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Increased Adherence to Physical Activity on Prescription (FAR) through mindfulness - a randomized study in primary care (FAR-MIND)

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Introduction

Patients who are physically inactive according to WHO recommendations, will be randomized to intervention with mindfulness, mindfulness and physical activity on prescription (FAR)® or FAR® only. The randomization will take place in conjunction with receiving a prescription for physical activity to evaluate the effect of mindfulness. The intervention will be followed up with questionnaires, accelerometers and analysis of biomarkers. The study will be preceded by a smaller pilot study with 90 patients to test the adaptability and the magnitude of the effects that can be expected.

Background

whereas cardiovascular disease is one of the leading causes of death in the industrialised world(1); Some causes of cardiovascular diseases are modifiable, such as lifestyle habits, while others are congenital. There is currently extensive evidence showing a link between unhealthy lifestyles and the onset of cardiovascular diseases (2). The risk factors and health factors are the same all over the world: exercise, diet, smoking, waist circumference, blood lipids, alcohol intake, diabetes, prediabetes and psychosocial health, and stress (2). Sweden's reduced mortality from cardiovascular disease can largely be explained by better clinical care in special departments for acute cardiac care with new treatment methods, but also increased primary prevention, which has been shown to have greater effects on survival than secondary preventive measures do (3). General screening of the entire population is a way of trying to identify individuals at risk before they fall ill or develop symptoms and seek treatment for them. For example, in general screening, it has been seen that a survey of lifestyle habits can predict the risk of developing cardiovascular diseases (4). Another way to go is opportunistic screening, i.e. to take the opportunity for screening, in connection with the individual contacting the health care system regardless of the reason for the visit. Opportunistic screening has proven to be an effective way to find high-risk individuals before they develop diabetes, among other things (5, 6), alcohol-related diseases (7) and elevated cholesterol levels (8). This screening method of individuals in contact with the healthcare system is presumed to be a better alternative than performing a general screening in the population to find individuals with an elevated risk of cardiovascular disease (9-13).

HeredityBiologically speaking, 50% of genetics are passed on from parent to child. The incidence both in terms of cardiovascular disease such as deep vein thrombosis, pulmonary embolism, aortic aneurysm, stroke

and myocardial infarction is linked both to parents and to siblings' illness (14-17) The genetic predisposition to disease can in turn be influenced by factors in the environment such as environment and lifestyles. This means that for those with a heredity, there is an additional increased risk associated with external harmful factors (18).

Prevention

A large number of intervention studies have studied how lifestyle changes affect the incidence of chronic diseases; For example, increased physical activity has been shown to lower the risk of diabetes, high blood pressure and obesity (19-26). A structured motivational health conversation shows both an immediate effect with changed lifestyle habits and a long-term effect with reduced self-reported illness in both diabetes and cardiovascular disease (27-29). It has also been shown that interventions focusing on both diet and exercise have a better effect through regular follow-up (25). In order to facilitate discussion regarding changes in health behaviour and to be able to do so successfully, training in conversation methodology is required for those who carry it out (30, 31).

Physical activityA Swedish study has shown that a large part of the waking hours of 50-64 year olds are dominated by sedentary sitting (about 60%). Only seven per cent of this age group meet the recommendation for physical activity in terms of both intensity and duration (32). With a sedentary lifestyle, the risk of several chronic conditions such as obesity, diabetes, hypertension and thus also an increased risk of metabolic syndrome and cardiovascular diseases increases (33-36). It is primarily aerobic physical activity that is considered to counteract and suppress the metabolic syndrome (37). The international recommendation of the WHO (2011) (38) is at least 150 minutes of physical activity per week of moderate intensity, or at least 75 minutes of high intensity. Physical activity on prescription (FAR)® (39) can be recommended as both primary and secondary prevention aimed at various disease states. The recommendations per disease state are described in the handbook Physical activity in disease prevention and treatment (FYSS) (40). The recommendations include the amount of physical activity, but not where the boundaries are with a sedentary lifestyle, i.e. how much of the hours of the day can be spent sitting still without affecting health (41). One problem is lack of adherence to recommendations on physical activity (42-45) and difficulty in objectively monitoring treatment outcomes. In diabetes care, for example, the possibility of following up treatment results with HbA1c has led to a therapeutic revolution.

A similar simple and inexpensive test to follow the effect of intervention with lifestyle habits such as physical activity would have been of great value to the patient and caregiver.

Self-rated healthSelf-rated health encompasses all the different dimensions of the individual, physical, mental as well as social (46). The individuals' self-perceived health is assessed by asking the question "How do you assess your general state of health in relation to peers?" with five response alternatives; Very good, good, somewhat, bad or very bad (47-49). Poor self-rated health is associated with unhealthy lifestyles (50). There are demonstrated epidemiological associations between self-rated health and early death from cardiovascular disease (51, 52). This association with morbidity and mortality is independent of known risk factors such as medical, social and demographic (52-57). However, it can be difficult to compare self-rated health between different countries as there are cultural differences (46, 58). There may also be variations between different age groups, but also over time (59). A correlation has been shown between poor self-rated health and various biomarkers such as increased levels of inflammatory markers such as CRP and increased white blood cell counts, but lower levels of haemoglobin, albumin and high-density lipoprotein (HDL) (60, 61). Associations between newer markers such as microRNAs (miRNAs) (see below) and self-rated health have not been studied. Heredity and correlation with self-rated health and lifestyle habits have also not been investigated before.

Stress and sleep

Subjective sleep problems have been shown in prospective studies to be associated with the onset of acute myocardial infarction after adjusting for a number of parameters. Above all, they were associated with sleep problems, early awakening and the feeling of not being sleepy (62). Both sleep problems and premature awakening are associated with some of the modifiable risk factors for cardiovascular disease, such as hypertension, obesity, diabetes and hyperlipidaemia (63-65). Studies have shown associations in those with sleep periods of 8 hours or more with low levels of physical activity. But also that those with less sleep than 6 h/day had an increased mortality rate (66). Sleep deprivation and sedentary behaviour also independently affect the mental health condition, where little sleep leads to increased stress and a higher degree of suicidal thoughts (67). Long-term stress causes sleep problems, but also an increased risk of cardiovascular disease (68). There is a connection between sleep deprivation, stress and endothelial function in the body's vessels, but it is unclear whether the increased risk of cardiovascular disease is due to the lack of sleep in the body.

or if there is an impact on endothelial function based on other factors that result from sleep deprivation (69).

MindfulnessMindfulness can be described as an approach with conscious presence, which is about living in greater awareness of oneself here and now without valuing thoughts and feelings. This approach works to ensure that the individual perceives the world as it is without being influenced by previous experiences, preconceptions or feelings, which in turn possibly strengthens the ability to make decisions in an objective way (70). Some association between the risk of cardiovascular disease and the ability to be consciously present has been demonstrated, with individuals with good cardiovascular health having a better ability to be consciously present (71). Overweight individuals can be helped with mindfulness to change their behavior and their relationship with food. This is especially true for negative behaviors such as binge eating, comfort eating, and snacking between main meals (72-74). A difference has been shown between those who are able to maintain their physical activity and those who discontinue, especially in conscious presence, acceptance and depression. It is not clear whether the individuals who continue to be physically active over time are so thanks to their conscious presence or whether it is a result of the physical activity itself (75).

BiomarkersMicroRNAs (miRNAs) are small non-coding RNA molecules that regulate the expression of RNAs, and thereby the expression of proteins. MiRNA is relatively stable in both serum and plasma. Some diseases have been associated with an altered expression in miRNAs, which has led to the use of miRNA analysis in the diagnosis and prognosis of some diseases (76, 77). Telomeres are the ends of chromosomes and act as protection against the breakdown of DNA. With an increased number of cell divisions, the telomeres become shorter and eventually become so short that the cell perceives the ends of the chromosome as damaged DNA and begins to break down, which is expressed in physical aging in the individual. Immediately after physical activity, there has been an altered expression of mRNA and miRNA molecules that regulate the length of telomeres, including an increased presence of the enzyme telomerase that protects the telomeres (78). However, this is controversial as other studies have shown that increased physical activity does not result in any significant change. However, a correlation has been shown between reduced sedentary lifestyle and an increased catheteric length (79, 80). There are few studies with mindfulness that have focused on telomeres, but those that have been done show an increased activity of telomerase (81). If a reduced risk of

cardiovascular disease through a change in lifestyle causes a concomitant change in the expression of miRNAs and telomere length has not been investigated so far (82).

The Health and Medical Services Act (1982:763) §5 states that disease prevention work is the responsibility of primary health care. This is further described in the guidelines in Region Skåne for the financial compensation system, which describe that primary health care should actively offer citizens health-promoting and disease prevention measures (83).

> *"The Provider is responsible for ensuring that its hired staff has knowledge of, and that there are procedures for, identifying, assessing, initiating and carrying out as well as following up correct measures regarding lifestyle habits, when relevant from the Patient's perspective and the current medical condition." (p. 27; Prerequisites for Accreditation and Agreement for Health Care Center in Health Choice Skåne for the year 2016)*

The guidelines cover both primary prevention, i.e. health counselling for healthy and at-risk groups, and secondary prevention for those already diagnosed with a disease. The mission of primary care, which is to prevent illness and worsening of pre-existing disease, is important for each individual, but also from a socio-economic perspective. Secondary preventive work has been actively conducted for many years in primary care with diabetes clinics, hypertension clinics, asthma/COPD clinics and clinics for smoking cessation.

Despite the fact that there is a clear disease prevention mission and knowledge that physical activity counteracts the onset of so-called well-being diseases, the inactive time is generally increasing in the population.

Purpose

To investigate whether mindfulness can increase adherence to FAR® in inactive individuals.

More specifically, we intend to:

1. Study whether mindfulness can strengthen adherence to FAR®, i.e. increase the amount of physical activity and reduce physical inactivity.
2. Study the effect of intervention on measured vital signs, routine blood tests, self-rated health, sleep and lifestyle habits.

3. Study the effect of intervention on biomarkers e.g. inflammation markers (cytokines), microRNA and telomeres as well as the relationship between biomarkers and physical activity/inactivity.

Hypothesis

The main hypothesis is that Mindfulness increases the compliance of inactive individuals and leads to a increased physical activity and reduced inactivity.

Hypothesis 1: Self-perceived sleep problems decrease and self-perceived health increases after mindfulness/FAR®-intervention.

Hypothesis 2 The intervention with FAR/® mindfulness affects biomarkers (e.g. cytokines, miRNAs, telomeres) in individuals with low levels of physical activity.

Studies

The following describes the implementation of the research project in the health choice units involved. The project, which consists of an intervention, will run from September 2016 until December 2018 at the latest. The project starts with a pilot study that ends after 6 months of follow-up. The health choice units involved will ask all individuals seeking care and are between 40-65 years old if they want to participate in the study

Inclusion/exclusion

Individuals between the ages of 40-65, regardless of why they visit any of the committed health choice units, will be asked to participate by asking if they are insufficiently physically active (<150 minutes per week at moderate intensity or <75 minutes per week at high intensity).

Exclusion Criteria: Dementia, severe mental disorder, new-onset untreated untreated unstable anginapectoris, or myocardial infarction within 6 weeks prior to study entry. Those with physical disabilities that prevent physical activity and individuals who do not master the Swedish language in speech and writing will be excluded. Patients who have abnormal values according to guidelines that require same-day or weekly medical consultation.

Procedure Inclusion

At the care units, everyone who visits will be asked about study participation. There will be posters with information at the entrances and in other suitable places. Those who wish to participate in the study agree to this by signing informed consent after receiving oral and written information. Information about the study will be provided by the district nurse/nurse involved in the study, who will then also collect the informed consent. The opportunity to ask questions about the study will be repeated at subsequent visits as well as an opportunity to discontinue their participation. The potential research subject should estimate their physical activity level in minutes per week for inclusion assessment. The research subjects are asked to come one morning for fasting blood sampling.

Measurement methods

Physical activity; Health-promoting physical activity is any physical activity that improves health and physical capacity without causing harm or posing a risk. The international recommendation of the WHO (2011) (38) is at least 150 minutes of physical activity per week at moderate intensity, or at least 75 minutes at high intensity. Intensity refers to how strenuous the activity is. Moderate intensity refers to housework, gardening, brisk walks or the like. High intensity refers to running, swimming, aerobics, or similar.

Accelerometer: The Actigraph GT3X is a digital motion meter that will be attached to the subject at waist height. The accelerometer records the time in motion as well as the time inactivity. Over a seven-day period, about 40,000 measurement points are collected per accelerometer.

FFMQ (Five Facets of Mindfulness); is an instrument that measures five aspects of mindfulness. It consists of 29 statements where it is assessed on a five-point scale how well the statement is true "Never/almost never", "Rarely", "Sometimes", "Often" or "Always". In the compilation, the answers are graded from one to five, grouped and analyzed based on the five aspects of mindfulness (84, 85). The aspects that are measured are the ability to: Observe, Not react (in the face of inner experiences), Describe, Not judge and Act consciously. ISI (Insomnia Severity Index); is a self-assessment questionnaire that measures insomnia in order to quickly obtain a measure of the severity of sleep disorders. The scale consists of 7 questions that evaluate falling asleep, sleep during the night, early waking up, the feeling of being rested, how the sleep problems affect daily life and how the sleep pattern worries the individual. For each question, the participants must take a position on how they have experienced their sleep habits over the past two

weeks and grading the answers from 0 to 4, where 0 stands for "not at all" and 4 stands for "very". Scores between 0 to 7 indicate the absence of significant sleep problems. Scores from 8 to 14 show some sleep problems but not as a sleep disorder. Scores from 15 to 21 indicatearcclinically significant moderate sleep disorder. Scores between 22 and 28 indicate clinically significant severe sleep problems (86, 87). Self-rated health; Self-rated health encompasses all the different dimensions of the individual, physical, mental as well as social (46). The individuals' self-perceived health is estimated through a simple question- How do you think your general health is in relation to peers- with five-answer alternatives; Very good, good, somewhat, bad or very bad (47-49).

Initial visit

At the visit, participants will provide blood samples, measurement of body constitution and vital parameters, and submit completed questionnaires for mapping the hereditary prevalence of cardiovascular disease and lifestyles, and will receive accelerometers to be worn for one week until the follow-up visit. The results from the sampling here constitute the study's baseline.

The visit includes:

1. Information about the study
2. Written informed consent

Questionnaires:1)
Country of birth,2)
Occupation4)
Illness5)
Medication

6) Family history/hereditary (siblings and parents). coronary artery disease, stroke, venous thrombosis, diabetes, hypertension7) Self-assessment of lifestyle habits according to the National Board of Health and Welfare's elaborated questions regarding lifestyle habits.8) Mindfulness assessment with FFMQ9) Self-assessment sleep with ISI

Clinical examination:

1) Length

2) Weight3)
Blood pressure.

Sampling:

Plasma samples and whole blood are taken fasting for;

1) Cholesterol, triglycerides, HDL, LDL.2) fP-glucose3) Venous blood samples for later analysis of biomarkers such as proteins, DNA, RNA and

miRNAs in order to see if they can be used as prognostic biomarkers, but also to see any change after intervention. We will also analyze telomer lengths in blood using qPCR method to see the association between risk of disease but also change after intervention. Please note that those who have given consent have also given consent for us to analyze their samples even if they choose to drop out before the intervention.

Follow-up visits

The individuals who wish to participate and meet the inclusion criteria will be offered a health consultation with the district nurse for review of collected material, blood samples and questionnaires. All patients who have abnormal values according to established guidelines will follow the flow chart for usual treatment. At this visit, inclusion and exclusion criteria are checked and the patient is again informed and has the opportunity to ask questions about the study. Patients who join the study will be randomized to either mindfulness, mindfulness with FAR®, or FAR® alone. Everything is documented partly in patient records but also in patient forms (case report form; CRF) together with the serial number.

The visit includes:

3. Feedback on collected information
4. Position on inclusion/exclusion criteria
5. Any additional measurements and sampling

Randomization

The randomization takes place after the inclusion in the study but before the follow-up visit where the research subject will find out which group they belong to. After inclusion, a commercial email is sent with serial number, gender and age to the contact person (peter.nymberg@med.lu.se)

which makes a computerized randomization based on chance. The patient or staff cannot choose which group they should belong to.

Serial number

After the patient has consented to join the study, they are assigned a serial number. This serial number replaces the patient's name and social security number and then follows the patient throughout the study. Personal data will be processed in accordance with the Personal Data Act (PUL1998:204). The identification lists will be sent to the CPF and stored there in a secure manner so that no one can independently access them and separate from the collected data for 20 years after the end of the study, after which they will be destroyed. Patients' individual data can be obtained directly from the healthcare professional participating in the study or from Associate Professor Bengt Zöller in charge of research. The results of the study will be published in international peer-reviewed scientific journals.

Intervention

Three different interventions will occur in the study, prescription for physical activity, mindfulness and a combination of both.

Prescription for Physical Activity (FAR)®

Prescription for physical activity (FAR)® is a method for motivating individuals to increase physical activity based on their own abilities and preferences. The prescription must be followed up after three months according to normal routines, for evaluation in this evaluation there is the possibility of a further prescription. FAR® should be prescribed after inclusion of the district nurse who meets the patient. When prescribing, patients should also be informed about the connection between sedentary lifestyle, activity and disease. If necessary, a physiotherapist will be consulted regarding the prescription of FAR,® this applies to those with musculoskeletal problems. Prescribing of FAR® will be performed further after 3 months with follow-up after an additional 3 months

Mindfulness

The mindfulness intervention consists of an 8-week course according to the Here & Now program (88), with a course occasion in groups (about 1.5 hours/time) each week, 20 minutes of individual daily meditation practice and short everyday exercises. The daily exercises require access to a computer/tablet or smartphone, where the participants log in with their serial number. Login

will be recorded to link to the adherence at group level of the daily exercises. The courses will be given in group form with 10 participants per group.

FAR® Group

Patients in this group will receive a Physical Activity Prescription (FAR)® at baseline and after 3 months.

Mindfulness group

This group receives only an 8-week mindfulness course with one meeting per week and 20 minutes of daily exercises.

Mindfulness/FAR® group

The patients randomized to this group receive an 8-week mindfulness course with one meeting per week and 20 minutes of daily individual exercises. These patients receive FAR® at baseline and after 3 months.

Case Report Form (CRF)

For each patient, a CRF will be kept where all measurements as well as the hereditary etc. are documented. The CRF does not contain any personal data but will be marked with the patient's serial number and stored at the care unit during the study period and then collected for the CPF after completed intervention and follow-up.

Questionnaire management

The assessment forms used during the study at baseline but also during follow-up are pseudonymized and replaced with sequential numbers assigned to the patient. In the same way, the health questionnaires that are completed in connection with the sampling are handled. After that, the copied forms are sent to CPF, the copies are saved at the care units. On CPF, data will be entered via REDCAP and saved in a server that does not have an internet connection. Random sampling of input data will be performed to check the consistency of input questionnaires and laboratory value.

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Interruption

In the full study, this is compensated for an expected non-response of 30%. If a person's participation is interrupted, he or she is counted as a non-member in the analysis and is not replaced by another person. People who are asked but do not want to be included in the study are not randomized and are therefore not counted as non-response.

Follow-up of intervention group and control group

All participants in the study will be evaluated with the same measurements and samples as at baseline, as well as control for unexpected effects. Patients will be asked at 3, 6 and 12 months to submit new samples and answer the same questionnaire as at baseline. This will be done by letter, in case of no-show, the patient will be called to make an appointment for sampling. They will also be allowed to wear an accelerometer for 7 days on these occasions. Samples to be analyzed are marked with the same serial number as before and the measured values must be documented both on the CRF and in the patient record.

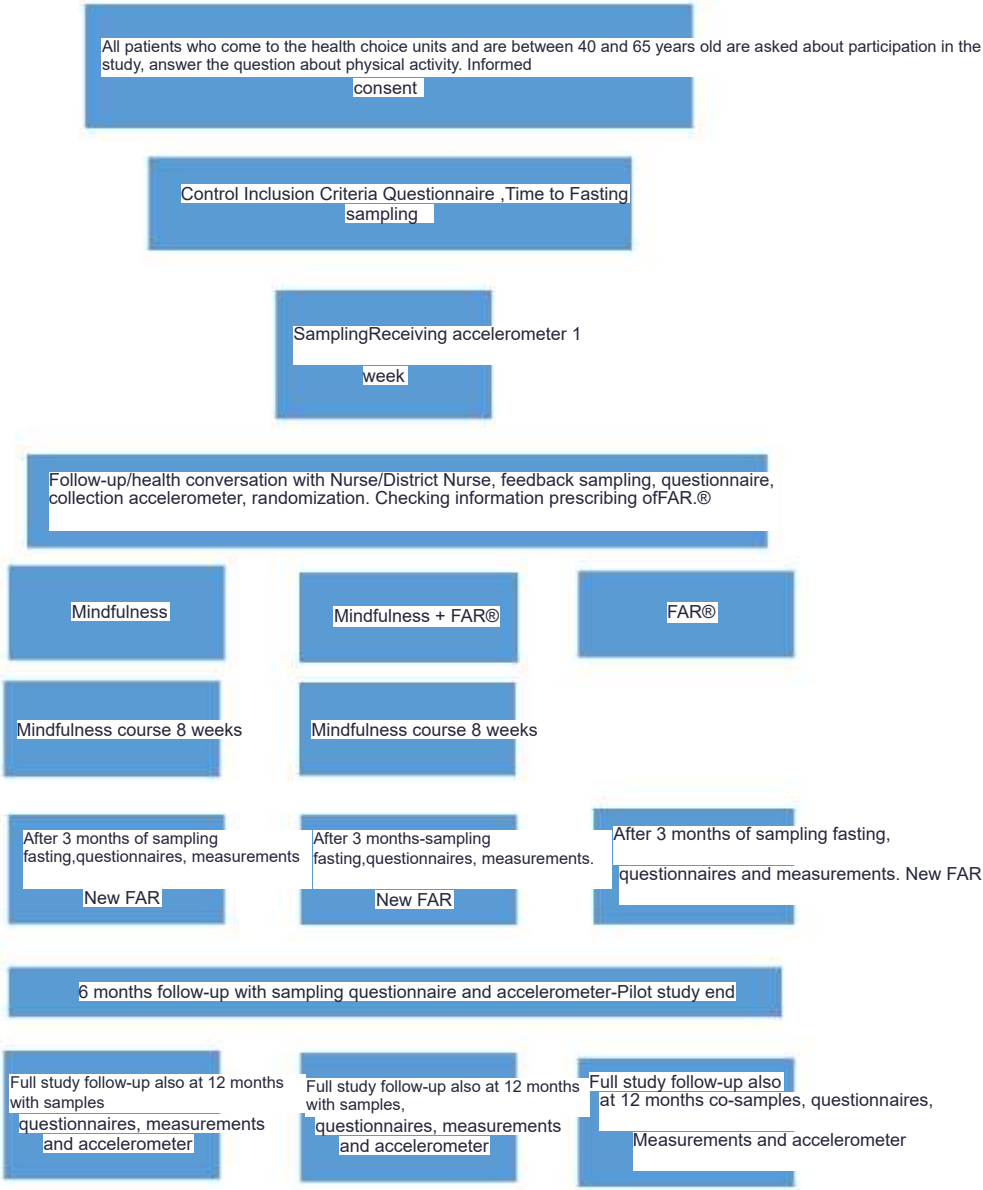
Samples for freezing

Participating health choice units perform venous sampling of the research samples according to the sampling kits sent out. This also means assisting in sending the marked test tubes to the laboratory for further handling and transport to the CPF. This refers to sampling before and after intervention and during follow-up. This means sampling at 0 months, 3 months, 6 months and at full study also at 12 months, which means four occasions per participant.

Tests and procedures

In vitro kits, including referrals, instructions and labels for labelling, will be prepared at the CPF laboratory and packed in boxes, one per participant and sampling. These boxes will be distributed to the participating health choice units. The unused tubes should be returned to the CPF after the study is completed. A detailed annex to instructions will be prepared by the CPF. The samples to be submitted to the CPF are marked with the date and the participant's serial number. Blood volume is 36 ml per test batch, a total of 108 ml after three rounds of tests and 144 ml after four rounds. It must be noted in the patient's medical record that samples have been taken as part of a research study.

Study Flowchart



Outcome measures

Association between self-rated health, lifestyle habits, heredity for cardiovascular disease, physical activity level, vital parameters and blood tests.

Change in physical inactivity and activity

Difference in inactivity between intervention group and control group as measured by accelerometer

Change in self-rated worry and anxiety according to PHQ 9 after intervention

Change in Conscious Presence According to FFMQ After Intervention

Change in sleep according to ISI after intervention

Differences in biomarker levels between the different intervention groups

Power calculation

We will carry out a pilot study in order to make a more accurate power calculation which will be based on the results of the pilot study (89). We plan to include 30 people per group in the pilot study, a total of 90 people.

The sample size for a full-scale intervention study with follow-up is based on a 1:1 ratio between the groups and calculated to N=321 in the intervention group and N=321 in the control group per group based on a power analysis with 5% significance level and 80% power. The non-response rate is calculated at about 30%. The calculation is based on other studies with compliance to physical activity on prescription as an outcome measure, where 50% of the individuals followed the recommendation on physical activity based on FAR,® we expect an increase of 25% from 50% to 62.5% adherence

Data analysis

Group comparison analysis will be conducted using chi-2 test for categorical variables. Quantitative variables will be analyzed with ANOVA or Kruskal-Wallis pre-normal-distributed and non-normally distributed variables, respectively. Correlations between different variables will be investigated using regression analyses (90).

Safety and ethical aspects

Participants in all groups are contacted by a doctor according to a flow chart if abnormal measurements appear or if physical symptoms occur during intervention that need to be assessed by a doctor. Conversations about lifestyle habits can raise thoughts and concerns about personal health, and if necessary, there will therefore be the opportunity to get feedback via the district nurse or your regular doctor. Personal identity number and name will be replaced with a serial number that follows the form and

samples through the study, which means that all data during analysis is completely without personal data and only marked with serial number. The identification lists will be kept at the health choice units until the analyses are completed, after which the identification lists will be stored at the CPF in a secure manner so that no unauthorised person can access them. Presentation of results from the study will take place at group level, which means that it is not possible to identify individuals. The individuals included in the study are covered by the Patient Injury Act (1996:799) as they are patients at visits to the health choice unit and are covered in clinical research by the same protection as if they were only patients. The study has received ethical approval from the Regional Ethics Review Board in Lund (2016/404). The study is registered on clinicaltrials.gov(20160826) rainr NCT02869854.

Economics

The research subjects participating in the study do not receive any compensation for loss of income or travel. Visits to the district nurse are currently free of charge, in the event of the introduction of a possible fee for visits to the district nurse, this should not affect the patients included in the study. The visits that may be relevant with a cost are if there is a need for treatment of a doctor/counsellor/physiotherapist contact. The health choice units are compensated with SEK 1200 per patient for the intrusion into the activities, which includes sampling and collection of data for the study. This refers to sampling before and after intervention and at follow-up after 3, 6 and 12 months. In total, the pilot study involves about 90 patients, 30 people in each group.

CPF covers the cost of all test tubes and blood analyses included in the study.
CPF is responsible for pre-printing forms, envelopes and return postage.

Expected benefits

Prevention of cardiovascular disease is of paramount importance as this is the most common cause of death in Sweden. Primary and secondary prevention of cardiovascular diseases means reduced suffering for patients and great socio-economic benefits (3). By reducing inactivity, the risk of developing the disease can be reduced. Measurement of self-rated health creates the conditions for patient-centred care by starting from the patient's experience. Patients perceive it as important to work with lifestyle habits in primary care (91) as health risks can be detected. Through lifestyle counselling in primary care, patients can receive guidance to a healthier life (91-93).

For the health choice units, this can lead to a more structured work on lifestyle habits and increased coverage, which can have a positive impact on the health choice units' finances. For the staff concerned, this can lead to increased job satisfaction.

Timetable

The pilot study is scheduled to begin in September 2016 and is expected to last no later than December 2019, The number of individuals included in the pilot study amounts to 88 individuals (180829). Full-scale study will be planned according to Power calculation based on pilot study. Analysis of collected blood samples in the biobank will be analyzed during the spring from February 2019 to December 2019 including statistical analysis and report writing.

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