PROJECT PLAN

Moving on! Can a tailored treatment in a primary care setting reduce symptoms, healthcare consumption, sick leave and prevent pain and hypertension in individuals with anxiety disorders?

Acronyms: CAU, care as usual. CBT, cognitive-behavioural therapy. CVD, cardiovascular diseases. GP, general practitioners. OR, odds ratio. PCCs, primary healthcare centers. PHRCs, primary healthcare rehabilitation centers. PHYSBI, Physical Fitness and Brain - an Interventional study. RMR, regional medical guidelines. VGR, region Västra Götaland.

Purpose and aims

Every third patient in the waiting room at a Swedish primary healthcare center is seeking help for common mental disorders including anxiety (1). Anxiety disorders substantially reduce quality of life and daily functioning and are, among mental disorders, the second leading cause of years lived with disability and the sixth-leading cause of disability globally (Global Burden of Disease Study, Lancet 2019). Anxiety disorders are also associated with elevated risks of pain, cardiovascular disease (CVD) and premature mortality (2), emphasizing the importance of finding effective treatment strategies that can be addressed in primary care.

Specific research questions

1. Can a tailored treatment and secondary prevention in a primary care setting reduce symptoms of anxiety, healthcare consumption, sick leave, pain and prevent hypertension in individuals with anxiety disorders?
2. Are there long-term effects at 1 year of follow-up regarding the outcome measures?
3. Is the treatment/secondary preventive strategy associated with health economic benefits?

State-of-the art

Anxiety disorders

Anxiety disorders are the most common mental disorders; one out of three may be affected at some point in life (3). Symptoms of anxiety range from feelings of unpleasantness and worry to a state of anxious arousal with bodily symptoms frequently found in Panic Disorder (PD) including flushed skin, shortness of breath, tremors, sweating, increased pulse and blood pressure and pupil dilation. Individuals with Generalized Anxiety Disorders (GAD) experience more constant worry and anxiety in several aspects of their daily lives. Other symptoms are muscle tension, pain and sleep disturbances that often can be misinterpreted as physical disorders. Women suffer from anxiety disorders more often than men (33% and 22% respectively over a lifetime) and the course is often chronic-recurrent (4). It has been estimated that 70% of individuals in Sweden who seek health care for symptoms of anxiety and depression initially contact primary care. Moreover, it is estimated that the Covid-19 pandemic brought on an additional 76.2 million cases of anxiety disorders globally, an increase of 26% (5). The standard treatments for anxiety disorders include cognitive-behavioural therapy (CBT) and pharmacological treatment with selective serotonin/norepinephrine reuptake inhibitors (6). They are associated with treatment barriers and disadvantages. For example, nearly one third of patients do not respond to pharmacological treatment, which may in part be due to adverse side effects and noncompliance (6). Further, anxiety disorders substantially reduce quality of life, cognitive and daily functioning and comorbidity of psychiatric and somatic nature is common (7-9). Given the burden of comorbidity and reduced capacity to work in persons with anxiety, the lack of research is surprising and alarming. For comparison, a review of modifiable risk factors for depression yielded more than five times the number of publications compared to anxiety disorders (10, 11).

Anxiety disorders, pain, and cardiovascular disease

Anxiety disorders are associated with increased prevalence of concurrent severe medical conditions, including cardiovascular disease, chronic pain, functional gastrointestinal diseases,

cancer and asthma (2, 12) as well as premature mortality (13). People diagnosed with anxiety disorders were reported to more likely have medical conditions including hypertension (OR 1.7), arthritis (OR 1.7), back/neck problems (OR 2.0), heart disease (OR 2.0), headache (OR 2.3), and multiple pains (OR 2.3), compared to a reference group in a large international study (14). The comorbidity of anxiety with cardiovascular disease and chronic pain could possibly be explained by common underlying biological processes. Allostatic load, inflammation, and hypothalamic–pituitary–adrenal reactivity may be central (15). Also, lifestyle factors such as sedentary behavior and higher prevalence of alcohol/substance use may help to explain the increased risk of medical conditions in individuals with anxiety disorders (16, 17).

Health promotion as a treatment and a secondary preventive measure

As mentioned above, individuals with anxiety disorders very often also have other medical conditions, further affecting their general health and wellbeing in a negative way. Moreover, modifiable risk factors for anxiety have been reported including cigarette smoking, alcohol use, stress, low physical activity, low social support and avoidance behaviour (10). If lifestyle-improvements can be obtained by health promotion interventions in this patient group, it may not only increase general health status but might also alleviate symptoms of anxiety.

Physical activity as a treatment and a secondary preventive measure

Similar to prevention and rehabilitation of cardiovascular disease and chronic pain (18), physical activity constitutes an important component in the prevention and treatment of anxiety (19). Physical activity can improve symptoms of anxiety (20) and recent findings indicate that anxiety could be an independent risk factor for cardiovascular disease (21), which further strengthens the use of exercise as treatment for patients with anxiety disorders. Hence, it is essential to develop interventions that may target not only mental but also physical health problems in people with anxiety disorders. The specific underlying mechanisms that may explain how exercise can reduce symptoms of anxiety are not fully explored. Theories include enhanced functional capacity, increased autonomy and improved self-esteem, and release of neurotrophic factors associated with neurogenesis, angiogenesis and neuroplasticity (22). For example, exercise per se may stimulate production of insulin-like growth factor 1 (IGF-1), which is associated with neuroplasticity and reduced anxiety-like behavior in mice (23).

Preliminary and previous results

The modified eHealth Lift in a primary health care context

We have previously evaluated, in a primary healthcare setting in Western Sweden, the implementation of a low-budget lifestyle improvement method (Hälsolyftet [The Health Lift]). We found that increased awareness resulted in readiness for own positive lifestyle changes in persons motivated for change (n=3691), with longstanding beneficial results on several risk factors (24). The method included person-centered counseling through own participant reflection and tailored support at the local primary care centre (PCC), offered to all persons visiting the PCC (n= 8 PCCs) for a wide range of health problems (24). Among health problems, anxiety disorders may well be included. The patient received a material consisting of separate questionnaires dealing with dietary habits, smoking, alcohol habits, physical activity, stress, living conditions, waist-hip-ratio and well-being expressed as a life ladder, present and future. Results were then converted into a health profile and a counsellor indicated what could be offered individually or in groups depending on the participant's wishes. For example, a smoking cessation group, motivational interviewing for risky alcohol use, stress management classes, FaR® (physical activity on prescription), and weight reduction groups. This person-centered method was based on strengthening the individual's own chosen health promoting activities and support for participation in municipal facilities. The program was shown to reach socioeconomically vulnerable and advantaged groups to the same extent and at least similar benefits (25). Through cooperation between the primary health care regional organization in region Västra Götaland (VGR) and the University of Gothenburg's Dept. of Primary Health Care, an academic course for primary care nurses and health educators was launched. The Health Lift method has been implemented in ordinary care at some PCCs in the VGR since 2015. Recently, researchers at Karolinska Institute developed a web-based version of the Health Lift (26).

The eHealth Lift, here referred to as *modified eHealth Lift*, which adds counselling and supporting, will be applied in the current project, including support from a care manager (vårdsamordnare) according to regional medical guidelines (RMR).

Exercise in the treatment of anxiety - The PHYSBI Intervention Study

We carried out a blinded, randomized, controlled clinical exercise intervention (RCT) within the primary care context (for study protocol, see (27)). There were key gaps in the literature regarding how the effects of physical exercise affect not only symptoms of anxiety but also other mental and physical health variables in patients with anxiety disorders including cognitive function, cardiovascular fitness, and work ability/sick leave. These were all issues that we addressed in the PHYSBI Study (Clinical Trial NCT03247270). Around 280 patients with anxiety disorders, aged 18-65 years, from six PCCs in two Swedish regions (VGR and Halland) took part in a 12-week exercise intervention of two different intensity levels (27). At study start, severity of anxiety among these patients was associated with impaired executive function related to working memory, independently of comorbid major depression (8). Both low and moderate/high intensity exercise reduced levels of anxiety and depression from baseline to post-treatment compared to the control group who received advice on physical activity according to public health recommendations (Fig 1) (16). Including both exercise intensities as a continuous parameter showed a significant intensity trend for anxiety symptoms. In addition, quality of life and workability (Wall et al., manuscript) and visuospatial ability (Nyberg et al., manuscript) was improved. We have recently decoded the 1-year follow-up data where the anxiety scores for the exercise intervention remained at the low level attained already at the 12-week follow-up, while anxiety scores reduced in the control group (Fig. 2). Between the 12-week follow-up and the 1-year follow-up, quality of life increased significantly in the intervention group (p=0.002) but not in the control group (p=0.356) (Fig. 3). At the 1-year follow-up, the intervention group still reported higher quality of life and work ability compared to the control group (p=0.006) (Wall et al., manuscript).

Taken together these findings strengthen the view that supervised, individualized physical exercise represents an effective treatment and secondary preventive long-lasting strategy for anxiety disorders and should be made more frequently available for persons with anxiety issues in primary care.

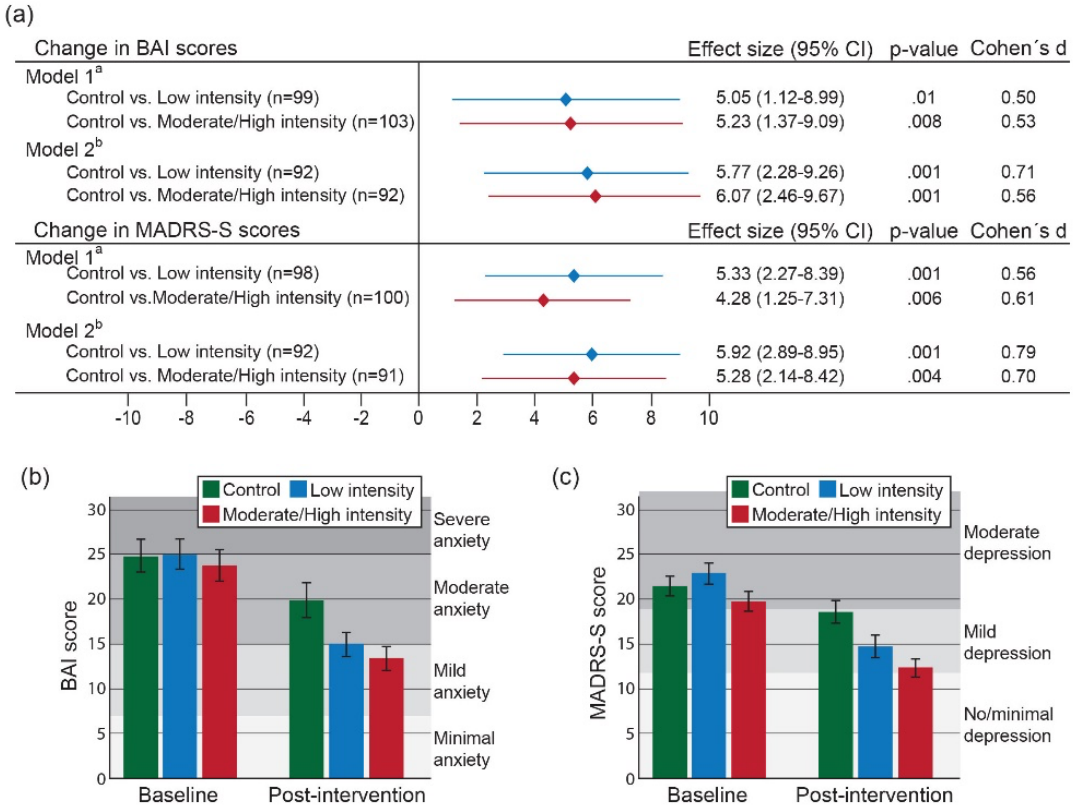

Fig. 1. 12-week follow-up data – symptoms of anxiety and depression.
Between-group treatment effects on self-rated anxiety symptoms (BAI scores) and depression symptoms (MADRS-S scores) (a). Effect sizes were accessed using analysis of covariance (ANCOVA) in a general linear model. For comparison the standardized mean differences, as expressed by Cohen's d are reported. a, Adjusted for sex and age b, Adjusted for sex, age and baseline psychoactive medication, major depression, BAI-score, cardiovascular and respiratory disorders, smoking and physical exercise at baseline. Mean BAI (b) and MADRS-S (c) scores at baseline and at post-intervention by exercise intervention group. Error bars show standard error of the estimated means. Severity levels for anxiety (b) minimal/mild (score 0–15), moderately (score 16–25) and severely (score 26–63) and for depression (c) no/minimal (score 0–12), mild (score 13–19) and moderate (score 20–34) are indicated in shades of gray.

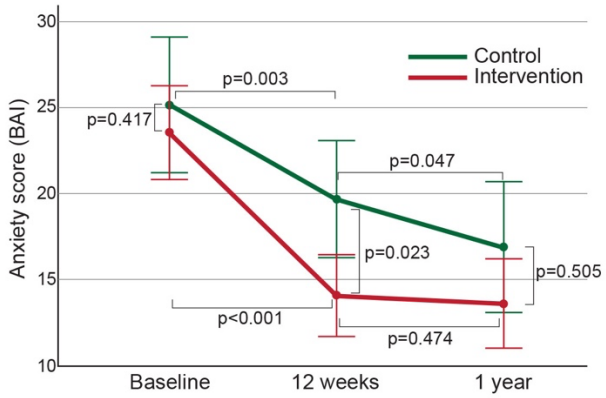

Fig. 2. 1-year follow-up data – symptoms of anxiety.
Mean (95% CI) scores of symptoms of anxiety (BAI) in the intervention group (n=75) and the control group (n=36) at baseline, after the 12-weeks intervention and at the 1-year follow up. Both within-group and between-group analyses were performed, and corresponding p-values are reported.

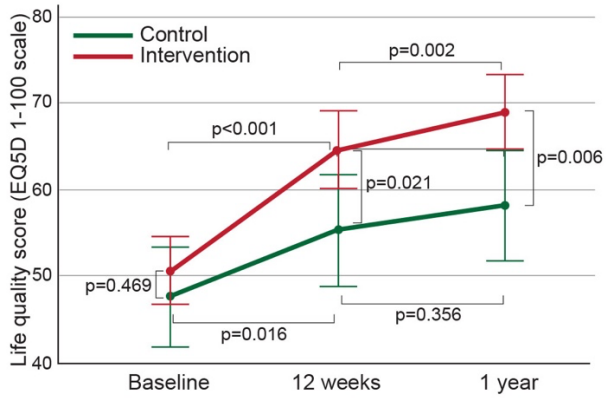

Fig. 3. 1-year follow-up data – quality of life.
Mean (95% CI) scores of quality of life (EQ5D 1-100 scale) in the intervention group (n=75) and the control group (n=36) at baseline, after the 12-weeks intervention and at the 1-year follow-up. Both within-group and between group analyses (Wilcoxon signed-rank test and Mann-Whitney U test, respectively) were performed and corresponding p-values are reported in the figure.

Significance and scientific novelty

Despite the high burden of anxiety, there are major knowledge gaps when it comes to secondary preventive measures. The intervention described in this application aim to reduce anxiety, improve the quality of life, work ability and health in primary health care patients with anxiety disorders. Little research has focused on lifestyle improvements or exercise specifically in the treatment of anxiety. In Sweden there are guidelines from The National Board of Health and welfare for treatment of depression with exercise, but guidelines for treatment of anxiety disorders are currently lacking. Also results from this study may extend the current understanding and practice in the field of treatment and secondary prevention of anxiety disorders within primary care.

There have been many different types of individual studies relating to improving physical activity, but the question remains which type of intervention is most effective? How should it be implemented in practice and from a system perspective? This project aims to combine, for the first time, evidence-based interventions to tailor a lifestyle intervention with different steps focusing on patient control and participation since the individual chooses the intervention arm. We will combine and evaluate two evidence-based lifestyle interventions: the modified eHealth Lift/Care manager

according to RMR, and PHYSBI, a promising new strategy with an intensive training program, a new approach for treating anxiety disorders. In PHYSBI we have already examined different dose regimens for anxiety in the primary care context regarding secondary preventive outcomes. Therefore, the most effective high dose regimen will be used.
If a simple intervention program in primary care can alleviate anxiety, improve quality of life, cognitive performance, and work ability, prevent pain and hypertension, this may have a great positive impact both at the individual level and from a societal perspective. In a longer-term perspective, improved treatment of anxiety might have the potential to prevent future marginalization and premature death among individuals with anxiety disorders. Should the health economic analysis show that the intervention is associated with reduced medical and sick-leave costs, these resources could be used elsewhere in an economically strained health care system.

We hope to increase the availability of person-centered, evidence-based and cost-effective measures to promote both physical and mental health in patients with anxiety disorders. Moreover, the interventions are designed to easily be implemented in regular primary care activities. Hence, the results from this study will contribute with knowledge, competence development and valuable practical guidelines for the primary care regarding treatment and secondary prevention for patients with anxiety disorders.

Project description (Fig. 4)

Design of study: A clinical intervention with a matched controlled design and two parallel arms, with three assessment points (baseline, post-intervention and 1 year of follow-up). The protocol was prepared in accordance with the SPIRIT 2013 statement (28) and will be registered at ClinicalTrial.gov.

Setting: Primary care centers in VGR, Sweden

Participants: Patients aged 18-65 diagnosed with anxiety disorders attending 22 PCCs within the VGR. Participants will be recruited by personnel at the PCCs (doctors, psychologists, nurses), through information material at the PCCs (posters, flyers and handouts) and by using the primary care system Medrave to identify and contact suitable patients. Patients diagnosed, by a GP, with anxiety disorders, including panic syndrome (F41.0), generalized anxiety (F41.1), mixed anxiety- and depression (F41.2 and F41.3), as well as anxiety NOS (F41.9) are included in the study. Patients with and without ongoing treatment with psychoactive medication (antidepressants or anxiolytics) are included. Exclusion criteria are pregnancy, physical difficulties in performing a physical exercise program, pathological electrocardiogram, low BMI (under 17.5), ongoing alcohol/substance abuse, ongoing exhaustion disorder or psychotic disorder, newly discovered (within 6 months) atrial fibrillation, high suicide risk as assessed by the GP, ongoing regular physical exercise program at a rehabilitation center as well as limited knowledge in the Swedish language. Participants will sign a written informed consent and informed about the possibility to withdraw from the study at any time without disadvantages (an interpreter will be provided if needed).

Matching: PCCs connected to a rehabilitation clinic will be assigned as intervention PCCs. These PCCs will be matched for the following variables 1) size of the PCC, 2) socioeconomy as Care Need Index (CNI) and 3) urban/rural. Matching will be executed in order to identify suitable PCCs with care as usual (controls).

The intervention: The 11 PCCs allocated to intervention will offer all patients with a registered anxiety diagnosis in the PCCs electronic patient register as well as patients newly diagnosed with any of the above listed disorders to participate in an intervention program. The patient chooses the intervention arm, and the focus is on person-centredness, control, empowerment and participation. The two intervention-options are:

1. Modified eHealth Lift, a digital development of the Health Lift, an evidence based lifestyle-intervention for health promotion and prevention in primary health care. This intervention will be executed together with care manager contact according to RMR.

2. The moderate-high intensity arm of PHYSBI, an individualized 12-week training program for anxiety disorders including 3 occasions/week. The moderate intensity arm of PHYSBI, which also will contain elements of high intensity, corresponds to 3.0-8.9 METs, Borg RPE 12-17 and 60-94% of maximal heart rate. The intervention includes cardiorespiratory and resistance training in a group-session (26). The study physiotherapists design individualized exercise programs during a single one-to-one session with the patients.

CAU (PCCs allocated to non-intervention): At Swedish PCCs, care as usual (CAU) for patients with anxiety disorders can consist of visits to various healthcare professionals (such as physicians, nurses, psychologists, therapists, physiotherapists). The treatment should follow the regional guidelines, which are based on the national evidence-based clinical guidelines for anxiety disorders (National guidelines for care of depression and anxiety disorders, The Swedish National Board of Health and Welfare, Stockholm 2020). These guidelines include psychopedagogic support, psychotherapy (cognitive behavioural therapy (CBT) face-to-face or internet-mediated), psychopharmaceutical treatment and/or sick listing (preferably partial). Patients diagnosed with anxiety disorders at PCCs allocated to CAU will be informed that their PCC is engaged in an ongoing comparative study. All individuals will be asked if they would like to participate in data collection and must give informed consent.

Outcome measures: Individual data on symptoms of anxiety, depression, general health, pain, sleep, fatigue, work ability, physical activity and perceived quality of life will be obtained through established self-assessment scales and collected for each intervention arm. Patients will self-report smoking, concurrent illnesses, pain, usage of prescribed drugs and physical activity using a questionnaire designed by the research team. Physical activity recordings with accelerometry, will be reported by the patients and registered by the research nurse. For participants in the modified eHealth lift, the health profile at baseline and after one year will be compared. We will also obtain data from the healthcare database VEGA (Database for health-care consumption in VGR), the national Patient register, the regional prescribed drug register Digitalis, the national Prescribed drug register and the MiDAS/DOA database at Försäkringskassan (includes data on sick leave >14 days).

The outcome measures for patients aged 18-65 diagnosed with anxiety disorders recorded after 3 months and 1 year are as follows:

- Main/primary outcome is symptoms of anxiety, reported using established psychiatric self-assessment scales (GAD7, HAD and MADRS-S; question 2)
- Symptoms of depression, pain, sleep, alcohol habits, fatigue, general health, work ability, physical activity and perceived quality of life, health literacy: established self-assessment scales (EQ-5D, PSQ, ISI, AUDIT, MFS, MADRS-S, IPAQ, C2WI, SFHL and HLS-19-Q12) and questionnaire data
- BMI and blood pressure (measured at PCC)
- Lifestyle questions (modified version of eHealth Lift)
- Health profile (modified version of eHealth Lift)
- Number of health care contacts with anxiety disorders: VEGA data including primary health care and hospital outpatient and inpatient care and the National Patient register, and questionnaire data.
- Psychopharmaceuticals and analgesics prescribed: Digitalis data and the Prescribed drug register and questionnaire data.
- Sick leave: MiDAS/DOA data and questionnaire data.
- Mental and Physical health: VEGA data and data from the National Patient register of ICD-10 diagnoses including common mental disorders (depression and different anxiety syndromes), pain and hypertension and questionnaire data.

Timeline and Workplan
During early 2024 a Clinical Trial registration will be submitted. We already have established contacts with gyms, the PHCRs and the Research and Development primary healthcare centres. During 2024 the collaborations with the primary healthcare organization, the PHCRs and health centres will be further established. A steering committee will be formed and the study procedures tested. During autumn 2024 the PCCs will be invited to participate. At the intervention PCCs, the recruitment of patients will be facilitated through a research nurse. At every PCC, a unique care manager manager which has been implemented at all PCCs in VGR since 2016 (29) handles the modified eHealth Lift, and the physiotherapists implement PHYSBI. The PHCRs will perform the PHYSBI arm and the involved PCCs will implement the modified eHealth Lift arm continuously during the intervention year of 2025. Study start date is anticipated to be in Jan 2025 and primary completion date in Dec 2026 (1 year of follow-up). Outcome data will be collected throughout the period 2025-2026. In 2026-2027 data will be processed, analyzed and scientific papers produced.

We cannot see any crucial risks that would hinder the execution of the proposed project. One difficulty may be the recruitment of participants, as always with clinical studies especially in primary health care. However, we will have a unique care manager and a research nurse to facilitate patient recruitment. In our previous PHYSBI study, the adherence rate was high (70%) at the 12-week follow-up.

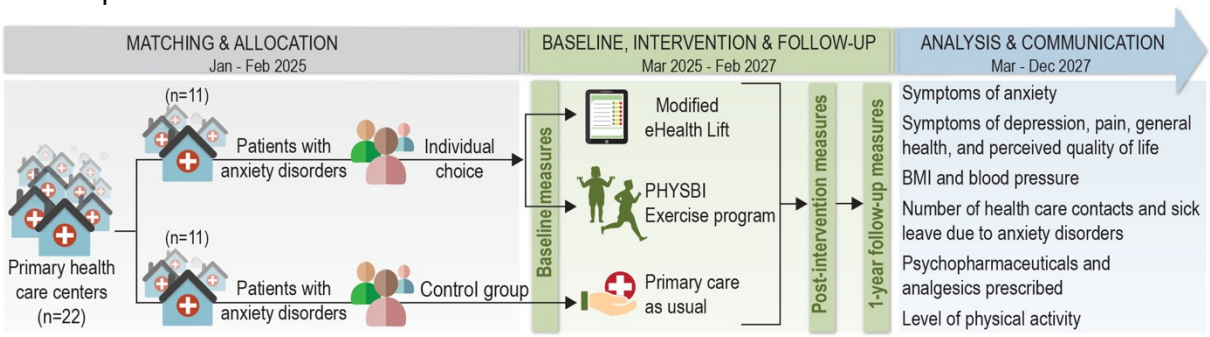

Fig. 4. Study design.

Data analysis and statistics: The majority of outcome variables are scale variables that may be treated as continuous variables and therefore primarily modelled using linear regression. These are scales for symptoms of anxiety, depression, pain, sleep, general health, perceived quality of life, sick leave days, number of health care contacts and number and types of psychopharmaceuticals prescribed. Data will be presented using descriptive statistics, including means and standard deviations for continuous variables, and frequencies and percentages for categorical variables Group differences by intervention status (modified eHealth Lift, PHYSBI, or CAU) will be assessed by Kruskal-Wallis test and chi-square tests, respectively. The average change in continuous outcomes will be analyzed using linear regression, with intervention as categorical predictor and baseline levels as covariates.

In the case of count data we will test whether Poisson or negative binomial models are more appropriate than linear regression. The correlation of outcomes between patients from the same PCC will be modelled using a hierarchical linear model including PCC as random effect. A more detailed analysis of the longitudinal change will be based on repeated-measure models that also account for the correlations within individuals. Interaction terms for PCC status and time will test whether time trends differ by intervention status. Binary endpoints such as sick leave will be analyzed using logistic regression with adjustment for correlations as described for the linear models. All regression models will be adjusted for age, sex, as well as for variables on PCC-level such as socioeconomy, number of patients listed per PCC (size), and proportion of patients with anxiety diagnoses.

Power considerations: We have performed power calculations based on 20 health centres distributed 50:50 i.e. 10 controls and 10 with two interventions. However, as patients are allowed

to choose between the two intervention types (modified eHealth Lift or PHYSBI) we will consider an unequal distribution of intervention types, e.g. 70:30 % for the modified eHealth Lift and PHYSBI. As the main outcome measures are continuous we consider Cohen's d = mean difference/SD as outcome measure, assuming small to medium effect size, i.e. d = 0.2 – 0.5 [51]. Power analysis was performed using a STATA procedure for one-way ANOVA. For a change (baseline to 3 months) we can observe effects sizes with d ≥ 0.2 and a power of ≥0.9 (significance level = 0.05) with a total of 320 individuals, distributed as 160 patients without intervention, 112 with the modified eHealth Lift, and 48 with PHYSBI. The same sample size will yield even larger statistical power if the group size for the modified eHealth Lift and PHYSBI were more alike.

Larger sample size is needed for binary endpoints such as sick leave. Assuming that about 5% of the patients will experience these endpoints during follow-up a total number of 1050 – 2200 will be needed to observe intervention-control differences by 2-3%. All our main outcome measures are continuous and since the numbers of health centres are comprehensive we conclude that the proposed analyses have sufficient statistical power to discriminate between the intervention-specific time trends. Based on our experience from the PHYSBI RCT we estimate that we can include 450 individuals with anxiety disorders undergoing the intervention year.

Health-economic analyses

Cost-effectiveness analyses will be performed separately, comparing the two intervention arms to no CAU, including both direct (healthcare and pharmaceutical utilization) and indirect (long-term sickness and absenteeism from work) costs. Cost-effectiveness analyses will be based on the primary data collected within the project and based on a combination of primary data and secondary data from other sources for lifetime time perspectives. The long-term analyses will be performed using a health-economic simulation model projecting the outcomes and cost-effectiveness at the 1-year follow-up to a longer time period (5 years and lifelong). More specifically, the within-study observed evolvement of the outcomes will be used to statistically project these outcomes for a 5-year and a lifelong time perspective. The most frequently used cost-effectiveness measures is the incremental cost-effectiveness ratio (ICER). This measure together with the net monetary benefit (NMB) will be used to characterize the cost-effectiveness of each intervention.

Sensitivity analyses with respect to these measures will be performed using either bootstrap techniques (when primary data is analyzed) or Monte Carlo simulation. The cost-effectiveness of an intervention aiming at improving health by targeting and affecting health-related behaviors depends on a couple of factors. Both the effect of the intervention on the propensity of the participants to maintain the within-intervention level of the targeted behavior over time, and the health effects attained by the new, improved level of the targeted behavior are of importance. Thus, the information about physical activity levels collected at the 1-year follow-up is essential to the health economic analyses. All analyses will follow the well-established methodology for performing health economic evaluations (30, 31). The simulation model that the planned analyses require will be constructed within the project using an accessible platform (Excel and the Visual Basic for Application facility). All health-economic analyses will be performed in collaboration with Kristian Bolin, Professor of health economics.

References

1. A N. 3.5.3 Omfattning – vad går att säga? God och nära vård - Rätt stöd till psykisk hälsa. Betänkande av utredningen Samordnad utveckling för god och nära vård. In: 2021:6 SouS, editor. Stockholm 2021: ISBN 978-91-525-0019-4; 2021. p. 164-6.
2. Batelaan NM, Seldenrijk A, Bot M, van Balkom AJ, Penninx BW. Anxiety and new onset of cardiovascular disease: critical review and meta-analysis. Br J Psychiatry. 2016;208(3):223-31.
3. Kessler RC, Petukhova M, Sampson NA, Zaslavsky AM, Wittchen HU. Twelve-month and lifetime prevalence and lifetime morbid risk of anxiety and mood disorders in the United States. Int J Methods Psychiatr Res. 2012;21(3):169-84.
4. Kessler RC, Ruscio, A.M., Shear, K., Wittchen, HU. Epidemiology of Anxiety Disorders. Stein M, Steckler, T., editor: Springer, Berlin, Heidelberg.; 2009.

5. Collaborators C-MD. Global prevalence and burden of depressive and anxiety disorders in 204 countries and territories in 2020 due to the COVID-19 pandemic. Lancet. 2021;398(10312):1700-12.
6. Baldwin DS, Anderson IM, Nutt DJ, Allgulander C, Bandelow B, den Boer JA, et al. Evidence-based pharmacological treatment of anxiety disorders, post-traumatic stress disorder and obsessive-compulsive disorder: a revision of the 2005 guidelines from the British Association for Psychopharmacology. J Psychopharmacol. 2014;28(5):403-39.
7. Balderston NL, Vytal KE, O'Connell K, Torrisi S, Letkiewicz A, Ernst M, et al. Anxiety Patients Show Reduced Working Memory Related dlPFC Activation During Safety and Threat. Depress Anxiety. 2017;34(1):25-36.
8. Nyberg J, Henriksson M, Wall A, Vestberg T, Westerlund M, Walser M, et al. Anxiety severity and cognitive function in primary care patients with anxiety disorder: a cross-sectional study. BMC Psychiatry. 2021;21(1):617.
9. Niles AN, Dour HJ, Stanton AL, Roy-Byrne PP, Stein MB, Sullivan G, et al. Anxiety and depressive symptoms and medical illness among adults with anxiety disorders. J Psychosom Res. 2015;78(2):109-15.
10. Zimmermann M, Chong AK, Vechiu C, Papa A. Modifiable risk and protective factors for anxiety disorders among adults: A systematic review. Psychiatry Res. 2020;285:112705.
11. Cairns KE, Yap MB, Pilkington PD, Jorm AF. Risk and protective factors for depression that adolescents can modify: a systematic review and meta-analysis of longitudinal studies. J Affect Disord. 2014;169:61-75.
12. Roy-Byrne PP, Davidson KW, Kessler RC, Asmundson GJ, Goodwin RD, Kubzansky L, et al. Anxiety disorders and comorbid medical illness. Gen Hosp Psychiatry. 2008;30(3):208-25.
13. Henriksson M, Nyberg J, Schioler L, Hensing G, Kuhn GH, Soderberg M, et al. Cause-specific mortality in Swedish males diagnosed with non-psychotic mental disorders in late adolescence: a prospective population-based study. J Epidemiol Community Health. 2018;72(7):582-8.
14. Scott KM, Bruffaerts R, Tsang A, Ormel J, Alonso J, Angermeyer MC, et al. Depression-anxiety relationships with chronic physical conditions: results from the World Mental Health Surveys. J Affect Disord. 2007;103(1-3):113-20.
15. Risbrough VB, Stein MB. Role of corticotropin releasing factor in anxiety disorders: a translational research perspective. Horm Behav. 2006;50(4):550-61.
16. Henriksson M, Wall A, Nyberg J, Adiels M, Lundin K, Bergh Y, et al. Effects of exercise on symptoms of anxiety in primary care patients: A randomized controlled trial. J Affect Disord. 2022;297:26-34.
17. Rudenstine S, Espinosa A, Kumar A. Depression and Anxiety Subgroups Across Alcohol Use Disorder and Substance Use in a National Epidemiologic Study. J Dual Diagn. 2020;16(3):299-311.
18. Ambrose KR, Golightly YM. Physical exercise as non-pharmacological treatment of chronic pain: why and when. Best practice & research Clinical rheumatology. 2015;29(1):120-30.
19. Kandola A, Stubbs B. Exercise and anxiety. Physical Exercise for Human Health. 2020:345-52.
20. Stubbs B, Vancampfort D, Rosenbaum S, Firth J, Cosco T, Veronese N, et al. An examination of the anxiolytic effects of exercise for people with anxiety and stress-related disorders: A meta-analysis. Psychiatry Res. 2017;249:102-8.
21. Karlsen HR, Matejschek F, Saksvik-Lehouillier I, Langvik E. Anxiety as a risk factor for cardiovascular disease independent of depression: A narrative review of current status and conflicting findings. Health Psychol Open. 2021;8(1):2055102920987462.
22. Matta Mello Portugal E, Cevada T, Sobral Monteiro-Junior R, Teixeira Guimaraes T, da Cruz Rubini E, Lattari E, et al. Neuroscience of exercise: from neurobiology mechanisms to mental health. Neuropsychobiology. 2013;68(1):1-14.
23. Ding Q, Vaynman S, Akhavan M, Ying Z, Gomez-Pinilla F. Insulin-like growth factor I interfaces with brain-derived neurotrophic factor-mediated synaptic plasticity to modulate aspects of exercise-induced cognitive function. Neuroscience. 2006;140(3):823-33.
24. Blomstrand A, Ariai N, Baar AC, Finbom-Forsgren BM, Thorn J, Bjorkelund C. Implementation of a low-budget, lifestyle-improvement method in an ordinary primary healthcare setting: a stepwise intervention study. BMJ open. 2012;2(4).
25. Waller M, Blomstrand A, Hogberg T, Ariai N, Thorn J, Hange D, et al. A primary care lifestyle programme suitable for socioeconomically vulnerable groups - an observational study. Scand J Prim Health Care. 2016;34(4):352-9.
26. Kolaas K, Axelsson E, Hedman-Lagerlöf E, Berman AH. Healthy lifestyle promotion via digital self-help for mental health patients in primary care: a pilot study including an embedded randomized recruitment trial. Prim Health Care Res Dev. 2023 Sep 20;24:e56.

27. Nyberg J, Henriksson M, Aberg ND, Wall A, Eggertsen R, Westerlund M, et al. Effects of exercise on symptoms of anxiety, cognitive ability and sick leave in patients with anxiety disorders in primary care: study protocol for PHYSBI, a randomized controlled trial. BMC Psychiatry. 2019;19(1):172.
28. Chan AW, Tetzlaff JM, Gotzsche PC, Altman DG, Mann H, Berlin JA, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. BMJ. 2013;346:e7586.
29. Sandheimer C, Bjorkelund C, Hensing G, Mehlig K, Hedenrud T. Implementation of a care manager organisation and its association with antidepressant medication patterns: a register-based study of primary care centres in Sweden. BMJ open. 2021;11(3):e044959.
30. Drummond MF, Sculpher MJ, Claxton K, Stoddart GL, Torrance GW. Methods for the economic evaluation of health care programmes: Oxford university press; 2015.
31. Briggs A, Sculpher M, Claxton K. Decision modelling for health economic evaluation: Oup Oxford; 2006.