently associated with visceral fat accumulation in healthy young adults. Int J Endocrinol 2014:586017. https://doi.org/10.1155/2014/586017
18. Maximov VN, Malyutina SK, Orlov PS, Ivanoschuk DE, Mikhailova SV, Shapkina MY et al (2019) Mitochondrial DNA copy number of leucocytes as ageing marker and risk factors for age-related diseases in human. Adv Gerontol 32(3):422–430
19. Takahashi PY, Jenkins GD, Welkie BP, McDonnell SK, Evans JM, Cerhan JR et al (2018) Association of mitochondrial DNA copy number with self-rated health status. Appl Clin Genet 11:121–127. https://doi.org/10.2147/TACG.S167640
20. van der Linde RM, Mavaddat N, Luben R, Brayne C, Simmons RK, Khaw KT et al (2013) Self-rated health and cardiovascular

disease incidence: results from a longitudinal population-based cohort in Norfolk, UK. PLoS ONE 8(6):e65290. https://doi.org/10.1371/journal.pone.0065290

21. Vyas CM, Ogata S, Reynolds CF, Mischoulon D, Chang G, Cook NR et al (2020) Lifestyle and behavioral factors and mitochondrial DNA copy number in a diverse cohort of mid-life and older adults. PLoS ONE 15(8):e0237235. https://doi.org/10.1371/journal.pone.0237235

22. von Wurmb-Schwark N, Ringleb A, Schwark T, Broese T, Weirich S, Schlaefke D et al (2008) The effect of chronic alcohol consumption on mitochondrial DNA mutagenesis in human blood. Mutat Res 637(1–2):73–79. https://doi.org/10.1016/j.mrfmmm.2007.07.003

23. Cakir Y, Yang Z, Knight CA, Pompilius M, Westbrook D, Bailey SM et al (2007) Effect of alcohol and tobacco smoke on mtDNA damage and atherogenesis. Free Radic Biol Med 43(9):1279–1288. https://doi.org/10.1016/j.freeradbiomed.2007.07.015

24. Chang YK, Kim DE, Cho SH, Kim JH (2016) Association between leukocyte mitochondrial DNA copy number and regular exercise in postmenopausal women. Korean J Fam Med 37(6):334–339. https://doi.org/10.4082/kjfm.2016.37.6.334

25. Eluamai A, Brooks K (2013) Effect of aerobic exercise on mitochondrial DNA and aging. J Exerc Sci Fit 11(1):1–5. https://doi.org/10.1016/j.jesf.2013.03.003

26. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F et al (2004) Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet 364(9438):937–952. https://doi.org/10.1016/S0140-6736(04)17018-9

27. Johansson M, Johansson L, Wennberg P, Lind M (2019) Physical activity and risk of first-time venous thromboembolism. Eur J Prev Cardiol 26(11):1181–1187. https://doi.org/10.1177/2047487319829310

28. Kunutsor SK, Makikallio TH, Seidu S, de Araujo CGS, Dey RS, Blom AW et al (2020) Physical activity and risk of venous thromboembolism: systematic review and meta-analysis of prospective cohort studies. Eur J Epidemiol 35(5):431–442. https://doi.org/10.1007/s10654-019-00579-2

29. Samsioe G, Lidfeldt J, Nerbrand C, Nilsson P (2010) The women's health in the Lund area (WHILA) study–an overview. Maturitas 65(1):37–45. https://doi.org/10.1016/j.maturitas.2009.11.009

30. Nymberg P, Stenman E, Calling S, Sundquist J, Sundquist K, Zoller B (2020) Self-rated health and venous thromboembolism among middle-aged women: a population-based cohort study. J Thromb Thrombolysis 49(3):344–351. https://doi.org/10.1007/s11239-019-01995-7

31. Memon AA, Zoller B, Hedelius A, Wang X, Stenman E, Sundquist J et al (2017) Quantification of mitochondrial DNA copy number in suspected cancer patients by a well optimized ddPCR method. Biomol Detect Quantif 13:32–39. https://doi.org/10.1016/j.bdq.2017.08.001

32. Hindson CM, Chevillet JR, Briggs HA, Gallichotte EN, Ruf IK, Hindson BJ et al (2013) Absolute quantification by droplet digital PCR versus analog real-time PCR. Nat Methods 10(10):1003–1005. https://doi.org/10.1038/nmeth.2633

33. WH Organization (2011) Global recommendations on physical activity for health. World Health Organization, Geneva

34. Borch KH, Braekkan SK, Mathiesen EB, Njolstad I, Wilsgaard T, Stormer J et al (2010) Anthropometric measures of obesity and risk of venous thromboembolism: the tromso study. Arterioscler Thromb Vasc Biol 30(1):121–127. https://doi.org/10.1161/ATVBAHA.109.188920

35. Xing J, Chen M, Wood CG, Lin J, Spitz MR, Ma J et al (2008) Mitochondrial DNA content: its genetic heritability and association with renal cell carcinoma. J Natl Cancer Inst 100(15):1104–1112. https://doi.org/10.1093/jnci/djn213

36. Steffen LM, Folsom AR, Cushman M, Jacobs DR Jr, Rosamond WD (2007) Greater fish, fruit, and vegetable intakes are related to lower incidence of venous thromboembolism: the longitudinal investigation of thromboembolism etiology. Circulation 115(2):188–195. https://doi.org/10.1161/CIRCULATIONAHA.106.641688

37. Mirtschink P, Jang C, Arany Z, Krek W (2018) Fructose metabolism, cardiometabolic risk, and the epidemic of coronary artery disease. Eur Heart J 39(26):2497–2505. https://doi.org/10.1093/eurheartj/ehx518

38. The LH (2018) Sugar, video games, and VTE: an unseen connection? Lancet Haematol 5(5):e181. https://doi.org/10.1016/s2352-3026(18)30052-8

39. Hansen-Krone IJ, Enga KF, Njølstad I, Hansen JB, Braekkan SK (2012) Heart healthy diet and risk of myocardial infarction and venous thromboembolism. The tromso study. Thromb Haemost 108(3):554–560

40. Bizien N, Noel-Savina E, Tromeur C, Delluc A, Mottier D, Leroyer C et al (2011) Age is a major risk factor of venous thromboembolism (VTE). Eur Respir J 38(Suppl 55):p3936

41. Anderson FA Jr, Spencer FA (2003) Risk factors for venous thromboembolism. Circulation 107(23 Suppl 1):I9-16. https://doi.org/10.1161/01.CIR.0000078469.07362.E6

42. Troiano RP, Berrigan D, Dodd KW, Masse LC, Tilert T, McDowell M (2008) Physical activity in the United States measured by accelerometer. Med Sci Sports Exerc 40(1):181–188. https://doi.org/10.1249/mss.0b013e31815a51b3

43. Forsen L, Loland NW, Vuillemin A, Chinapaw MJ, van Poppel MN, Mokkink LB et al (2010) Self-administered physical activity questionnaires for the elderly: a systematic review of measurement properties. Sports Med 40(7):601–623. https://doi.org/10.2165/11531350-000000000-00000

44. Skuratovskaia D, Litvinova L, Vulf M, Zatolokin P, Popadin K, Mazunin I (2019) From normal to obesity and back: the associations between mitochondrial dna copy number, gender, and body mass index. Cells. https://doi.org/10.3390/cells8050430

45. Mengel-From J, Svane AM, Pertoldi C, Nygaard Kristensen T, Loeschcke V, Skytthe A et al (2019) Advanced parental age at conception and sex affects mitochondrial DNA copy number in human and fruit flies. J Gerontol A Biol Sci Med Sci 74(12):1853–1860. https://doi.org/10.1093/gerona/glz070

46. Kristensen TN, Loeschcke V, Tan Q, Pertoldi C, Mengel-From J (2019) Sex and age specific reduction in stress resistance and mitochondrial DNA copy number in Drosophila melanogaster. Sci Rep 9(1):12305. https://doi.org/10.1038/s41598-019-48752-7

47. Ludvigsson JF, Andersson E, Ekbom A, Feychting M, Kim JL, Reuterwall C, Heurgren M, Olausson PO (2011) External review and validation of the Swedish national inpatient register. BMC Public Health 11:450. https://doi.org/10.1186/1471-2458-11-450

48. Rosengren A, Fredén M, Hansson PO, Wilhelmsen L, Wedel H, Eriksson H (2008) Psychosocial factors and venous thromboembolism: a long-term follow-up study of Swedish men. J Thromb Haemost 6(4):558–564. https://doi.org/10.1111/j.1538-7836.2007.02857.x (Epub 2007 Nov 27)

49. Isma N, Svensson PJ, Gottsäter A, Lindblad B (2009) Prospective analysis of risk factors and distribution of venous thromboembolism in the population-based Malmö Thrombophilia Study (MATS). Thromb Res 124(6):663–666

50. Petrauskiene V, Falk M, Waernbaum I, Norberg M, Eriksson JW (2005) The risk of venous thromboembolism is markedly elevated in patients with diabetes. Diabetologia 48:1017–1021

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.