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Patient-reported Outcomes in Peripheral Artery Disease: Measurement, Determinants and Treatment Effects

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List of Abbreviations

ABI	Ankle-brachial Index
AUDIT-C	Alcohol Use Disorders Identification Test-Consumption
BMI	Body Mass Index
CAU	Care-as-usual
CLI	Critical limb ischaemia
COPD	Chronic obstructive pulmonary disease
COSMIN INstruments	COnsensus-based Standards for the selection of health status Measurement
EQ5D-5L	European Quality of Life 5 Dimensions 5 Level Version
FCCHL	Functional Communicative Critical Health Literacy
FFKA	Freiburg Questionnaire for Physical Activity
FTND	Fagerström Test for Nicotine Dependence
GAD-7	Generalized Anxiety Disorder Assessment
HADS	Hospital Anxiety and Depression Scale
HEP	Home-based exercise program
HLQ	Health Literacy Questionnaire
HRQoL	Health-related quality of life
IC	Intermittent claudication
ICD-10-GM	International Classification of Diseases 10th Revision, German Modification
ITT	Intention-to-treat
MARS-D	Medication Adherence Report Scale
mITT	Modified intention-to-treat
NCD	Noncommunicable disease
PAD	Peripheral artery disease
PAM-13	Patient Activation Measure-13
PHQ-9	Patient Health Questionnaire-9
PROMs	patient-reported outcome measures
PROs	patient-reported outcomes
RCT	Randomized controlled trial
SEP	Supervised walking exercise program
SF-12	Short Form 12 Health Survey
SF-36	Short Form 36 Health Survey

SOC	Stages of Change Questionnaire
TBHC	Telephone-based health coaching
VascuQoL-25	Vascular Quality of Life Questionnaire-25
WELCH	Walking Estimated-Limitation Calculated by History
WIQ	Walking Impairment Questionnaire
ZAPA	Fragebogen zur Zufriedenheit in der ambulanten Versorgung – Schwerpunkt Patientenbeteiligung (engl. Questionnaire on satisfaction in outpatient care - focus on patient participation)

Background

Chronic noncommunicable diseases (NCDs) are a major cause of morbidity and mortality worldwide [1, 2]. Among these NCDs, peripheral artery disease (PAD) stands out as a leading cause of disability and death in both developed and developing countries [3]. PAD is a cardiovascular disease characterized by narrowed or blocked arteries in the legs, resulting in reduced blood flow. The primary cause of PAD is the accumulation of plaque in the arteries, known as atherosclerosis [4, 5].

PAD encompasses a wide clinical spectrum, and many patients do not exhibit any symptoms initially. However, as the arteries continue to narrow, symptoms may arise when insufficient oxygen reaches the extremities, typically the legs. The most common symptom is intermittent claudication (IC), which manifests as pain in the lower limbs during physical activity, resolving after a brief period of rest. The intensity of pain caused by IC can vary, ranging from mild to severe, and usually occurs when walking a certain distance. A serious complication of PAD is critical limb ischemia (CLI), which occurs when blood flow reduction is significant enough to cause pain at rest or tissue damage (ulceration or gangrene). In severe cases of CLI, amputation may be required if a limb is damaged due to reduced blood flow [6].

Epidemiology and Risk Factors of Peripheral Artery Disease

The prevalence of PAD has grown markedly in recent decades; between 2000 and 2010, the prevalence of PAD rose by 25% and is now the third most common cardiovascular disease worldwide, affecting up to 240 million people [7, 8]. In Germany, the prevalence in the general population increased significantly from 1.9% to 3.1% between 2009 and 2018 [9]. Furthermore, hospitalizations related to PAD increased by 20.7% between 2005 and 2009, while hospital reimbursement costs for PAD treatment grew by 21% between 2007 and 2009 [10].

The prevalence of PAD is strongly age-dependent, with higher rates observed among the elderly population [11]. Globally, it is estimated that 5.4% of individuals aged 45 to 49 and 18.6% of those aged 85 to 89 are affected by PAD [7]. In Germany, the prevalence rate in the general population ranges from 3% to 10%, with an increase to approximately 20% among individuals over 70 years of age [12]. Besides older age, other risk factors associated with PAD include male sex, cigarette smoking, hypertension, hyperlipidemia, diabetes, and a history of other cardiovascular diseases [8]. Notably, cigarette smoking is the most significant risk factor for the development of PAD [11, 13].

A sedentary lifestyle may also increase the risk of PAD [14], while exercise and physical activity have protective effects against its development [15]. Due to the aging world population and the increase in PAD risk factors, the prevalence of PAD is likely to further increase steadily in the future [11, 16].

Mental Health and Health Behavior Factors in Peripheral Artery Disease

In addition to traditional risk factors, numerous studies have emphasized the significance of mental health as a risk factor for cardiovascular disease and the development of PAD [17-19]. Mental health problems are highly prevalent among PAD patients [20-23], with young female patients being at particularly elevated risk [23-27]. The presence of mental disorders, especially depression, has been linked to PAD diagnosis [28], impaired walking ability [26, 29-32], severe leg symptoms [21], and a higher risk of mortality and other adverse events [19, 22, 26, 29-31, 33-35]. Furthermore, depressive symptoms are linked to lower health-related quality of life (HRQoL), highlighting the impact of mental distress on how PAD patients perceive their overall well-being [27, 36].

Given the various associations between mental health and PAD, researchers have begun to investigate possible mechanisms and pathways underlying this relationship. Alongside biological mechanisms, poor health behaviors have been identified as mediators in this association [18]. For example, mental distress has been linked to an increased desire to smoke [37], which in turn contributes to the development and progression of PAD [33], ultimately resulting in diminished HRQoL [38]. Similarly, the burden of mental health significantly increases the likelihood of engaging in risky alcohol consumption [39], which is considered a risk factor for cardiovascular disease and PAD [40-45].

Overall, the existing evidence indicates that the interplay between PAD status, mental health, risky health behaviors and HRQoL in PAD patients are complex and interconnected. Gaining a better understanding of these relationships is crucial for identifying modifiable targets for interventions that can slow or halt the progression of PAD—and thereby improve HRQoL.

Treatment of Peripheral Artery Disease

Based on medical guidelines and depending on the severity, there are a number of therapies for the management of PAD. These include lifestyle modifications to reduce the risk of PAD and

cardiovascular events (e.g. heart attack or stroke), including smoking cessation and participating in exercise training; taking medications (antiplatelet therapy; statins, and antihypertensive medications); and, if required, surgical revascularization procedures (e.g. angioplasty or stenting, bypass surgery, or atherectomy) [5, 46, 47]. Although effective medical PAD management is critical to mitigating the risk of adverse events, compared to other cardiovascular diseases, PAD is poorly recognized by clinicians and is often insufficiently managed [48, 49].

Increasing physical activity is generally beneficial for patients with PAD, making exercise a crucial component of PAD treatment. A supervised exercise program (SEP) is particularly valuable for individuals with IC, as it enables them to work with an experienced exercise professional who can assist in developing a safe and effective exercise plan while monitoring their progress. SEPs have been proven effective in treating PAD with IC [50], and are recommended as a first-line therapy [5, 46, 47]. Despite robust evidence supporting their efficacy [50, 51], SEPs are underutilized due to barriers in healthcare and patient-related factors. These barriers include limited course availability, restricted reimbursement of course fees, and low patient adherence [52-54].

As an alternative, structured home-based exercise programs (HEPs) have emerged as a safe and effective treatment option [55-60]. Unlike supervised clinical settings, structured HEPs can be conducted at home, allowing patients to exercise at their convenience. Several structured HEPs have demonstrated improvements in performance-based [61-70], patient-reported [61-68, 70] and cardiorespiratory fitness [69] outcomes. However HEPs may not be suitable for all patients, particularly those with severe PAD or comorbidities that require closer medical supervision [71].

For patients with more severe PAD or those who do not respond adequately to lifestyle modifications and medication therapy, surgical revascularization procedures may be considered. Angioplasty or stenting involves the insertion of a balloon or stent to widen the narrowed artery. Another option is bypass surgery, where a detour is created using a graft to bypass the blocked artery. Atherectomy, on the other hand, is a procedure that involves removing plaque buildup from the artery.

The choice of treatment depends on a variety of factors, including the severity of PAD, the presence of comorbidities, and the individual patient's preferences and goals. A multidisciplinary approach is often necessary to provide a holistic treatment plan customized to the individual patient. Despite available treatment options, more efforts are needed to ensure that PAD is properly recognized and managed to reduce the risk of adverse events and improve patient outcomes.

Diagnosis and Measurement of Treatment Outcomes in Peripheral Artery Disease

Accurately diagnosing and measuring treatment outcomes in PAD requires a comprehensive approach that involves clinical evaluation, medical history assessment, and various diagnostic tests. The ankle-brachial index (ABI), which compares blood pressure in the ankles to that in the arms, serves as a common screening tool for PAD. In addition, computed tomography angiography (CTA), magnetic resonance angiography (MRA) and duplex ultrasound provide anatomical details about arterial blockages [5, 46, 47].

Once diagnosed, measuring treatment outcomes is key to assessing the effectiveness of interventions and informing further treatment decision-making. Measuring treatment outcomes in PAD focuses on assessing improvement in symptoms, functional status (i.e., patients' ability to perform physical activities), and HRQoL. In PAD patients with IC symptoms, functional status is assessed by meausuring the ability of the patient to perform activities of daily living, mobility, and physical capacity. Treadmill tests are commonly performed to assess functional capacity and walking performance. Typically, these tests measure the distance that patients with PAOD can walk without pain along with their maximum walking distance [72]. An alternative measure, the 6-minute walk test, has been proposed to better reflect walking activity in daily life [73].

While functional tests, such as treadmill tests, have limitations as they represent an artificial form of walking that may not accurately reflect everyday walking [73], they have been primarily utilized in exercise program effectiveness studies in PAD [74]. However, they may not fully capture the patient's subjective experience and perception of their health status. Additionally, treadmills are costly and not readily available in most healthcare settings. Consequently, there is growing recognition of the importance of patient-reported outcomes (PROs) as an important adjunct to objective measures when evaluating treatment effects in PAD patients. PROs provide a patient perspective that is not captured by clinical and performance-based measures of PAD [75] and emphasize the patient's viewpoint by collecting information that is relevant to them [76]. PROs in PAD may include the patient's self-assessment of symptoms (pain), functional limitations (physical functioning), HRQoL, and the impact of PAD on various aspects of daily life [77]. These measures allow for a more comprehensive evaluation of disease progression, treatment efficacy, and the impact of interventions on patients' lives.

Patient-reported Outcomes in Peripheral Artery Disease

In contrast to objective measures, PROs are health constructs that are reported directly by patients rather than measured by health care professionals. PROs are usually reported through patient-reported outcome measures (PROMs), typically in the form of validated self-report questionnaires [75]. To capture the impact of disease from the patient's perspective, these instruments can help healthcare providers to understand the effects of a disease on patients and to track changes in their symptoms over time. These measures, which are based on a person's own perceptions and experiences, can include a wide variety of health-relevant concepts, such as symptoms, symptom burden, functional limitations across various domains, health behaviors, and multidimensional concepts such as HRQoL, which typically consist of scales that jointly assess symptoms and functional limitations [78].

There are several PROMs specifically designed to measure walking impairment and HRQoL in PAD. Two PAD-specific PROMs that have undergone extensive validation processes are the Walking Impairment Questionnaire (WIQ) and the Vascular Quality of Life Questionnaire-25 (VascuQoL-25) [79]. The WIQ is an established, reliable, and valid instrument for assessing walking impairment in patients with PAD that includes three domains: Walking distance, walking speed, and stair climbing. WIQ scores are sensitive to the effect of treatment [80, 81], and are strongly correlated with maximum walking distance [82-84], objective measures of walking disability [85], and ABI [84]. In addition, the WIQ is able to predict all-cause mortality and cardiovascular mortality [86]. In contrast to the WIQ, which is used to assess walking disability, the VascuQoL-25 assesses PAD-specific HRQoL and is divided into five subscales: Pain, Symptoms, Activities, Social, and Emotional. All subscales and the composite score of the VascuQoL-25 correlate strongly with functional status outcomes [87, 88]. The VascuQoL-25 has also been shown to be sensitive to changes in PAD severity [88, 89].

Furthermore, there are alternative PROMs available for assessing HRQoL, although they are not specifically designed for PAD. However, they allow for comparisons to be made across different conditions and settings. One frequently used generic PROM for measuring HRQoL in PAD is the Short Form 36 Health Survey (SF-36) [90]. Nonetheless, condition-specific PROMs are generally more responsive to change than generic ones and provide a more targeted assessment of PAD-related concerns [91].

Despite the availability of numerous condition-specific PROMs for PAD, their length often poses a challenge, as longer questionnaires are associated with higher attrition rates [92]. This is particularly relevant for PAD patients with multiple comorbidities who may find it difficult to complete lengthy assessments. Therefore there is a need for shorter PROMs that are still psychometrically valid. This has led to the development of the 'Walking Estimated-Limitation Calculated by History' (WELCH) questionnaire, which is a brief and psychometrically validated questionnaire that requires minimal completion time for assessing walking impairment in PAD patients, with the intention to be used routinely in clinical practice [93]. Compared to the WIQ, the WELCH has been considered less prone to errors when self-administered by the patient [93, 94], while correlating well with treadmill walking. [93, 95-97] WELCH scores range from 0 (i.e., patient is able to walk for a maximum of 30 seconds at slow speed) to 100 (i.e., patient is able to walk 3 hours or more at fast speed). To be proposed as a routine tool in the future, further external validation in larger samples and other languages are required [98].

Overall, PAD-specific PROMs have proven to be reliable and accurate in capturing information about walking impairment, functional status, and HRQoL, often assessing multiple health dimensions simultaneously [99]. Although there is no single best PROM for PAD, many of these measures have successfully met important validation milestones, with a growing body of comparative effectiveness evidence that compares the effects of different PAD treatments using both disease-specific and generic PROMs [99]. Nonetheless, although there is an increasing emphasis on PROMs to inform treatment decisions and evaluate the effectiveness of interventions [5, 100], their application in PAD trials is limited, inconsistent and non-standardized [74]. Moreover, when PROMs are utilized, they often yield different results compared to objective measures [101]. For example, the correlation between hemodynamic variables like the ABI and HRQoL measurements is generally weak [88, 102, 103], indicating that subjective factors such as stress and pain influence reported HRQoL well beyond clinical indicators [104]. To provide patient-centered care, it is crucial to incorporate PROMs into the management of PAD while acknowledging the discrepancy between PROs and objective measures [74]. This approach emphasizes the patient's perspective by collecting information that is relevant and meaningful to them [76].

Research Aims and Objectives

This dissertation aims to contribute to the advancement of patient-centered care in the field of PAD by exploring and validating the use of PROMs from various perspectives. The overall goal is

to promote the effective utilization of PROMs to enhance health outcomes for PAD patients. To accomplish this, the specific research objectives are as follows:

1. Investigate the interrelationships between different constructs measured by PROMs, including self-reported walking impairment, mental burden, risky health behaviors, and HRQoL. Despite assessing distinct outcomes, these PROMs are expected to be strongly and significantly correlated. A theory-based structural equation model will be applied to examine these interrelationships (Research Objective 1). Understanding these associations will enable better risk stratification for adverse PAD outcomes with opportunities to enhance protective factors and reduce risk factors through targeted healthcare interventions.

2. Psychometrically validate the German adaptation of the 'Walking Estimated-Limitation Calculated by History' (WELCH) questionnaire, which assesses self-reported walking impairment. With this psychometric validation study, it is intended to provide evidence on various measurement properties of the German version of the WELCH following the classical test theory framework, including the evaluation of feasibility, reliability, validity and responsiveness (Research Objective 2).

3. Assess the effectiveness of a telephone-based health coaching (TBHC) program for patients with chronic conditions (Research Objective 3.1) and a home-based exercise program utilizing TBHC and telemonitored exercise training specifically for PAD patients (Research Objective 3.2). The effectiveness of these interventions will be measured using several PROMs. By incorporating PROMs, which go beyond objective measures and encompass various health-relevant concepts from the patient's perspective, these studies aligns with the principles of patient-centered care. This approach enables researchers to assess the effectiveness of interventions based on patients' subjective perceptions of improvements in their health and overall well-being. Table 1 provides an overview of the research objectives.

Table 1. Overview of research objectives

Research Objective 1	Impact of walking impairment on mental health, risk behaviors, and HRQoL in patients with intermittent claudication
Research Objective 2	Psychometric properties of the German version of the WELCH questionnaire to assess self-reported walking impairment
Research Objective 3.1	Effectiveness of TBHC for patients with chronic conditions
Research Objective 3.2	Effectiveness of TBHC and telemonitored exercise training in PAD

Data Collection and Methods

The dissertation was carried out as part of two randomized controlled trials (RCTs): 1) "TBHC for patients with chronic conditions (Telecoach)" and 2) "TBHC and telemonitored exercise training for PAD patients with IC (TeGeCoach)". This section provides an overview of both studies, followed by a description of the methods employed to address each research objective. Detailed information on both studies can be found in the published study protocols [105, 106].

Telecoach Trial

Study design

A prospective, pragmatic, open-label RCT was conducted to compare TBHC with care-as-usual (CAU) in the management of chronic illnesses (total N= 10 815). The study duration was four years with data collection taking place at baseline (T_0), 12 months (T_1), 24 months (T_2), and 36 months (T_3) [105].

The study was conducted in accordance with the Declaration of Helsinki 2008. Approval for this study was granted by the Ethics Committee of the Medical Association of Hamburg.

Participants

To be eligible to participate in the study, participants had to be at last 18 years of age and insured at KKH statutory health insurance. Furthermore, participants had to have at least one of the following diagnoses: diabetes, coronary artery disease, asthma, hypertension, heart failure, chronic obstructive pulmonary disease (COPD), chronic depression or schizophrenia. Exclusion criteria were insufficient command of the German language, hardness of hearing, and inability to use a phone.

Recruitment and Treatment Allocation

Recruitment took place between June 2010 and October 2011. A total of 10,815 participants were eligible for the study. Prior to obtaining informed consent, eligible participants were randomly assigned to either the intervention or control group using Zelen's single-consent design [107]. Stratified random allocation was used based on sociodemographic characteristics, with a ratio of

5:1 (intervention n = 7,582; control n = 3,233). Participants assigned to the intervention group were invited to participate in TBHC and received an acquisition call. After sending back the informed consent, they were considered TBHC participants (n = 3,229). If participants did not send back the confirmation of participation, they were considered TBHC decliners (n = 4,353). This means that the intervention group comprised both TBHC participants and TBHC decliners. Participants in the control group were not invited to receive TBHC but could still opt in for participation, automatically resulting in study exclusion.

Participants received study information, relevant forms, and a baseline questionnaire by mail. To control costs, approximately n = 3,000 participants from both the TBHC decliners and control group were randomly selected to receive questionnaires.

Intervention

The TBHC concept, initially developed by Health Dialog Inc. and adapted by KKH statutory health insurance, was based on motivational interviewing, goal-setting, and shared decision-making [108]. The conversations were led by coaches following a non-directive approach. The minimum contact frequency between coaches and participants was defined as at least one telephone contact every six weeks, with a maximum intervention duration of two years. The intervention was tailored to chronic conditions with similar self-management strategies, known as "campaigns". Each campaign had a specific treatment manual: 1) Asthma, COPD, type 2 diabetes, hypertension, and/or coronary artery disease (“chronic campaign”), 3) heart failure (“heart failure campaign”) and 4) depression or schizophrenia (“mental health campaign”). Coaching was tailored to each participant's needs, and coaches had access to a web library and software program with informational materials and tools to document individual goals and medications.

The control group received usual treatment without access to TBHC.

Outcome measures

The primary outcome measure was the duration between enrollment and hospital readmission within a two-year period, as documented in routine health insurance data. Secondary outcomes included hospital care services (admission rates, days, and costs), outpatient physician and non-physician services, rehabilitation services, medication use, number and duration of work incapacity, and mortality.

Furthermore, several PROs were assessed using validated instruments and self-developed items, as shown in Table 2. Briefly, HRQoL was assessed using the 12-item Short Form Survey (SF-12) [109] and the visual analogue scale of the European Quality of Life 5 Dimensions 5 Level Version (EQ5D-5L) [110]. Health behaviors were assessed using the Alcohol Use Disorders Identification Test (AUDIT-C) [111-113], the Medication Adherence Report Scale (MARS-D) [114], and the Freiburg Questionnaire for Physical Activity (FFKA) [115] and various self-developed items. Symptoms of depression and anxiety were measured using the Hospital Anxiety and Depression Scale (HADS) [116]. Other psychosocial outcomes included the Patient Activation Measure-13 (PAM-13) [117, 118], the Functional Communicative Critical Health Literacy (FCCHL) [119], and the Stages of Change Questionnaire (SOC) [120]. Finally, clinical parameters were collected directly from patients using self-developed items.

Table 2. Overview of patient-reported outcomes in the Telecoach Trial

Outcome	Measure [validated instrument/self-developed items]
HRQoL	
Mental QoL	Short Form 12 Health Survey (SF-12) [109] mental subscale
Physical QoL	Short Form 12 Health Survey [109] physical subscale
Health status	European Quality of Life 5 Dimensions 5 Level Version (EQ-5D) Visual Analogue Scale [110]
Health behavior	
Alcohol consumption	Alcohol Use Disorders Identification Test (AUDIT-C) [111]
Medication adherence	Medication Adherence Report Scale (MARS-D) [114]
Smoking	Self-developed items
Measuring blood pressure	Self-developed items
Measuring blood sugar	Self-developed items
Foot monitoring self	Self-developed items
Foot monitoring by physician	Self-developed items
Physical activity	Freiburg Questionnaire for Physical Activity (FFKA)[115]
Body Mass Index (BMI)	Self-reported (height, weight)
Clinical parameters	
Blood pressure	Self-developed items
Hb_{A1C}	Self-developed items
Cholesterol	Self-developed items
NYHA status	Self-developed items
Psychosocial outcomes	
Patient activation	Patient Activation Measure-13 (PAM-13) [117, 118]
Stages of change	Stages of Change Questionnaire (SOC) [120]
Health literacy	Functional Communicative Critical Health Literacy (FCCHL) [119]
Anxiety	Hospital Anxiety and Depression Scale-anxiety subscale (HADS-A) [116]
Depression	Hospital Anxiety and Depression Scale-depression subscale (HADS-D) [116]
Total score	Hospital Anxiety and Depression Scale-distress; total score (HADS-T) [116]

All outcomes were assessed at T_0, T_1, T_2, T_3

T_0 = Baseline; T_1, = 12 months after baseline; T_2 = 24 months after baseline; T_3 = 36 months after baseline

TeGeCoach Trial

Study design

The TeGeCoach trial was a two-arm, parallel-group, open-label, pragmatic, randomized, controlled superiority trial with N = 1,982 participants conducted in collaboration with three German statutory health insurance funds (KKH Kaufmännische Krankenkasse, TK Techniker Krankenkasse, and mhplus Krankenkasse). The trial took place from April 2018 to February 2021. Data collection occurred at baseline (T_0), 12 months (T_1), and 24 months (T_2) [106].

The study adhered to the Good Clinical Practice quality standards and the Declaration of Helsinki 2008. Approval was obtained from the Ethics Committee of the Medical Association of Hamburg.

Participants

Inclusion and exclusion criteria are shown in Table 3. Participants needed to fulfill specific requirements, including being registered with one of the participating statutory health insurance funds, being between 35 and 80 years old, German-speaking, and having a primary or secondary diagnosis of PAD at Fontaine stage IIa (>200 m) or IIb (<200 m) within the past 36 months (corresponding ICD-10-German Modification codes I70.21, I70.22 and I73.9).

Exclusion criteria included immobility beyond claudication (Fontaine stage III or IV), physical conditions that interfere with the intervention (e.g., COPD), cognitive disorders, severe and persistent mental disorders, suicidality, life-threatening illnesses, active or recent participation in other PAD trials, ongoing hospitalization, alcoholism and/or other drug dependency, and heart failure-graded NYHA classes III and IV.

Table 3. Inclusion and exclusion criteria for the TeGeCoach trial

Inclusion criteria	Exclusion criteria
○ ≥35 years and ≤80 years ○ Insured at one of the participating statutory health insurance funds ○ Access to a telephone ○ Primary or secondary diagnosis of PAD at Fontaine stage IIa/b within the last 36 months ○ No primary or secondary diagnosis of PAD at Fontaine stage I within the last 12 months ○ No diagnosis of Fontaine stage III/IV within the last 36 months	○ Immobility that goes beyond claudication ○ (Chronic) physical conditions that interfere with the intervention ○ Cognitive disorders ○ Severe and persistent mental disorders ○ Suicidality ○ Life-threatening illnesses ○ Active or recent participation in any other PAD intervention trial ○ Ongoing hospitalisation ○ Alcoholism and/or other drug dependency ○ Heart failure graded NYHA classes III and IV

Recruitment

Recruitment was carried out by the participating health insurance funds. The first patient was enrolled on 26 April 2018 and the last on 20 December 2018. A total of 63,209 eligible patients were identified using ICD-10-GM diagnosis codes and invited to participate. The health insurance fund provided potential participants with information about the study and confirmed the PAD diagnosis. Study information, consent and permission forms were sent by mail to potential participants. Reminder phone calls were made to those who did not return the required documents. Participants who provided informed consent received a pseudonym from the health insurance fund's data warehouse.

To receive TeGeCoach, participants of the intervention group had to be supervised by a physician of their choice or an already contracted physician provided by the participants' health coaches. Participants for whom no physician was found, did not receive the intervention due to safety reasons. A total of 1 265 physicians were invited to participate in the TeGeCoach intervention, of which 627 were successfully recruited and enrolled. Physicians received financial incentives for their participation offered by the respective health insurance fund.

Treatment allocation and blinding

Participants were assigned to either the TeGeCoach intervention group or the control group (CAU) in a 1:1 ratio, stratified by health coaching center, using a permuted block method (intervention n = 994; control n = 988).

Blinding was not feasible due to obvious differences between TeGeCoach and CAU. However, a blinded analysis was achieved by employing an independent data analyst and withholding information on the treatment allocation until the completion of analytical decisions.

Intervention

TeGeCoach is a structured home-based exercise program (HEP) consisting of telemonitored intermittent walking exercise supervised by a physician, along with TBHC. The program lasted for 12 months and was based on the transtheoretical model of behavior change, motivational interviewing, active listening and shared decision-making.

Patients wore an activity tracker device that transmitted data to the health coaching platform daily. Their walking capacity was assessed at baseline to determine the appropriate training level. The assignment to a training level was reviewed by the respective physician in order to ensure patients' safety. Patients were instructed to engage in brisk walking exercises (> 50 steps/min) at least five days a week for a specific duration based on their training level. Depending on the particular training level, patients exercised for 15 minutes (level A), 30 minutes (level B) or 60 minutes (level C) including breaks.

The TBHC component included nine structured coaching calls of 30 - 60 minutes, during which the patients' progress, adherence to the walking plan, and relevant PAD topics were discussed. Additional calls were made in the event that no data was received or exercise thresholds were not met.

The control group received usual medical care provided by the statutory healthcare system, along with PAD patient information leaflets.

Outcome measures

The primary outcome measure was walking impairment, assessed using the Walking Impairment Questionnaire (WIQ) [80, 81, 85, 121].

Table 4. Overview of patient-reported outcomes in the TeGeCoach trial

Outcome	Instrument
Walking impairment (primary outcome)	Walking Impairment Questionnaire (WIQ)[80, 81, 85, 121]
Generic HRQoL	12-item Short Form Survey (SF-12) [109], *European Quality of Life 5 Dimensions 5 Level Version (EQ5D-5L) [110, 122]
PAD-specific HRQoL	Vascular Quality of Life Questionnaire-25 (VascuQoL-25) [87, 88]
Depression	Patient Health Questionnaire-9 (PHQ-9) [123]
Generalized anxiety disorder	Generalized Anxiety Disorder Assessment (GAD-7) [124]
Alcohol use	Alcohol Use Disorders Identification Test (AUDIT-C) [111-113]
Nicotine dependence	Fagerström Test for Nicotine Dependence (FTND) [125]
Health literacy	Health Literacy Questionnaire (HLQ) [126, 127]
Patient activation	Patient Activation Measure-13 (PAM-13) [117, 118]

All outcomes were assessed at T_0, T_1, T_2
T_0 = Baseline; T_1, = 12 months after baseline; T_2 = 24 months after baseline
*not reported in this dissertation

Secondary outcomes are displayed in Table 4. Briefly, HRQoL was assessed using the European Quality of Life 5 Dimensions (EQ5D-5L, not reported in this dissertation) [110, 122], the 12-item Short Form Survey (SF-12) [109] and the Vascular Quality of Life Questionnaire-25 (VascuQoL-25) [87, 88]. Depression and anxiety symptoms were assessed using the Patient Health Questionnaire-9 (PHQ-9) [123] and the Generalized Anxiety Disorder-7 (GAD-7) [124]. Health behaviors were assessed using the Alcohol Consumption Questions of the Alcohol Use Disorders

Identification Test (AUDIT-C) [111-113] and the Fagerström Test for Nicotine Dependence (FTND) [125]. Other outcomes included the Health Literacy Questionnaire (HLQ) [126, 127] and the Patient Activation Measure-13 (PAM-13) [117, 118].

In the TeGeCoach group, patient satisfaction with the intervention was evaluated at T_1 using the German Questionnaire on satisfaction in outpatient care - focus on patient participation (in German: Fragebogen zur Zufriedenheit in der ambulanten Versorgung – Schwerpunkt Patientenbeteiligung, ZAPA) [128].

Finally, the economic evaluation of TeGeCoach was conducted using claims data from the participating statutory health insurance funds. For a detailed description of health economic outcomes and additional information about the trial, see study protocol [106].

Results

Impact of Walking Impairment on Mental Health, Risk behaviors, and Health-Related Quality of Life in Patients with Intermittent Claudication (Research Objective 1)

Rezvani F, Pelt M, Härter M, Dirmaier J (2022) Effects of walking impairment on mental health burden, health risk behavior and quality of life in patients with intermittent claudication: A cross-sectional path analysis. PLoS ONE 17(9): e0273747. https://doi.org/10.1371/journal.pone.0273747

Objective

The primary symptom of peripheral artery disease is intermittent claudication, which refers to the experience of leg pain when walking. The present study investigates the extent to which walking impairment is associated with health-related quality of life, mental distress and risky health behavior.

Methods

A theory-based, cross-sectional path model was empirically examined using pre-intervention baseline data from the TeGeCoach trial [106]. The study included 1,696 patients, including measures of walking impairment (WIQ), health-related quality of life (SF-12), mental burden (GAD-7, PHQ-9), nicotine- and alcohol-related risk behavior (Fagerström-Test, AUDIT-C). Sociodemographic characteristics and comorbid conditions were included in the postulated model a priori to minimize confounding effects.

Results

Walking impairment was associated with an increase in depressive ($\beta = -.36$, $p < .001$) and anxiety symptoms ($\beta = -.24$, $p < .001$). The prevalence of depressive and anxiety symptoms was 48.3% and 35.5%, respectively, with female patients and those of younger age being at greater risk. Depressive symptoms were predictive of an increased tobacco use ($\beta = .21$; $p < .001$). Walking impairment had direct adverse effects on physical quality of life had adverse effects on physical quality of life ($\beta = .60$, $p < .001$) and indirect effects mediated by depressive symptoms ($\beta = -.16$,

$p < .001$). Walking impairment also had indirect effects on mental quality of life mediated by depressive ($\beta = -.43$, $p < .001$) and anxiety symptoms ($\beta = -.35$, $p < .001$).

Conclusions

The findings highlight the complex and interconnected relationships between walking impairment, mental distress, risky health behaviors, and HRQoL in PAD patients with intermittent claudication. A comprehensive treatment strategy that focuses on improving walking impairment through exercise training is crucial for enhancing HRQoL. Additionally, addressing depressive and anxiety symptoms through mental health treatment and promoting behavior change (e.g., smoking cessation) as a secondary prevention measure for PAD are important considerations.

Psychometric Properties of the German-language WELCH questionnaire for Measuring Self-Reported Walking Impairment (Research Objective 2)

Rezvani F, Härter M, Dirmaier J (2021) Measuring walking impairment in patients with intermittent claudication: psychometric properties of the Walking Estimated-Limitation Calculated by History (WELCH) questionnaire. PeerJ 9: e12039. https://doi.org/10.7717/peerj.12039

Objective

Patient-reported outcome measures can facilitate the assessment of walking impairment in peripheral artery disease patients with intermittent claudication in clinical trials and practice. The study aimed to assess the psychometric properties of the German version of the 'Walking Estimated-Limitation Calculated by History' (WELCH) questionnaire.

Methods

The psychometric evaluation of the WELCH was conducted within the framework of the TeGeCoach trial [106]. Analyses was based on subgroups of 1,696 patients at baseline and 1,233 patients at the 12-month follow-up (post-intervention) who completed the WELCH and other self-report measures. The assessed properties included feasibility, test-retest reliability, construct validity (convergent, divergent and known-groups validity), and responsiveness using established psychometric methods.

Results

The WELCH questionnaire exhibited favorable psychometric properties. It showed minimal floor or ceiling effects, with less than 15% of participants achieving the lowest or highest possible scores. The questionnaire demonstrated good test-retest reliability (ICC = .81, 95% CI [.71 – .88]) and was well-suited for self-completion by patients, with less than 5% missing data per item. WELCH scores demonstrated moderate to strong correlations with related measures of walking impairment at both time points (WIQ: r = .56 − .74; VascuQoL-25 activity subscale: r = .61 − .66). Furthermore, it effectively differentiated between patients with varying levels of quality of life, even when adjusting for confounding factors ($t = 13.67$, $p < .001$, $d = 0.96$). Divergent validity was indicated by weaker correlations between the WELCH and general anxiety at both time points (GAD-7: r = -.14 − -.22). The WELCH improved by 6.61 points following exercise treatment (SD

= 17.04, 95% CI [5.13 – 8.10], d = 0.39) and was able to identify large clinically important improvements observed on the walking distance (AUC = .78, 95% CI [.71 – .84]) and speed subscales (AUC = .77, 95% CI [.68 – .86]) of the WIQ.

Conclusions

The WELCH questionnaire is considered a feasible, reliable, and valid patient-reported outcome measure for assessing walking impairment in patients with peripheral artery disease. Although the WELCH questionnaire showed responsiveness to changes in walking impairment, further studies are necessary to conclusively determine its ability to detect intervention effects.

Effectiveness of Telephone Health Coaching for Patients with Chronic Conditions (Research Objective 3.1)

Dwinger S, Rezvani F, Kriston L, Herbarth L, Härter M, Dirmaier J (2020) Effects of telephone-based health coaching on patient- reported outcomes and health behavior change: A randomized controlled trial. PLoS ONE 15(9): e0236861. https://doi.org/10.1371/journal. pone.0236861

Objective

The increasing prevalence of chronic diseases poses major challenges for both patients and healthcare systems. TBHC has emerged as a promising approach to promote self-management in individuals with chronic conditions. This study aimed to evaluate the impact of a TBHC program on patient-reported outcomes in people with chronic conditions.

Methods

The effectiveness of TBHC compared to usual care was evaluated within the framework of the Telecoach trial using available baseline, 12-month follow-up, 24-month follow-up**,** and 36-month follow-up data [129]. HRQoL was assessed with the SF-12 and the EQ-5D visual analogue scale. Health behaviors were assessed using the AUDIT-C, the MARS-D, the FFKA and several self-developed instruments. Other psychosocial outcomes included patient activation (PAM), health literacy (FCCHL), behavior change (SOC), and depression and anxiety symptoms (HADS). Finally, clinical parameters were collected using self-developed instruments. Statistical analyses were conducted in a modified intention-to-treat population, excluding participants who did not attend TBHC (intervention n = 1,767; control n = 1,222), using mixed models. Data analyses were performed using R version 9.2 and IBM SPSS Statistics 23, with statistical significance set at $p < .05$.

Results

TBHC led to significantly superior outcomes compared with usual care in terms of physical activity in hours per week ($p = .030$) and metabolic rate per week ($p = .048$), BMI ($p = .009$), measuring blood pressure ($p < .001$), patient activation ($p < .001$), health literacy ($p < .001$), and stages of change ($p = .005$). However, the effect sizes for these outcomes were considered small ($d < 0.20$). Conversely, TBHC did not have a significant effect on patient-reported measures of HRQoL,

alcohol consumption, smoking, medication adherence, blood sugar measurement, foot monitoring, anxiety, or depression symptoms.

Conclusions

TBHC showed small positive effects on several patient-reported outcomes and appeared to promote some healthy behaviors in individuals with chronic conditions. Future research should focus on analyzing the effective components of the intervention and identifying those who benefit most from TBHC.

Effectiveness of Telephone Health Coaching and Telemonitored Exercise Training in Peripheral Artery Disease (Research Objective 3.2)

Rezvani F, Heider D, Härter M, König HH, Bienert F, Brinkmann J, Herbarth L, Kramer E, Steinisch P, Freudenstein F, Terhalle R, Grosse Y, Bock S, Posselt J, Beutel C, Reif F, Kirchhoff F, Neuschwander C, Löffler F, Brunner L, Dickmeis, P, Heidenthal T, Schmitz L, Chase DP, Seelenmeyer C, Alscher MD, Tegtbur U, Dirmaier J (2020) Telephone health coaching with exercise monitoring using wearable activity trackers (TeGeCoach) for improving walking impairment in peripheral artery disease: study protocol for a randomized controlled trial and economic evaluation. BMJ Open 10(6): e032146. http://doi.org/10.1136/bmjopen-2019-032146

Rezvani F, Heider D, König HH, Herbarth L, Steinisch P, Schuhmann F, Böbinger H, Krack G, Korth T, Thomsen L, Chase DP, Schreiber R, Alscher MD, Finger B, Härter M, Dirmaier J (2024) Telephone health coaching with remote exercise monitoring (TeGeCoach) in peripheral artery disease: A pragmatic, multicenter randomized controlled trial. Deutsches Ärzteblatt International 121: 323-30 https://doi.org/10.3238/arztebl.m2024.0008

Objective

Structured home-based exercise programs emerged as a safe and potentially effective treatment of intermittent claudication. The aim is to determine the effect of a remote, home-based exercise program (TeGeCoach) on patient-reported outcomes in PAD patients with intermittent claudication.

Methods

The effectiveness of a home-based exercise program compared with usual care was assessed within the framework of the TeGeCoach trial using available baseline, 12-month follow-up, and 24-month follow-up data [106]. The primary outcome was self-reported walking impairment measured by the WIQ total score. Secondary outcomes included WIQ subdomains (speed, distance, stair climbing), HRQoL (SF-12, VascuQoL-25), severity of depression and anxiety symptoms (PHQ-9, GAD-7), patient activation (PAM-13), health literacy (HLQ), alcohol use (AUDIT-C), and tobacco dependence (FTND). Statistical analyses were conducted in both intention-to-treat (ITT), i.e., all randomized patients with available baseline data (intervention n = 806; control n = 879) and modified intention-to-treat (mITT) populations, i.e., post randomization exclusion of patients without access to TeGeCoach (intervention n = 590; control n = 879), using mixed longitudinal models. Statistical significance was determined by $p < .05$, and effect sizes were calculated using

Cohen's d (≥ 0.80 large, 0.50 – 0.80 moderate, 0.20 – 0.50 small). For secondary outcomes, effect sizes d < 0.20 were regarded as clinically negligible.

Results

In the ITT population, there was a significant difference between groups in favor of TeGeCoach regarding walking impairment, the primary outcome [$F(3, 2094) = 15.02$, $p < .0001$]. The difference was 6.30 points at 12-month follow-up (95% CI [4.02 – 8.59], Bonferroni-corrected $p < .0001$, $d = 0.26$) and 4.55 points and at 24-month follow-up (95% CI [2.20 – 6.91], Bonferroni-corrected $p < .0001$, $d = 0.19$). In the mITT population, several secondary outcomes showed small group differences in favor of TeGeCoach at 12-month follow-up: WIQ walking distance ($d = 0.39$), WIQ walking speed ($d = 0.28$), WIQ stair climbing ($d = 0.20$), SF-12 physical component ($d = 0.26$), VascuQoL-25 subscales ($d = 0.22 – 0.33$), and PAM-13 ($d = 0.30$). At 24-month follow-up, all outcomes showed clinically negligible differences, except for WIQ walking distance ($d = 0.24$) and WIQ walking speed ($d = 0.21$).

Conclusions

Significant reductions in patient-reported walking impairment provides strong support for the utilization of remote, technology-based home-based programs in the management of intermittent claudication. TeGeCoach expands the ability to provide guideline and evidence-based exercise to those unable to access supervised exercise programs, particularly in the context of the COVID-19 pandemic.

Discussion

The dissertation pursued three research objectives.

Research Objective 1 aimed to explore the interrelationships among various constructs measured by PROMs, including walking impairment, mental health, risky health behaviors, and HRQoL. The aim was to gain a comprehensive understanding of how these factors are interconnected.

Research Objective 2 aimed to validate the German version of the Walking Estimated-Limitation Calculated by History (WELCH) questionnaire using classical test theory methods.

Lastly, Research Objective 3 had two components. Research Objective 3.1 aimed to evaluate the effect of TBHC on PROMs in patients with chronic conditions, while Research Objective 3.2 specifically focused on patients with PAD.

Collectively, these research objectives aimed to advance the understanding and application of PROMs in the context of PAD, with the goal of improving patient-centered care and enhancing the overall health of patients with this condition.

Summary of Results

In pursuit of the research objectives of this dissertation outlined above, five independent publications were provided. Table 5 presents a summary of the key findings and the corresponding publications.

Publication 1 [130] investigated the association between patient-reported walking impairment, mental health burden, health behavior and HRQoL in a cohort of PAD patients with IC (Research Objective 1). The path analysis revealed that poor walking ability in PAD patients with IC was linked to depressive symptoms, anxiety, and lower HRQoL. The severity of depressive and anxiety symptoms partially mediated the effect of impaired walking on mental HRQoL. Additionally, depressive symptoms and anxiety were found to increase the likelihood of tobacco smoking in PAD patients.

Publication 2 [131] examined the psychometric properties of a PROM for PAD patients, the 'Walking Estimated-Limitation Calculated by History' questionnaire (Research Objective 2). The WELCH questionnaire was found to be feasible, reliable, and valid for assessing self-reported walking impairment in PAD patients with IC. The WELCH was also able to detect large

improvements from exercise therapies in walking distance and speed, suggesting that the WELCH is responsive to treatment. In addition, the brief nature of the WELCH makes it particularly attractive compared to other questionnaires.

Publication 3 [129] investigated the effect of a TBHC program (Telecoach) on PROMs in individuals with chronic conditions compared with standard clinical care (Research Objective 3.1). Telecoach was tailored to major chronic conditions by employing three campaigns: "chronic campaign", "heart failure campaign", and "mental health campaign". Independent of the campaign, Telecoach resulted in significant improvements in patient-reported physical activity, patient activation, and health literacy.

Publications 4 and 5 [study protocol: 106; results: paper in preparation] investigated the effect of TBHC program with telemonitored exercise training (TeGeCoach) in patients with PAD compared with standard clinical care (Research Objective 3.2). TeGeCoach resulted in significant improvements in patient reported walking impairment, the primary outcome. Furthermore, TeGeCoach produced small to moderate effects on several domains of general and PAD-specific HRQoL and patient activation.

Table 5. Overview of main findings and corresponding publications

Research Objective	Results	Publication
1	***Impact of walking disability on mental health, risk behaviors, and quality of life in patients with intermittent claudication*** → The experience of HRQoL in PAD patients was strongly predicted by patient-reported walking impairment and mental burden (depressive symptoms and anxiety) → Depressive symptoms and anxiety increased the likelihood of tobacco smoking → Recommendation of a patient-centered PAD care approach through regular PROM assessments to improve HRQoL	Rezvani F, Pelt M, Härter M, Dirmaier J (2022) Effects of walking impairment on mental health burden, health risk behavior and quality of life in patients with intermittent claudication: A cross-sectional path analysis. PLoS ONE 17(9): e0273747. https://doi.org/10.1371/journal.pone.0273747
2	***Psychometric properties of the German version of the WELCH questionnaire to assess self-reported walking impairment*** → Well suited for self-completion (< 5% missing data per item) → No floor or ceiling effects (< 15% achieved lowest or highest possible scores) → Good test-retest reliability (ICC = .81, 95% CI [.71 – .88]) → Convergent and divergent validity: moderate to strong correlations with related measures of walking impairment (WIQ: r = .56 − .74; VascuQoL-25 activity: r = .61 − .66); weak correlation with general anxiety (GAD-7: r = -.14 − -.22)	Rezvani F, Härter M, Dirmaier J (2021) Measuring walking impairment in patients with intermittent claudication: psychometric properties of the Walking Estimated-Limitation Calculated by History (WELCH) questionnaire. PeerJ 9: e12039. https://doi.org/10.7717/peerj.12039

	→ Known-Groups validity: distinguished well among patients with poor and high HRQoL (t = 13.67, p < .001, d = 0.96) → Responsiveness: improved by 6.61 points (SD = 17.04, 95% CI [5.13 – 8.10], d = 0.39) in response to exercise treatment; identified large clinically important improvements in WIQ walking distance (AUC = .78, 95% CI [.71 – .84]) and WIQ walking speed (AUC = .77, 95% CI [.68 – .86]) → The WELCH is a feasible, reliable, and valid for assessing self-reported walking impairment in PAD patients with IC	
3.1	***Effectiveness of TBHC for patients with chronic conditions (TeleCoach)*** → Telecoach led to significant improvements in patient-reported physical activity (p = .030), patient activation (p < .001), and health literacy (p < .001) in a modified intention-to-treat population → The corresponding effect sizes were all considered small (d < 0.20) → The use of telephone health coaching for patients with chronic condition is associated with beneficial effects on several patient-reported outcomes	Dwinger S, Rezvani F, Kriston L, Herbarth L, Härter M, Dirmaier J (2020) Effects of telephone-based health coaching on patient-reported outcomes and health behavior change: A randomized controlled trial. PLoS ONE 15(9): e0236861. https://doi.org/10.1371/journal.pone.0236861
3.2	***Effectiveness of TBHC and telemonitored exercise training in PAD (TeGeCoach)*** → Primary outcome: TeGeCoach resulted in significant improvements in patient reported walking impairment (WIQ, p < .0001) in an intention-to-treat population → Secondary outcomes: TeGeCoach produced small to moderate effects on walking distance (d = 0.39), walking speed (d = 0.28), stair climbing (d = 0.20), physical HRQoL (d = 0.26), PAD-specific HRQoL (d = 0.24 - 0.48) and patient activation (d = 0.30) in a modified intention-to-treat population → The use of telephone health coaching and telemonitored exercise training for PAD patients is associated with beneficial effects on several patient-reported outcomes	Rezvani F, Heider D, Härter M, König HH, Bienert F, Brinkmann J, Herbarth L, Kramer E, Steinisch P, Freudenstein F, Terhalle R, Grosse Y, Bock S, Posselt J, Beutel C, Reif F, Kirchhoff F, Neuschwander C, Löffler F, Brunner L, Dickmeis, P, Heidenthal T, Schmitz L, Chase DP, Seelenmeyer C, Alscher MD, Tegtbur U, Dirmaier J (2020) Telephone health coaching with exercise monitoring using wearable activity trackers (TeGeCoach) for improving walking impairment in peripheral artery disease: study protocol for a randomized controlled trial and economic evaluation. BMJ Open 10(6): e032146. http://doi.org/10.1136/bmjopen-2019-032146 Rezvani F, Heider D, König HH, Herbarth L, Steinisch P, Schuhmann F, Böbinger H, Krack G, Korth T, Thomsen L, Chase DP, Schreiber R, Alscher MD, Finger B, Härter M, Dirmaier J (2024) Telephone health coaching with remote exercise monitoring (TeGeCoach) in peripheral artery disease: A pragmatic, multicenter randomized controlled trial. Deutsches Ärzteblatt International 121: 323-30 https://doi.org/10.3238/arztebl.m2024.0008

Comprehensive Discussion

The current dissertation contributes to the expansion of knowledge regarding the use of PROMs in PAD patients. As the impact of PAD extends beyond physical symptoms, PROMs offer valuable insights into how PAD and its treatment impact patients from their own perspective, which cannot be solely captured by biomedical outcomes. Certain "subjective" health outcomes, such as symptoms (e.g., pain), functional outcomes (disability or activity limitations, e.g., physical and

emotional functioning) and HRQoL are challenging to measure objectively and are therefore best captured through PROMs. Moreover, patients can also provide valuable information about their health behaviors and treatment satisfaction, providing some unique benefits compared to objective or clinically rated measures.

With increasing focus on patient-centered care, PROMs are increasingly being used to assess the impact of PAD on patients' HRQoL. Reflecting the physical, social, and psychological well-being of PAD patients, HRQoL, is increasingly viewed by clinicians and other stakeholders as an important indicator of treatment success [90, 132]. However, one research gap in the field of PROMs for PAD patients is what other patient-relevant outcomes primarily predict the experience of HRQoL in PAD patients. In a comprehensive path analysis, Publication 1 found that the experience of HRQoL in PAD patients was strongly predicted by several patient-reported constructs. Specifically, patient-reported walking disability and self-reported mental health burden emerged as significant predictors of HRQoL. These findings align with previous studies which have shown that the experience of HRQoL in PAD patients is primarily predicted by patient-reported measurements of physical function [102, 133], but is only marginally associated with clinical markers and objective measurements of walking impairment [103, 134, 135], as well as HRQoL assessments by clinicians [136]. These associations emphasize the importance of PROM assessments in helping clinicians optimize patient-centered care for PAD patients by ensuring that healthcare decisions are based on a comprehensive assessment of patient relevant outcomes. Specifically, the findings highlight opportunities to improve HRQoL and advocate for an integrated, multidisciplinary, patient-centered PAD care approach that incorporates the patient experience through regular PROM assessments and addresses the complex care needs of PAD patients. Further work is needed to determine how exactly PROMs can be used in clinical practice for improving HRQoL and other patient relevant outcomes in PAD patients.

While there are increasing demands to measure PROMs and incorporate them into the clinical care of PAD patients, many of the PAD-specific PROMs currently used in the field of PAD are very long and often do not meet criteria for validation [79, 99]. Before implementing PROMs, it is essential to establish their psychometric appropriateness specifically for the intended patient population. Numerous PROMs have been developed and validated for use in PAD patients; however, it is well documented that many PROMs in the field of PAD are of questionable quality, and only a limited number of them have been examined in terms of responsiveness, which is crucial for assessing treatment effects [99]. Even more strangely, a significant number of psychometric validation studies conducted in the field of PAD do not follow the established quality standards

for evaluating the psychometric properties of PROMs [98]. The improper use of PROMs in clinical PAD research is increasingly concerning and has the potential to in unjustifiable health care recommendations, especially as PROMs are increasingly used as outcomes in effectiveness trials.

Recognizing this gap in knowledge, Publication 2 was to conduct a validation study of a PROM for measuring walking impairment following the principles of classical test theory—the WELCH questionnaire. The WELCH was found to enable the assessment of walking impairment in PAD patients while compensating for limitations of others PROMs, with the intention to be used in routine clinical practice. Given the promising feasibility, validity, and responsiveness of the WELCH, clinicians can quickly gain insight into the PAD patient's walking impairment condition without the need for cumbersome and time-consuming functional assessments. The WELCH has been translated and cross-validated into various languages, but the present study is the first to WELCH the psychometric properties of the WELCH in a German PAD population. Further high-quality validation studies are necessary to determine suitable PROMs for implementation in clinical settings. In this context, however, it is important to establish minimum quality standards and encourage the standardization of study methodologies. The COnsensus-based Standards for the selection of health status Measurement INstruments (COSMIN) checklist, for instance, sets universal quality criteria and provides a rigorous methodological framework that helps to minimize methodological biases.

When properly validated, PROMs provide valuable insights into the benefits of new interventions from the perspective of PAD patients. The integration of PROMs in clinical PAD research enables the identification of specific concerns that patients face, leading to informed treatment decisions, enhanced patient satisfaction, and improved treatment outcomes.Therefore, PROMs are frequently incorporated into PAD trials as secondary endpoints to aid in the interpretation of the primary endpoint. Additionally, they can be utilized as exploratory or tertiary endpoints, with the aim of generating hypotheses for subsequent investigations. Exercise trials, for instance, commonly utilize PROMs, demonstrating their effectiveness in enhancing patient-reported walking ability and HRQoL [137]. Moreover, the increasing importance of cost-effectiveness evaluations has further increased the demand for incorporating PROMs in PAD trials.

Despite increasing calls [138], a significant research gap exists as PROMs are not typically used as primary endpoints, often due to uncertainty regarding their appropriate application. To address this gap, Research Objective 3 was to evaluate the impact of a TBHC program on various PROMs for patients with chronic conditions (3.1) and specifically those with PAD (3.2). Both trials

demonstrated noteworthy treatment effects on several PROMs. A significant finding was that the interventions had a considerable influence on patients' ability and willingness to manage their chronic conditions, known as patient activation and measured by the PAM-13, in both patients with chronic conditions specifically patients with PAD. Overall, this emphasizes the significance of PROMs in measuring patient-relevant treatment effects, as certain aspects of health, such as patient activation, cannot be measured using objective endpoints.

To conclude, in the era of patient-centered care, PROMs play a crucial role in assessing the impact of PAD on patient relevant outcomes. Further efforts should be made to improve the quality and validation of PAD-specific PROMs. With ongoing advancements in the field, PROMs will continue to be instrumental in assessing the patient's reported disease burden, evaluating treatments and interventions, and ultimately enhancing the care provided to PAD patients.

Strengths and Limitations of Individual Studies

The main strengths of the research conducted in this dissertation are the rigorous theoretical approach, thorough and stringent research methodology, and careful analyses. All individual studies were conducted according to the highest standards and best practices of the scientific method. Furthermore, all studies were conducted with very large sample sizes, which overall resulted in high statistical power. As a result, it was possible to draw statistically robust and firm conclusions concerning the research findings.

In Publication 1, several causal hypotheses were formulated on the basis of the underlying theory and then translated into a path model. The model fit was then evaluated for plausibility and modified using a series of goodness-of-fit tests. The methodological approach combines confirmatory and an exploratory approaches to data analysis in which hypotheses are first generated based on theory and then empirically tested. This resulted in a path model that provides a comprehensive perspective on the interrelationships between multiple patient-relevant measures in PAD patients. However, when interpreting the findings of the path analysis, it is important to note that it has limitations in establishing the direction of causality and temporal relationships between the PROMs, which can only be determined through longitudinal studies. Nevertheless, the findings from the path analysis serve as valuable inputs for generating causal hypotheses and guiding future studies.

In Publication 2, the psychometric validation of the WELCH questionnaire was based on the COSMIN checklist, which establishes guidelines for the psychometric validation of health status

PROMs and provides a rigorous methodological structure that helps minimize methodological bias. This means that the measurement properties have been thoroughly evaluated to the highest scientific standards to ensure that the WELCH is a reliable, valid, and useful tool for measuring walking impairment in patients with PAD. However, it is important to acknowledge a limitation of the validation process, which relied solely on self-report measures and subjective assessments, lacking objective measures of walking impairment. Consequently, the criterion validity of the WELCH questionnaire could not be established, highlighting the need for future research incorporating objective measures to further strengthen its validation.

Finally, in Publication 3, 4 and 5, two clinical trials in PAD and chronically ill patients were conducted, which are considered the gold standard for evaluating the effectiveness of interventions. The inclusion of PROMs as primary and secondary endpoints enabled a comprehensive assessment of the interventions' impact on various aspects, including patients' symptoms, HRQoL, functional capacity, and other relevant measures. These studies employed a pragmatic study design, conducted in real-world settings, which enhanced the generalizability and external validity of the findings. However, it is important to acknowledge that the absence of objective outcomes in these trials represents a limitation. Objective outcomes typically provide direct measurements of physiological or clinical changes resulting from the treatment and can capture subtle effects that may not be captured by PROMs alone. Relying solely on PROMs introduces the potential for subjective bias, particularly in unblinded trials where patients are aware of the treatment assignment. This awareness may lead patients to consciously or unconsciously modify their responses based on their expectations or perceptions of the treatment received. To address this limitation, future studies should consider incorporating objective measures that are less susceptible to subjective bias, in conjunction with PROMs. This combined approach would yield a more comprehensive and reliable evaluation of treatment effectiveness.

Implications for Research and Clinical Practice

Following a patient-centered approach, PROMs are indispensable for assessing outcomes most important to PAD patients, including symptoms, HRQoL, and functional status. With a growing comparative effectiveness evidence base of PAD treatments and interventions, PROMs are now also increasingly used as study endpoints to measure the effect of treatments from the patients' perspective and to help researchers understand the true impact of a treatment on patients' lives [139]. From 2004-2007 to 2007-2013, the use of PROMs increased from 14% to 27% of trials registered on ClinicalTrials.gov [140, 141]. This upward trend in PROMs usage in clinical trials may

be attributed to encouragement from regulatory agencies[142], continued calls from medical societies and experts [138, 143] and recommendations outlined in medical guidelines [144].

In the realm of clinical PAD research, there is a growing consensus that PAD trials should incorporate PROMs as study endpoints to promote better patient-centered research [74]. Moreover, the utilization of PROMs tends to be more cost-effective than other measures, such as physical examinations, and data can be collected electronically, reducing the need for additional appointments and medical staff time. Additionally, the use of PROMs in PAD trials may increase patient recruitment and engagement, as patients are more likely to participate in a study that focuses on outcomes of their interest and are more likely to continue participation if they feel that their experiences are being taken into account. Nonetheless, it is crucial to acknowledge that while PROMs are integral for a comprehensive understanding of treatment effects, they should be viewed as complementary to and not as a substitute for objective measures [99]. Considering the frequent variability in outcomes between PROMs and objective measures [101], it is advisable to use a combination of multiple PROMs and objective measures for assessing walking impairment.

Despite PROMs have received much attention in PAD research contexts, their integration into clinical settings remains limited [74]. Clinicians have traditionally been trained to assess clinical measurements, while the assessment of PROMs is a relatively recent development. However, at the individual patient level, PROMs can prove particularly useful for NCDs such as PAD, as patients are likely to live with their disease for many years so that many efforts are aimed at alleviating symptom burden and slowing disease progression rather than finding a cure. The use of PROMs enables healthcare professionals better understand the impact of PAD on patients' lives by providing real-time information about symptoms, functional status, and HRQoL. This information allows for personalized treatment approaches tailored to the specific needs of each patient. For example, if a patient reports that pain is their primary concern, a physician may consider prescribing medication to treat their symptoms. Conversely, if a patient indicates that mobility is their biggest concern, a physician may recommend an exercise program. Additionally, one challenge many clinicians may face is selecting which patients are appropriate for initial exercise therapy and determining the appropriate intensity, frequency, and duration, or whether a revascularization strategy should be considered first instead. The use and assessment of PROMs can be valuable in aiding these decision-making processes.

PROMs have another crucial role in clinical settings, which is measuring treatment outcomes. The Inter-Society Consensus for the Management of Peripheral Arterial Disease, a guideline for the

management of peripheral arterial disease, acknowledges the significance of incorporating PROMs when evaluating the success of IC treatment in clinical practice [144]. Furthermore, PROMs can be used to quantify the quality of PAD care in real time and monitor treatments effectiveness over time through routine PRO assessments, which is known as "measurement-based care" [145]. By regularly assessing patients' symptoms and HRQoL, health professionals can determine whether a treatment is effective and adjust the plan accordingly. For example, if a patient's PROM scores indicate worsening symptoms or decreased HRQoL, their healthcare provider may adjust their treatment plan or refer them for additional support. By integrating PROMs into clinicians' decision making, PROMs can be useful in helping physicians make more informed decisions about treatment options and tailor treatment to individual patients, believing that patient themselves are experts in assessing their own well-being.

In doing so, clinicians have access to a range of PROMs for PAD patients. For instance, one commonly used PROM is the WIQ, which assesses a patient's walking ability across different distances and speeds. Alternatively, the VascuQol-25 focuses on measuring the impact of the condition on a patient's HRQoL, encompassing physical, emotional, and social aspects. However, the selection of a specific PROM may be influenced by various factors, including patients' characteristics, the burden of administration, and treatment strategies. It is crucial for clinicians to select well-validated PROMs that align closely with the treatment and the expected outcomes to ensure comprehensive coverage of relevant domains important to patients.

Overall, PROMs can be a valuable tool for clinicians and researchers in the field of PAD. This development paves the way for a future in which health care will particularly focus on optimizing the health status of PAD patients via PRO measurements [146, 147], with the goal to better meet the care needs of PAD patients. Healthcare providers should consider incorporating PROMs into their clinical practice to better understand the patient's experience of the condition and to tailor treatment plans to meet their individual needs. By incorporating PROMs into routine practice, the shift towards patient-centered care in PAD treatment can be realized. However, the successful implementation of a "measurement-based" approach relies on collaborative efforts between clinicians and patients in collecting and interpreting PROM data.

Limitations of and Recommendations for using PROMs in Peripheral Artery Disease

The use of PROMs in PAD is gaining importance, as patients are considered the gold standard source of information for assessing patient-related concepts. However, there are also limitations to the use of PROMs in PAD patients. First, PROMs are based on patient self-report and therefore may not always be accurate or complete. Specifically, PROMs may be subject to response bias and may not reflect objective changes in a patient's health status, potentially resulting in overestimation or underestimation of their functional limitations. Objective measures of walking distance are important indicators of disease severity and response to treatment that may not be fully captured by PROMs [148]. For healthcare providers, it is therefore important to use a combination of PROMs and objective measures to fully capture the experience of PAD patients.

Second, PAD is a complex and heterogeneous condition that affects patients differently. A single PROM may not capture the unique aspects of each patient's experience with PAD. For instance, the commonly used WIQ focuses primarily on walking ability but may not capture other important domains, such as pain and emotional well-being. For a comprehensive picture of the patient's condition, it is therefore advisable to use several PROMs together or multidimensional PROMs (e.g. VascuQol-25) that cover different areas of PAD.

Third, PROMs may not adequately capture the dynamic nature of PAD. Fluctuations in functional limitations due to factors like comorbid diseases and disease progression can impact patients' experiences. The presence of diabetes, for example, is associated with lower self-reported walking distance and HRQoL [149]. In addition, the presence of diabetes could reduce the perception of symptoms of ischemia, which, paradoxically, positively influence the perception of walking ability. This is problematic given that PROMs may be used for clinical PAD classification, clinical decision making (e.g. invasive versus noninvasive approaches), and measurement of treatment outcomes. When developing and validating PROMs, it is therefore of great importance to define and describe exactly for which clinical population the specific PROM is intended. Moreover, when choosing PROMs for clinical practice and trials, it is essential to take into account the specific characteristics of the target population.

Lastly, some PROMs in the field of PAD may have limited sensitivity to change (responsiveness), making it challenging to detect small changes in disease status or treatment response. To date, very few validation studies of responsiveness of PRO instruments have been conducted, and these have

often found a lack of or limited responsiveness [98, 99]. Given the frequent use of PROMs in clinical trials and the call for PROMs to be used as part of a measurement-based approach to PAD care, it is of great importance to consider the sensitivity to change in the context of different treatment options, otherwise treatment effects that are rather small may not be properly detected. As an example, the WELCH validation study conducted as part of this dissertation demonstrated that it was sensitive to large exercise treatment effects, but not to smaller effects [131]. This poses a challenge since many PAD therapies tend to have relatively modest effects. To date, the WIQ and VascuQol-6 have been shown to respond well to revascularization and may therefore be suitable for measuring treatment effects [99] However, further psychometric validation studies are needed assessing the responsiveness of PROMs in greater detail.

Despite these limitations, PROMs are valuable tools for understanding the overall impact of PAD on patients' lives and assessing treatment effectiveness. It is important to acknowledge these limitations when interpreting results and to continue conducting psychometric validation studies to address existing gaps, particularly regarding responsiveness.

Conclusions

The dissertation highlights the importance of PROMs in evaluating the impact of PAD on patients' HRQoL and other patient-centered outcomes. It emphasizes the potential for improving patient-centered care for PAD patients by integrating PROM assessments while addressing their complex care needs. The findings of the dissertation hold significant implications for clinical practice, research, and healthcare policy, forming the basis for future research and development in this important area.

Despite the value of PROMs in assessing patient relevant outcomes, the quality of many PAD-specific PROMs remains questionable. This necessitates high-quality validation studies and standardization of study methodology. As a response, the WELCH questionnaire has undergone comprehensive psychometric validation following COSMIN criteria and has shown promise in terms of feasibility, validity, and responsiveness. It provides clinicians with a rapid and effective method of assessing walking impairment of PAD patients, reducing the reliance on time-consuming functional assessments.

Furthermore, the dissertation explores the effect of a TBHC program on various PROMs for patients with chronic conditions, including those with PAD. The findings demonstrate that PROMs provide a greater insight into the true impact of treatment on patients' lives. Incorporating

PROMs in clinical PAD research is essential in identifying areas of concern from a patient's perspective and informing treatment decisions. Moreover, the use of PROMs in evaluating the effectiveness of interventions can help tailor interventions to meet individual patient needs. Consequently, PROMs play a vital role in assessing the impact of interventions, providing a more comprehensive assessment of treatment outcomes and advancing patient-centered care.

By using PROMs, clinicians can identify areas where interventions can enhance patient outcomes and improve the quality of care provided. Ongoing advances in the development and validation of PAD-specific PROMs offer tremendous potential to enhance the management and care of PAD patients, leading to improved overall health outcomes. Thus, it is imperative to promote the adoption of PROMs in clinical practice and research to advance the management and outcomes of PAD patients. In conclusion, the dissertation demonstrates that PROMs have enormous potential in the realm of PAD, providing valuable insights into patients' perspectives and helping clinicians provide more effective and patient-centered care.

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Publications

Publication 1: Effects of walking impairment on mental health burden, health risk behavior and quality of life in patients with intermittent claudication: A cross-sectional path analysis

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RESEARCH ARTICLE

Effects of walking impairment on mental health burden, health risk behavior and quality of life in patients with intermittent claudication: A cross-sectional path analysis

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Abstract

Introduction

Intermittent claudication is the leading symptom of peripheral artery disease (leg pain when walking). The present study investigates the extent to which walking impairment is associated with health-related quality of life, mental health and health risk behavior.

Methods

A theory-based, cross-sectional path model was empirically examined using pre-intervention baseline data from a multicenter, randomized-controlled trial of patients with intermittent claudication (*PAD-TeGeCoach*). Data were available from 1 696 patients who completed a battery of questionnaires between April 14, 2018 and March 12, 2019, including measures of walking impairment (Walking Impairment Questionnaire), health-related quality of life (SF-12), mental burden (GAD-7, PHQ-9), nicotine- and alcohol-related risk behavior (Fagerström-Test, AUDIT-C). Sociodemographic characteristics and comorbid conditions were included in the postulated model a priori to minimize confounding effects.

Results

Walking impairment was associated with an increase in depressive ($\beta = -.36$, $p < .001$) and anxiety symptoms ($\beta = -.24$, $p < .001$). The prevalence of depressive and anxiety symptoms was 48.3% and 35.5%, respectively, with female patients and those of younger age being at greater risk. Depressive symptoms were predictive of an increased tobacco use ($\beta = .21$; $p < .001$). Walking impairment had adverse effects on physical quality of life, both directly ($\beta = .60$, $p < .001$) and indirectly mediated through depressive symptoms ($\beta = -.16$, $p < .001$); and indirectly on mental quality of life mediated through depressive ($\beta = -.43$, $p < .001$) and anxiety symptoms ($\beta = -.35$, $p < .001$).

Federal Joint Committee (G- BA), the highest decision- making body of the joint self-government of physicians, dentists, hospitals and health insurance funds in Germany. The use of grant funds is monitored by the German Aerospace Center (Deutsches Zentrum für Luft- und Raumfahrt; DLR). Neither the G- BA nor the DLR was involved in the actual conduct of this work (ie, study design, data collection and analysis, decision to publish, or preparation of the manuscript).

Competing interests: The authors have declared that no competing interests exist.

Discussion

The findings underscore the need for a comprehensive treatment strategy in patients with intermittent claudication. Measures to improve walking impairment (e.g. exercise training) are key to enhance quality of life and should be the primary treatment. As a key mediator of mental quality of life, depressive and anxiety symptoms should be addressed by rigorously including mental health treatment. Risky health behaviors should be approached by promoting behavior change (e.g. smoking cessation) as a secondary prevention of peripheral artery disease.

Introduction

Peripheral Artery Disease (PAD) affects up to 240 million people worldwide and ranks as the third leading cause of atherosclerotic morbidity after coronary artery disease and stroke [1], making it one of the leading causes of disability [2–4]. The hallmark symptom in symptomatic PAD patients is Intermittent Claudication (IC), which is characterized by muscle pain in the legs during walking and which subsides with short periods of rest [5]. Confronted with walking impairment and reduced mobility, these symptoms reflect the progressive narrowing of the peripheral arteries and the resulting reduction of blood supply [6, 7] that, if left untreated, can result in amputation [8] and death [9].

There is growing evidence that psychosocial factors are linked to functional outcomes and play a substantial role in the pathogenesis of PAD [10]. Depressive and anxiety symptoms are highly prevalent among PAD patients [11–13], which in turn have been shown to be associated with poor walking ability [14–18] and severe leg symptoms (i.e. pain at rest) [12], putting PAD patients at greater (long term) risk for mortality and other adverse PAD events [13–17, 19–22]. Prior studies have also demonstrated the negative impact of PAD and IC symptoms on health-related quality of life (HRQoL) [23–26], which again was found to have prognostic value in predicting long-term survival in PAD patients [27]. Experiencing depressive symptoms are associated with significantly lower HRQoL compared with their non-depressed counterparts, highlighting the impact of mental health symptoms on the PAD patient's subjective appraisal of their health status [28, 29].

While the association of mental health status with PAD is well established, an important next step is to understand the underlying mechanisms (and directionality) to allow targeted interventions. Although still subject of vigorous debate [10], several potential behavioral mediators have been proposed; one of them, tobacco smoking, which is known as a potent risk factor for developing PAD, was also found to be a important factor in the relationship between depression and subsequent PAD events [19]. Likewise, mental distress has been reported to be associated with increased amounts of alcohol consumption [30], which in turn has been identified as a risk factor for PAD [31–36]. Overall, the current evidence indicates risky health behaviors as a pathway through which mental health burden is causing poor PAD outcomes [10].

The present study addresses several important questions for the psychosocial management of symptomatic PAD, with the goal to determine whether and how walking impairment is associated with diminished HRQoL and mental burden in PAD patients that suffer from IC. With increased interest in health status and patient-based measures in cardiovascular research, identifying their respective determinants is increasingly important. Furthermore, this study

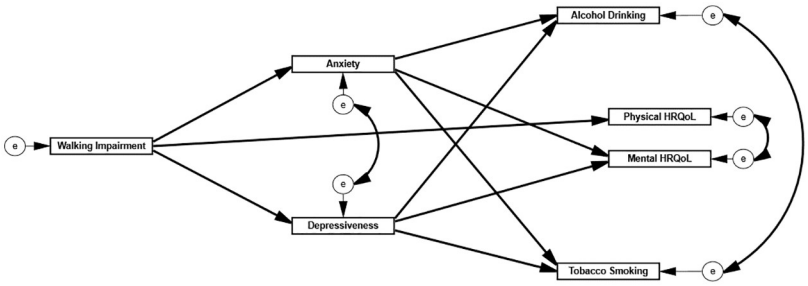

Fig 1. Theory-based path analysis model regarding the influence of walking impairment on mental burden, health risk behavior, physical and mental HRQoL in PAD patients.

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also investigates the impact of mental health problems (i.e. depressive and anxiety symptoms) with risky health behaviors (i.e. alcohol and tobacco consumption), which in the long-term could be major drivers of a negative clinical PAD course [10]. A theory-driven, cross-sectional path model based on previous literature was therefore postulated (Fig 1) and empirically examined to explore the interrelationships among these constructs. The postulated model assumed an association between walking impairment and mental health burden (i.e. depressive and anxiety symptoms; Hypothesis 1), which in turn is linked to an increase in health risk behavior (i.e. tobacco smoking and alcohol drinking; Hypothesis 2). Moreover, walking impairment was hypothesized to have a direct, negative effect on physical HRQoL (Hypothesis 3) and an indirect, negative effect on mental HRQoL mediated by an increase of depressive and anxiety symptoms (Hypothesis 4). A better understanding of these relationships may foster the development of treatment strategies to improve HRQoL and emotional well-being in PAD patients, which may also indirectly have secondary benefits on PAD status.

Methods

Design

The present path analysis uses cross-sectional baseline data (i.e. pre-intervention) drawn from a larger data set that was collected as part of a multicenter, randomized-controlled trial (RCT) designed to test the effectiveness of a 12-month long telemedicine-guided home-based exercise program for patients with IC, *PAD-TeGeCoach* (CT.gov trial registration: NCT03496948). Methods of the *PAD-TeGeCoach* effectiveness trial are reported elsewhere in detail [37]. Ethical approval was granted by the ethics committee of the Medical Association of Hamburg. All patients provided written informed consent.

Study population and recruitment

Participants were recruited using routinely collected health insurance data (electronic health records) from three German statutory health insurance funds (in German: *Gesetzliche Krankenversicherung*): Kaufmännische Krankenkasse, Techniker Krankenkasse, mhplus Krankenkasse. These three statutory health insurance funds together have approx. 12.1 million insured (TK: 10.5 million; KKH: 1.6 million; MH: 0.54 million) and cover 16.5% of all statutory insured citizens in Germany. Consequently, the patient population is likely to represent the PAD patient population presenting in a usual care setting.

Eligible patients were between 35 and 80 years old, and had a medically confirmed diagnosis of PAD at Fontaine stadium IIa (IC $>$ 200 meters) or IIb (IC $<$ 200 meters) within the last 36 months. Patients were excluded from the study if they had asymptomatic PAD within the

last 12 months (Fontaine stadium I) or rest pain within the last 36 months (Fontaine stadium III or IV). Patients with active or recent participation in other PAD intervention trials, medical conditions that contradict physical activity, cognitive disorders, severe mental disorders (including a clinical diagnosis of substance use disorder), suicidality, life-threatening illnesses, ongoing hospitalization, and heart failure (NYHA class III/IV) were also excluded.

The study population was derived from the *PAD-TeGeCoach* RCT; approximately 63 000 who met the inclusion criteria were identified as potential participants and were invited to participate. Of those, 1 982 elected to participate (recruitment rate 3.2%) and were randomized either into the intervention arm or the routine care group (see S1 Fig). There were 11 participants who withdrew after enrollment (data deletion request n = 1, randomized without informed consent n = 1, met exclusion criteria n = 8, lack of verification of PAD diagnosis n = 1).

Measures

The data used for this study (i.e. baseline data from the *PAD-TeGeCoach* RCT) were collected between April 14, 2018 and March 12, 2019. Enrolled patients received a battery of self-administered questionnaires by mail (paper-pencil) and were asked to return them using a prepaid envelope. The participants could call the study team when they encountered problems completing the questionnaires. A total of 1 696 patients returned their study questionnaire, which falls within the usual range of mail surveys [38].

IC symptoms: Walking Impairment Questionnaire (WIQ). The Walking Impairment Questionnaire (WIQ) is a well-established instrument of assessing walking impairment for different degrees of difficulty across three domains: walking distance, walking speed and stair-climbing. Response options for all items comprise a five-point Likert scale ranging from "unable to do" to "no difficulty". Domain scores are generated by multiplying the score for each item by a weighting factor based on the degree of difficulty and then summing all the products together. Scores are then divided by the maximum score of the respective domain to obtain a percentage score, from 0% (i.e. fully impaired) to 100% (i.e. not impaired). WIQ scores are strongly correlated with maximum walking distance [39, 40], objective measures of walking impairment [41], as well as the ankle-brachial index [42].

Generic HRQoL: SF-12. The SF-12 is a self-assessment questionnaire with 12 items measuring generic HRQoL [43]. The instrument covers eight health domains: physical functioning, role limitations due to physical health problems, bodily pain, general health, vitality, social functioning, role limitations due to emotional problems and mental health. These domains result in two summary measure scores: Physical Component Summary and the Mental Component Summary. Summary measure scores range from 0 (lowest HRQoL) to 100 (highest HRQoL). The SF-12 is a short version of the SF-36 with good psychometric properties [43]. The SF-12 has been used extensively in both cross-sectional and longitudinal PAD studies to assess (changes in) health status [e.g. 44, 45]. The Mental Component Summary score of the SF-12 was shown to be a valid measure of mental health in the general population [46, 47]. Furthermore, the Physical Component Summary score is associated with PAD severity as measured by the ankle-brachial index [45].

Depressive symptoms: PHQ-9. The PHQ-9 is a depression symptom screening instrument with 9 items asking patients how much they were bothered by symptoms over the last two weeks, with scores on a 4-point scale from 'not at all' to 'nearly every day'. The sum score ranges from 0 to 27 and indicates the degree of depression. Scores of ≥ 5, ≥ 10, and ≥ 15 represent mild, moderate, and severe levels of depression, respectively. A cut-off score of ≥ 10 was found to have a sensitivity and specificity of 0.88 for detecting clinical depression [48].

Anxiety symptoms: GAD-7. The GAD-7 is a 7-item screening instrument assessing the core symptoms of generalized anxiety disorder (GAD) over the past two weeks. The answer options are identical to the PHQ-9, with scores on a 4-point scale from 0 ('not at all') to 3 ('nearly every day'). The sum score ranges from 0 to 21 with cut-off scores of 5, 10 and 15 representing mild, moderate and severe levels of anxiety, respectively. A cutoff score of $\geq$ 10 has a sensitivity of 89% and a specificity of 82% for identifying GAD [49]. A study conducted in the German general population confirmed the instrument's good psychometric properties [50].

Tobacco smoking: Fagerström Test. The Fagerström Test for Nicotine Dependence [51] is a screening instrument assessing nicotine dependence with respect to cigarette smoking. It consists of six items which are either scored from 0 to 3 (multiple choice items) or 0 to 1 (yes/no items). The sum score ranges from 0 to 10 with higher scores indicating more intense tobacco dependence. The FTND is a revised version of the Fagerström Tolerance Questionnaire (FTQ) [52] with equally good psychometric properties [53]. The Fagerström Test was completed only by those who identified themselves as smokers (n = 668).

Alcohol consumption: AUDIT-C. The Alcohol Use Disorders Identification Test-Consumption [54] is a short screening instrument consisting of the original AUDIT's first three items assessing alcohol consumption. Items are scored on a scale ranging from 0 to 4. As a result, the sum score ranges from 0 to 12. Cut-off scores of 3 and 4 are used for women and men to identify patients at increased risk for alcohol-related disorders, whereas a cut-off score of 4 or 5 indicates risky consumption. Research confirmed the validity of the AUDIT-C and found equally good psychometric properties in the AUDIT-C as in the original version [55].

Other measures. Along with patient-reported outcome measures (PROMs), sociodemographic and biological variables (age, sex, height, weight, body mass index, education level, household income/economic status, marital status and employment status) and comorbidities (hyperlipidemia, diabetes mellitus, hypertension, lung disease and reduced kidney function) were self-reported during the baseline assessment.

Statistical analyses

Secondary analyses were performed using cross-sectional baseline data from a parent RCT (i.e. before study interventions were implemented; S1 Fig). Missing data in PROM items (i.e. incomplete information collected from a respondent) were handled via the Expectation-Maximization (EM) imputation algorithm in IBM SPSS Statistics 25, which is an effective and straightforward maximum likelihood technique to manage incomplete data so that there was be no systematic losses of participants who missed single items [56]. EM is recommended to be used in structural equation modeling [57]. An EM estimator is unbiased and efficient when the missing mechanism is missing completely at random or missing at random [58]. Moreover, the EM algorithm is effective when variables had up to 30% missing values. Consequently, participants that had an item nonresponse of $>$ 30% were removed from the analysis dataset (n = 9). Accordingly, data from 1 687 PAD patients were used for this study. In addition, several PROMs were compared against normative data, which were available from previous studies (GAD-7 [50]; PHQ-9 [59, 60]; SF-12 [61]).

Taking consideration of existing literature, a theory-driven path analysis with full information maximum likelihood estimation was conducted to estimate the simultaneous interrelationships between the variables of interest (treated as continuous), while adjusting a priori for empirically identified confounders (i.e. in path models at $p < .05$: sociodemographic variables, body mass index, comorbidities). Path analysis, which is an extension of multiple regression analysis, is a type of structural equation modeling to clarify (potentially causal) relationships between the variables assessed. The absolute and relative goodness of fit of the models were

assessed based on standard measures of fit; the CMIN/DF statistic (i.e. normed chi-square), the Tucker–Lewis index (TLI), the comparative fit index (CFI), and the root mean square error of approximation (RMSEA). CMIN/DF < 3 indicates an acceptable fit between hypothetical model and sample data [62]. The cut-off for good fit for TLI and CFI is ≥ 0.95 and ≥ 0.90. With values closer to 0 representing good fit, the cut-off for RMSEA, which is an absolute measure of fit, is $< .08$, indicating excellent fit between model specification and the observed data [63, 64]. Based on model fit indicators, the original model was modified by iteratively including and/or constraining paths and correlations. To arrive at a good model fit, model substructures were assessed based on (standardized) regression weights (i.e. magnitude and $p < .05$), residual error covariance and modification indices. Several iterations were carried out to arrive at the final revised model. Statistical analyses were performed using IBM SPSS Statistics 25 and SPSS Amos (IBM Corporation, Armonk, New York, United States). Effect sizes (i.e. magnitude of the relationships between path model parameters) were based on Pearson's r correlation coefficients and the standardized beta coefficient (β), with small, medium and large effect sizes indicated by the following r's/ β's, respectively: .10, .30, .50. Effect sizes $< .10$ are considered negligible regardless of statistical significance in order to avoid possible overinterpretation of small effects.

Results

Study sample characteristics

Demographic, socioeconomic and clinical characteristics of the study sample are displayed in Table 1. Most patients were male (67.6%) with a mean age of 66.3 years (SD = 8.6 years; range: 35–81). 64.3% were married, and 81.6% had at least one child. The three most common self-reported comorbidities were hypertension (72.4%), high cholesterol (57.1%) and diabetes mellitus (25.9%). A number of patients had a history of a cardiovascular event; 12.9% of PAD patients suffered from a myocardial infarction (i.e. heart attack), 8.8% had a stroke in the past. Most patients received medication to help control their PAD and cardiovascular comorbidities, such as platelet function inhibitors (81.1%), antihypertensive agents (74.1%) or statins (58.2%). 29.5% underwent revascularization surgery.

Descriptive statistics

Mental burden. The estimated proportion of patients with mild depressive symptoms (PHQ-9 score 5–9) was 30.2% (n = 509). Moderate or severe depressive symptoms, which has been reported to indicate clinical depression, were found in 18.1% (n = 304) of patients (PHQ-9 score ≥ 10). Mild anxiety symptoms (GAD-7 score 5–9) were found in 25.8% (n = 435) of patients, while 9.7% (n = 164) had moderate to severe anxiety symptoms (GAD-7 score ≥ 10) and thus showed signs of clinical anxiety. Compared to the general German population [50, 59, 60], the study population showed substantially higher levels of depression (approx. 84^{th} percentile), and anxiety symptoms (approx. 69^{th} percentile).

Health risk behavior. Among the smokers subgroup (n = 668, 39.6% of study participants), low or moderate level of tobacco dependence (Fagerström score 0–4) was identified in 56.3% of patients (n = 376, 22.3% of study participants). The estimated proportion of patients with high or very high tobacco dependence among smokers (Fagerström score 5–10) was 43.7% (n = 292, 17.3% of study participants). Regarding alcohol use, 16.1% (n = 272) were at risk of alcohol-related disorder (AUDIT-C score = 3 in women; = 4 in men), while 29.1% (n = 491) were screened positive for risky consumption (AUDIT-C score ≥ 4 in women; ≥ 5 in men).

Table 1. Characteristics of the study sample.

Variable	n / M	% / SD	range
Sociodemographic characteristics			
Gender			
Female	525	31.1	
Male	1 141	67.6	
Age (in years)	66.29	8.63	35–81
Body Mass Index	28.07	5.04	15–76
Comorbidities/Diseases (multiple choices possible)			
Myocardial infarction	217	12.9	
Stroke	148	8.8	
Metabolism disorder (high cholesterol)	964	57.1	
Angina pectoris	224	13.3	
Lung disease	270	16.0	
Heart Failure	258	15.3	
Hypertension	1 221	72.4	
Diabetes	437	25.9	
Cancer	155	9.2	
Drugs (multiple choices possible)			
Antihypertensive agents	1 250	74.1	
Platelet function inhibitor	1 368	81.1	
Statins	981	58.2	
Other	918	54.4	
Revascularization			
Yes	498	29.5	
No	931	55.2	
PROMs			
Walking Impairment (WIQ)			
Walking distance	55.75	29.20	0–100
Walking speed	48.84	24.93	0–100
Stair Climbing	59.66	25.88	0–100
Generic HRQoL (SF-12)			
Physical	37.92	9.78	12–61
Mental	51.03	11.18	13–70
Mental health			
Depressiveness (PHQ-9)			
Mild (5–9)	509	30.2	
Moderate(10–14)	212	12.6	
Severe (15–27)	92	5.5	
Generalized Anxiety (GAD-7)			
Mild (5–9)	435	25.8	
Moderate(10–14)	119	7.1	
Severe (15–21)	45	2.7	
Health Risk behavior			
Alcohol consumption (AUDIT-C)			
Risk of alcohol related disorder (= 3 in women; = 4 in men)	272	16.1	
Risky consumption (≥4 in women; ≥5 in men)	491	29.1	
Tobacco dependence (Fagerström, n = 668)			
Low (0–2)	156	23.4	

(*Continued*)

Table 1. (Continued)

Variable	n / M	% / SD	range
Moderate (3–4)	220	32.9	
Strong (5–6)	180	26.9	
Very strong dependence (7–10)	112	16.8	

Some participants did not provide complete information; the number of responses (n) may therefore deviate from the final dataset (N = 1 687).

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HRQoL. In comparison to the non-clinical German population [61], physical aspects of HRQoL among PAD patients appeared to be severely impaired (approx. 17th percentile; SF-12 physical composite score: M = 37.92, SD = 9.78), whereas mental aspects of HRQoL were only mildly compromised (approx. 45th percentile; SF-12 mental composite score M = 51.03, SD = 11.18).

Path analysis

Original and revised model through respecification. A theory-driven path analysis (Fig 2) was performed to evaluate the interrelationships between walking impairment (WIQ), HRQoL (SF-12 mental and physical composite scores), health risk behavior (AUDIT-C; Fagerström-Test) and mental health measures (GAD7; PHQ9). The original model failed to show a sufficiently good fit (CMIN/DF = 10.223; TLI = .942; CFI = .981; RMSEA = .074). As a next step, the model was controlled for potentially confounding effects (i.e. sociodemographic factors, body mass index, comorbidities) and respecified accordingly; goodness-of-fit indices indicated to include age and sex as confounders (represented by grey lines in Fig 2). After controlling for confounding effects, the goodness-of-fit indices showed a better fit to the observed data (CMIN/DF = 7.506; TLI = .939; CFI = .982; RMSEA = .062). Modification indices and residual variances indicated to add one path to the original model, as represented by a red line in Fig 2, which further improved the overall model fit (CMIN/DF = 2.743; TLI = .984; CFI = .996; RMSEA = .032). As a last step, two paths and one error covariance that were not significant were constrained to 0 (represented by thin lines in Fig 2). The results from all model

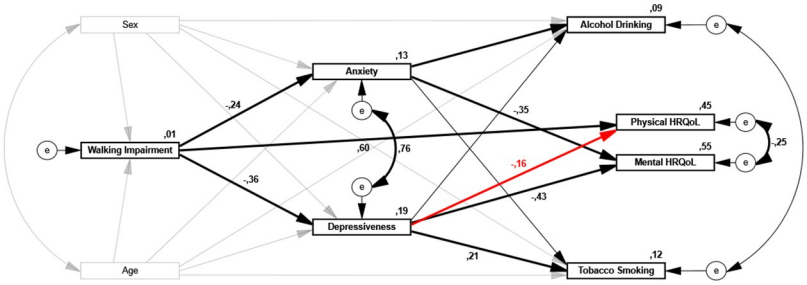

Fig 2. Final path analysis model testing the influence of walking impairment on mental burden, health risk behavior, physical and mental HRQoL in PAD patients (N = 1 687). The numbers on the arrows are standardized regression coefficients (β) that indicate the magnitude of effects between variables (coefficients < .10 not shown). Pathways are represented by thick lines, pathways that were constrained to 0 due to model respecification are represented by thin lines. Grey lines represent added covariates to the model (i.e. age, sex) for adjustment of confounding (coefficients not shown; see Table 2). The numbers above the boxes indicate the total proportion of variance explained in the model (R^2).

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Table 2. Decomposition of direct effects from the path analysis (Regression and error covariances).

Effect	B / Cov	S.E.	β / r	z	p	R^2
On Walking Impairment						.013
Of Sex	5.369	1.261	**.104**	4.257	***	
Of Age	-.156	.068	-.056	-2.293	.022	
On Anxiety Symptoms						.133
Of Sex	-.792	.203	-.090	-3.909	***	
Of Age	-.120	.011	**-.254**	-11.048	***	
Of Walking Impairment	-.040	.004	**-.237**	-10.395	***	
On Depressiveness						.189
Of Sex	-.960	.224	-.096	-4.282	***	
Of Age	-.120	.012	**-.221**	-9.964	***	
Of Walking Impairment	-.069	.004	**-.356**	-16.104	***	
On Physical HRQoL						.446
Of Depressiveness	-.328	.040	**-.157**	-8.116	***	
Of Walking Impairment	.243	.008	**.596**	31.732	***	
On Mental HRQoL						.549
Of Anxiety Symptoms	-.955	.071	**-.350**	-13.434	***	
Of Depressiveness	-1.031	.063	**-.432**	-16.388	***	
On Alcohol Drinking						.092
Of Sex	1.512	.123	**.291**	12.315	***	
Of Age	-.022	.007	-.079	-3.250	.001	
Of Anxiety Symptoms	-.035	.014	-.059	-2.420	.016	
On Tobacco Smoking						.119
Of Sex	.381	.180	.078	2.114	.035	
Of Age	-.063	.010	**-.239**	-6.372	***	
Of Depressiveness	.101	.018	**.208**	5.549	***	
Covariance Between Sex						
And Age	.424	.099	**.106**	4.290	***	
Error Covariance Between Depressiveness						
And Anxiety Symptoms	12.208	.490	**.764**	24.906	***	
Error Covariance Between Mental HRQoL						
And Physical HRQoL	-13.726	1.366	**-.252**	-10.047	***	

Table columns: unstandardized beta (B) or covariance (Cov) coefficient, the standard error for the unstandardized beta or covariance (S.E.), the standardized beta (β) or Pearson correlation coefficient (r), the critical ratio (z), and the probability value (p; *** < .001). β / r >.10 are highlighted in bold.

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iterations are presented in S2 File. Following these iterations, the goodness-of-fit indices showed an excellent fit between the observed data and the revised model (CMIN/DF = 2.345; TLI = .987; CFI = .996; RMSEA = .028). The final revised model, with accompanying path coefficients (i.e. standardized regression weights) and squared multiple correlations, is presented in Fig 2. The results of the decomposition of effects based on the path analysis model are shown in Table 2.

Walking impairment, mental health burden and health risk behavior. Limitations due to IC symptoms were associated with an overall increase in mental burden; in the model, walking impairment had a moderate direct effect on depressive symptoms (β = -.36) and, to a lesser extent, on anxiety symptoms (β = -.24). The model explained 19% and 13% of the variance in depressive and anxiety symptoms, with age and sex accounting for a large portion of the total explained variance (Table 2).

Depressive symptoms, in turn, had a small to moderate direct effect on the amount of tobacco smoking (β = .21), while anxiety symptoms had a negligible direct effect on alcohol drinking (β = -.06). The model explained 12% and 9% of the variance in tobacco and alcohol use, but again with age and sex accounting for the large portion of the explained variance. The indirect effects of walking impairment on tobacco and alcohol use mediated through mental health burden (i.e. depressive and anxiety symptoms) are considered negligible (total indirect β's $< .10$).

Walking impairment on health-related quality of life. Walking impairment had a large direct effect on lower physical HRQoL (β = .60). In addition, walking impairment was also substantially predictive of lower mental HRQoL, although fully mediated by an increase in depressive and anxiety symptoms (total indirect β = .24). Overall, the model explained 45% and 55% of the variance in physical and mental HRQoL.

Discussion

Mental health

The descriptive results show that patients with PAD are at much higher risk of presenting depressive symptoms compared with the general population [59, 60]. The reported prevalence is in good agreement with previous studies [17]; for instance, depression or depressive symptoms have been observed in 16% [14], 19.6% [13], 21.7% [15], 24% [65], 30% [12], up to 36.1% shortly before revascularization [66], compared to 48.3% showing at least mild depressive symptoms in this study, and of these, 18.1% showings signs of clinical depression (PHQ-9 score $>$ = 10). Finally, results from the path model confirm that young female PAD patients are at modestly higher risk to develop depressive symptoms [17, 29, 67, 68].

Moreover, the path analysis results support the hypothesis that poor walking ability contributes to depressive symptoms [14–17, 65, 69]. These findings support previous studies that show an association between PAD outcomes and depressive symptoms. PAD patients suffering from depressive symptoms are more likely to have other clinical symptoms such as chest discomfort, shortness of breath, and heart palpitations [15]. In addition, comorbid depressive symptoms are associated with an increased risk of PAD events [19], secondary cardiovascular events [22], major amputations [20, 70] and mortality [13]. Finally, PAD patients with depressive symptoms are less willing to exercise [69] and more likely to have recurrent symptoms after revascularization [66], which may further aggravate PAD symptoms. Although the current indicate a single direction of effect, the relationship between depression and PAD outcomes has been hypothesized to be bi-directional in a mutually reinforcing cycle, meaning that PAD outcomes are thought to increase depression and vice versa [71].

The body of literature examining other mental health issues in PAD patients is limited, as much of the literature tends to focus on the relationship between depression and PAD. That being said, the descriptive results show that PAD patients are also at much higher risk of having comorbid anxiety symptoms compared with the general population [50]. Anxiety symptoms were observed in 35.6%, which is comparable to 30% [12] and 24.4% [11] in other studies. The path analysis results support the hypothesis that poor walking ability contributes to anxiety symptoms. As for depression, it is reasonable to assume that anxiety disorders and PAD outcomes are also in a bidirectional relationship, as anxiety has been previously identified as a risk factor for the development of IC [18] and is associated with severe leg symptoms (i.e. pain at rest) [12]. Furthermore, it was shown that anxiety enhances the detrimental effect of depressive symptoms on health status after revascularization [72]. Future studies should further explore this association and whether tailored mental health interventions would improve PAD outcomes.

Health risk behavior

The descriptive results also demonstrate that PAD patients, especially men of younger age, are at great risk of engaging in health risk behavior such as tobacco use and excessive alcohol consumption. In the present study, 45.2% of patients were identified to be at risk of an alcohol-related disorder or exhibit risky alcohol consumption, compared to 39% found in a previous study [73]. Additionally, 39.6% of PAD patients were identified as smokers. Other research investigating home-based exercise programs in PAD patients reported smoking frequencies ranging from as little as 21.4% [44] up to 86.1% [74], suggesting a considerable heterogeneity between studies. Such health risk behavior can cause profound damage to vascular health. In particular, tobacco use is the single most important cause and leading risk factor of PAD [3] with a threshold- [75], dose-response-relationship [76], fostering progression of functional impairment [77, 78] and thereby resulting in a reduced HRQoL [78]. In terms of alcohol consumption, a U- or J-shape dose-response relationship between alcohol use and PAD has been suggested in various studies, meaning that low-to-moderate alcohol consumption, (particularly of red wine [79]) may result in a reduction of cardiovascular events and mortality [32–34, 80], while heavy/risky drinking is severely detrimental to PAD [31–36].

Mounting evidence suggests that risky health behaviors are part of the underlying mechanistic link between mental health status and PAD outcomes [10]. The path analysis results support the hypothesis that mental distress results in an increased desire to smoke among PAD patients [19], which in turn may contribute to the pathogenesis and deterioration of PAD. Regardless of PAD status, smoking is generally suggested as a self-medication strategy to cope with mental distress [81, 82]. However, there is evidence of a bidirectional relationship between depression and smoking, in which depressive symptoms lead to self-medication by smoking, which in turn causes changes in the dopaminergic system leading to depressed mood [82]—a vicious that eventually leads to a further deterioration of PAD.

One unanticipated result of the study was that mental burden was not associated with an increase in alcohol use. In the general population, the current literature suggests a causal linkage of alcohol use increasing the risk for depression, while alcohol being used to self-medicate symptoms of depression to reduce emotional distress [83]. These findings cannot be confirmed for PAD patients, suggesting that alcohol use plays no major role in the mechanistic relationship between mental distress and negative PAD outcomes. However, it is important to note that patients with a clinically diagnosed affective and/or substance use disorder were excluded from the study, which may have affected the current results. It is possible that severely depressed patients and those suffering severely from anxiety are more likely to show stronger signs of alcohol use disorder [84], which however remains to be investigated in further studies.

HRQoL

Compared to the general population, PAD patients were also found to have an impaired HRQoL, which is largely consistent with previous studies that have demonstrated poor HRQoL in PAD patients [45, 85, 86]. Similar to previous studies [23, 24, 45, 85], lower HRQoL was more evident for the physical aspects of HRQoL.

Moreover, in accordance with previous findings [23–26], the current path analysis support the hypothesis that poor HRQoL is largely related to increasing walking impairment. For mental HRQoL, this effect was largely mediated by the PAD patient's magnitude of depressive and anxiety symptoms, which highlights that the reduction of HRQoL is to large extent due to IC's detrimental effect on mental health [46]. The detrimental effect of mental health on HRQoL measures has been well demonstrated in previous studies [28, 29]. Similarly, in patients with

chronic heart failure, depression predicted physical and mental aspects of HRQoL [87]. Notably, these effects were independent of other physically debilitating comorbidities that also have an impact on patients' HRQoL (e.g. lung diseases).

Implications for clinical practice

The path analysis results provide a reasonable explanation of the complex interaction between functional walking limitations, mental burden, health risk behavior and quality of life in PAD patients, holding important clinical and public health implications. First and foremost, improving IC symptoms is a vital treatment approach for PAD patients, since walking impairment was found to be a crucial determinant of mental burden and HRQoL. Because the improvement of HRQoL is a key therapeutic goal in the treatment of PAD patients, staying physically active with appropriate exercise programs and other treatment modalities to improve walking impairment (e.g. revascularization) remains an integral key part of PAD treatment. The secondary benefits of walking improvement on HRQoL through exercise therapy is well established [88–90]. Importantly, to monitor changes in walking impairment as a result of treatment, the treating clinicians should use patient-reported measures of functional disability [25, 26], as these are the primary predictor of HRQoL [25, 26]. In contrast, HRQoL in PAD patients is only marginally associated with clinical markers as well as objective measurements of walking impairment [91–93], or HRQoL assessments of physicians [94], suggesting that the experience of HRQoL is not fully reflected by these surrogate measures. The importance of HRQoL, reflecting the physical, social and mental well-being of PAD patients, is being increasingly recognized by physicians and stakeholders (patients, relatives, etc.) as a significant indicator of treatment success [95, 96], which is nowadays also acknowledged in several international guidelines [5, 97, 98].

Second, the presence of mental health issues has been related to adverse health outcomes and influences the prognosis and treatment response of PAD, which points to the importance of integrating psychological aspects into therapy conversations. To break the self-perpetuating circle between mental health burden and PAD progression (i.e., amputation, cardiovascular events) [13–17, 19–22], vascular care providers should pay close attention to mental health challenges of PAD patients by integrating mental health care providers in an interdisciplinary/collaborative care model [17], which likely would have secondary benefits in reducing PAD risk and improving HRQoL. In patients with corona artery disease, previous studies have demonstrated the positive impact of depression and anxiety care and stress management on cardiovascular and psychological outcomes [99–101]. Likewise, the treatment of depressive symptoms improve physical functioning in older adults [102], which should therefore be considered a viable therapeutic approach in the management of PAD. Remarkably, there is already a guideline on addressing depression for patients with coronary artery disease [103], recommending to use the PHQ-9 to screen for depression, but not yet for PAD, which should be urgently addressed in the near future as psychosocial stressors play a critical role in PAD development and progression. For instance, psychological distress [104], including work-related stress [105], was found to elevate the risk for PAD and show a poor PAD recovery pathway [29].

Third, reducing health risk behavior should always be a key target of PAD management for effectively reducing adverse PAD outcomes, as tobacco and excessive alcohol use are known to be potent factors in the development and progression of PAD. Changes in health risk behavior should be also addressed through the delivery of PAD lifestyle interventions ([106], e.g. smoking cessation programs), which are usually guided by conceptual frameworks for risk behavior modification (for an overview, see [107]). The use of lifestyle interventions is currently low,

although they have substantial secondary cardiovascular benefits and may prevent further worsening of PAD [106]. Finally, it has been speculated that depressed patients use smoking as a form of self-medication to relieve symptoms; accordingly, modifying risk health behaviors could be achieved by improving mental health. In fact, there is good evidence that psychological interventions are effective in reducing smoking by people with mental health problems [108], which may in turn have a beneficial effect on the patient's PAD status and HRQoL.

Limitations

Several potential limitations must be mentioned when interpreting the findings of this study. Since all measures were collected cross-sectional, no certain conclusions can be drawn about temporal and causal relationships. Therefore, the directional arrows in the path analysis should be interpreted with great caution, as path analysis cannot prove causality out of a cross-sectional study (which can be proven only through the correct research design), but rather intended to test whether the data are consistent with the postulated causal model based on theoretical considerations. With that said, the current models can help to generate causal hypotheses for future studies, even more so given the "real-world" setting of this study with a study sample that is highly representative of PAD patients with IC.

Furthermore, despite the largely theory-driven approach, it is important to treat some of the results with caution, as some of them show trivial effect sizes although being statistically significant. For path analysis, an adequate sample size should normally be ten times the amount of the parameters as a rule of thumb, whereas in this study the sample is almost 200 times higher, which increases the power of detecting very small effects resulting in statistical significance. Although larger studies such as this one are unquestionably valuable and generally viewed as a favorable development, with all parameter values estimated with higher accuracy, it is important to consider how clinically and practically 'relevant' these effects really are in relation to prior literature. Therefore, to avoid an overinterpretation of effects ('large sample size fallacy'), it is important to interpret all effects in the model appropriately according to their size, and not treat statistical significance synonymously with practical significance [109]. At the same time, the large sample size can be regarded as a strength of the study, as the current findings comprise robust evidence and are most likely not caused by a statistical artifact.

Conclusions

In conclusion, the present results demonstrate that PAD patients often experience substantial impairment in terms of functional health status, mental burden and HRQoL. In order to better understand the complex relationship between these factors, the study sought to integrate clinical indicators and psychosocial aspects of PAD into a single theoretical model, thereby supporting a more comprehensive, multimodal therapeutic approach to PAD. The findings clearly indicate the importance of not only including somatic health status in the treatment of PAD, but also accounting for psychosocial aspects in PAD. To expand the explanatory ability of the complex relationships in the field of PAD, future research should put greater efforts in a theory-based approach using more sophisticated multivariate data analysis techniques (e.g. structural equation models) that defines the entire set of relationships.

Supporting information

S1 Fig. Flow chart of the randomized-controlled trial.
(TIF)

S1 File. All relevant study data (SPSS file).
(SAV)

S2 File. Model iterations.
(PDF)

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Publication 2: Measuring walking impairment in patients with intermittent claudication: psychometric properties of the Walking Estimated-Limitation Calculated by History (WELCH) questionnaire

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Measuring walking impairment in patients with intermittent claudication: psychometric properties of the Walking Estimated-Limitation Calculated by History (WELCH) questionnaire

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ABSTRACT

Objectives. Patient-reported outcome measures can facilitate the assessment of walking impairment in peripheral artery disease patients with intermittent claudication in clinical trials and practice. The aim of this study was to test the psychometric properties of the German version of the 'Walking Estimated-Limitation Calculated by History' (WELCH) questionnaire.

Methods. The assessed properties included feasibility, test-retest reliability, construct validity (i.e., convergent, divergent and known-groups validity) and responsiveness using classic psychometric methods. Psychometric properties were tested as part of a randomized controlled home-based exercise trial for patients with symptomatic peripheral artery disease at Fontaine stage IIA/B.

Results. Analyses were conducted in subgroups of 1,696 patients at baseline and 1,233 patients at 12-month follow-up (i.e., post-intervention) who completed the WELCH along with a battery of other self-report measures. The WELCH did not exhibit relevant floor or ceiling effects (< 15% achieved lowest or highest possible scores), showed evidence for good test-retest reliability (ICC = .81, 95% CI [.71–.88]) and was found to be well suited for self-completion by patients (< 5% missing data per item). WELCH scores showed moderate to strong correlations with related measures of walking impairment at both time points (Walking Impairment Questionnaire: $r = .56 - .74$; VascuQoL-25 activity subscale: $r = .61 - .66$) and distinguished well among patients with poor and high quality of life when adjusting for confounders ($t = 13.67$, $p < .001$, $d = .96$). Adequate divergent validity was indicated by a weaker correlation between the WELCH and general anxiety at both time points (GAD-7: $r = -.14$ *to* $-.22$). The WELCH improved by 6.61 points (SD = 17.04, 95% CI [5.13–8.10], $d = 0.39$) in response to exercise treatment and was able to identify large clinically important improvements observed on the walking distance (AUC = .78, 95% CI [.71–.84]) and speed subscales (AUC = .77, 95% CI [.68–.86]) of the Walking Impairment Questionnaire.

Conclusions. The WELCH is considered a feasible, reliable and valid patient-reported outcome measure for the measurement of walking impairment in patients with peripheral artery disease. The WELCH showed evidence for responsiveness to changes

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in walking impairment, yet further studies are warranted to conclusively determine the WELCH's ability to detect intervention effects.

Subjects Evidence Based Medicine, Internal Medicine, Statistics
Keywords Peripheral artery disease, Intermittent claudication, Patient-reported outcome measures, Patient perspective, Patient-oriented research

INTRODUCTION

Peripheral Artery Disease (PAD) is a global public health problem affecting an estimated 200 million people worldwide and has become one of the leading causes of disability and death over recent decades (*Criqui & Aboyans, 2015*; *Sampson et al., 2014*; *Song et al., 2019*). The most common symptom is intermittent claudication (IC), which refers to cramping leg pain that is caused by exercise due to insufficient blood flow (*Criqui & Aboyans, 2015*; *Aboyans et al., 2018*).

Rapid clinical assessment of walking impairment in symptomatic PAD patients is crucial in vascular surgery practice, providing a clinically relevant endpoint from the patient perspective by reflecting walking difficulties in everyday life and therefore considered a better tool for measuring patient-reported walking ability than functional surrogate endpoints (*Frans et al., 2013*). The 'Walking Estimated-Limitation Calculated by History' (WELCH) questionnaire is a brief patient-reported outcome measure (PROM) instrument that requires minimal completion time for assessing walking capacity, with the intention to be used routinely in clinical practice (*Ouedraogo et al., 2013*). The WELCH has been translated and cross-validated into various languages (*Ouedraogo et al., 2013*; *Abraham et al., 2014a*; *Cucato et al., 2016*; *Abraham et al., 2014b*; *Tew et al., 2014*), has shown good feasibility results as it is easy to score and, compared to other PROMs, considered less prone to errors when self-administered by the patient (*Ouedraogo et al., 2013*; *Ouedraogo et al., 2011*), while correlating well with treadmill walking (*Ouedraogo et al., 2013*; *Tew et al., 2014*; *Henni et al., 2019*; *Fouasson-Chailloux et al., 2015*). To be proposed as a routine tool in the future, however, further external validation in larger samples and other languages are required. The purpose of the current study is, therefore, to psychometrically validate the WELCH in a German cohort of symptomatic PAD patients.

METHODS

Design

The WELCH was validated as part of a prospective, randomized controlled trial (RCT) evaluating the effectiveness of a 12-month long home-based exercise program for patients with IC, PAD-TeGeCoach. The study protocol was registered and published elsewhere (ClinicalTrials.gov trial registration: NCT03496948) (*Rezvani et al., 2020*). The study was conducted in accordance with the Declaration of Helsinki and was approved by the ethics committee of the Medical Association of Hamburg (reference number: PV5708). All patients provided written informed consent.

Study population

Approximately 63,000 PAD patients with IC symptoms aged 35–85 with a clinically confirmed ICD-diagnosis of PAD at Fontaine stadium IIa (*i.e.,* IC > 200 m) or IIb (*i.e.,* IC < 200 m) within the last 36 months were identified using routinely collected health insurance data from inpatient and outpatient encounters. Patients were excluded, if they had asymptomatic PAD within the last 12 months (Fontaine stadium I) or rest pain within the last 36 months (Fontaine stadium III or IV). As the diagnosis of PAD is often flawed, especially in outpatient settings, participants were interviewed about their IC symptoms prior to enrollment to verify the diagnosis of symptomatic PAD. A sample of 1,982 PAD patients (recruitment rate approx. 3.2%) were enrolled and randomized either into the exercise intervention (PAD-TeGeCoach) or the routine care group (see Fig. 1 for RCT flow chart). 11 participants (TeGeCoach $n = 10$; routine care $n = 1$) were withdrawn prematurely after randomization (data deletion request $n = 1$, randomized without informed consent $n = 1$, met exclusion criteria $n = 8$, lack of verification of PAD diagnosis $n = 1$), leading to a final sample size of 1,971 PAD patients (TeGeCoach $n = 984$; routine care $n = 987$).

Measures

Only RCT data from measures relevant to the present study were used and are described in detail elsewhere (*Rezvani et al., 2020*). While the WELCH was specified in the trial registry as a secondary outcome, the authors failed to include it the study protocol. Notwithstanding this, the (internal and external) validity of the current study is not expected to be compromised as the trial was registered prospectively (*i.e.,* before recruitment).

Participants received a battery of paper-based questionnaires by mail at each time point and were asked to return them using a prepaid envelope. To maximize return rates, participants who had not returned the questionnaire in time received a postal reminder after 2–4 weeks. All participants were followed up at 12 months, irrespective of whether questionnaires had been returned at baseline. The participants could call the study team when they encountered problems completing the questionnaires.

'Walking estimated-limitation calculated by history' (WELCH) questionnaire

The German version used in this study was requested and made available by the authors of the WELCH, which officially has not yet been psychometrically validated (see Supplementary Files). The WELCH was forward translated into German by a native-speaking health professional who was not a member of the WELCH development team, and was then closely back translated into French by the authors to ensure appropriate wording. After two rounds of forward and backwards translation, comparing the original and back-translated French versions, a version was reached that was considered acceptable by the authors. The WELCH consists of four items; items 1–3 are eight-point ordinal items, ranging from ''impossible'' to ''3 h or more'', and assess the maximum duration that patients can maintain walking at different speeds in comparison to friends and relatives (*i.e.,* slower/same/faster). Item 4 is a five-point ordinal item, ranging from ''much slower'' to ''faster'', and assesses the usual walking *speed* compared to friends and relatives. The

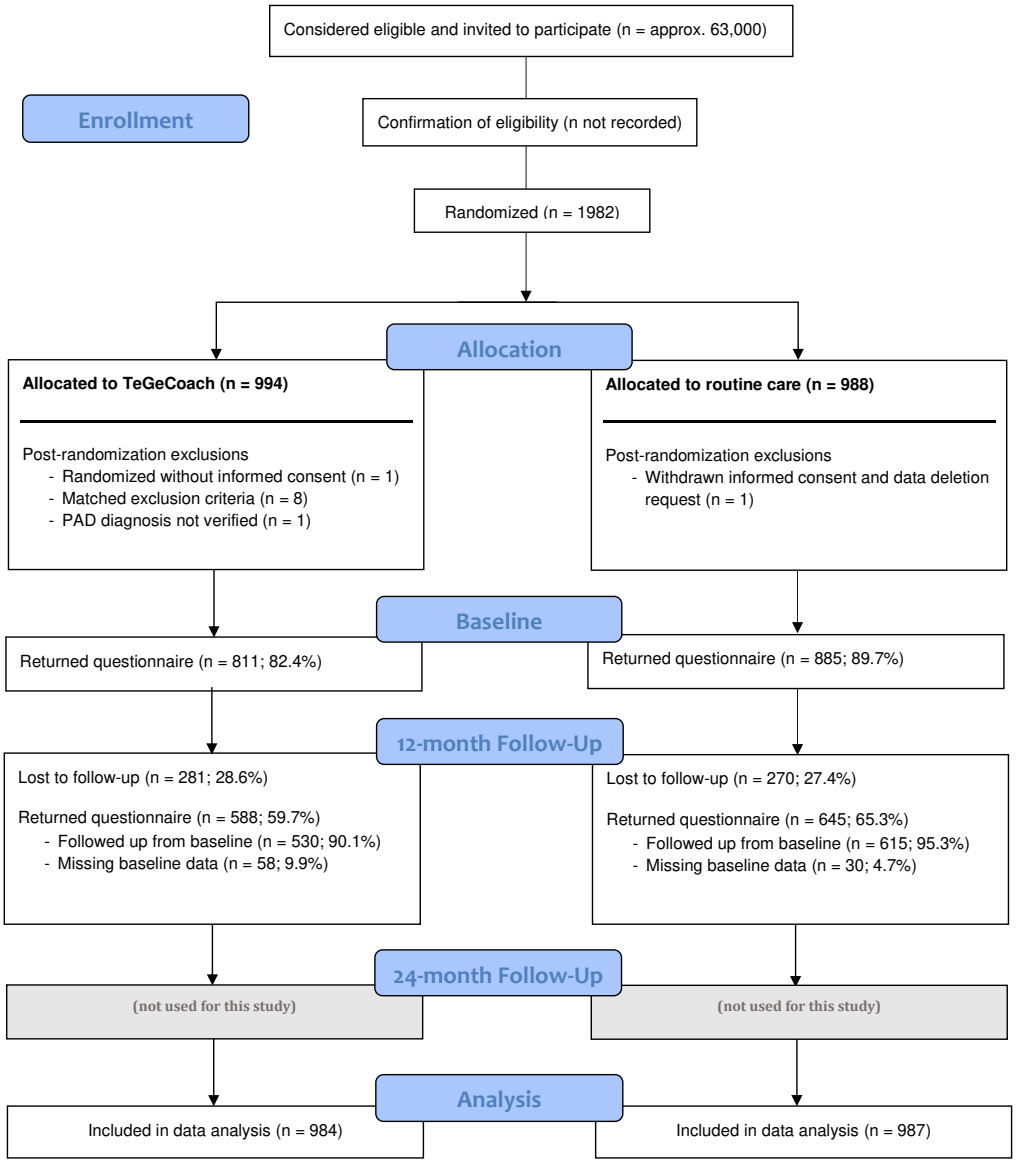

Figure 1 **Flow chart of the study design.**

Full-size DOI: 10.7717/peerj.12039/fig-1

WELCH score is generated by computing the sum of items 1–3, minus one, and multiplying it by the answer of item 4, *i.e.*, [(Item 1 + Item 2 + Item 3) –1] × Item 4. It is assumed that patients are able to walk at least 30 s at low speed so that the sum of the first three items is never 0. WELCH scores thus range from 0 (*i.e.*, patient is able to walk for a maximum of 30 s at slow speed) to 100 (*i.e.*, patient is able to walk 3 h or more at fast speed). Missing values were handled as indicated by the WELCH authors; for items 1–3 (maximum walking duration), missing values were replaced by the mean of the other two available items (*i.e.*, mean imputation), whereas for item 4, missing values were automatically replaced

by 3 (*Ouedraogo et al., 2013*). The German version of the WELCH can be found in the Supplementary Files.

Walking Impairment Questionnaire (WIQ)

The Walking Impairment Questionnaire (WIQ) is considered a reliable and valid instrument for assessing walking impairment for different degrees of difficulty across three domains: walking distance, walking speed and stair-climbing (*Regensteiner et al., 1990*; *McDermott et al., 1998*; *Sagar et al., 2012*; *Tew et al., 2013*). WIQ scores are considered responsive to the effect of treatment (*Regensteiner et al., 1990*; *Nicolai et al., 2009*) and are strongly correlated with maximum walking distance (*Frans et al., 2013*; *Tew et al., 2013*), objective measures of walking impairment (*McDermott et al., 1998*), as well as the ankle-brachial index (*Myers et al., 2008*). The proportion of missing values was < 5% for all WIQ items. Item and scale-level missing data were not imputed.

Kings College Vascular Quality of Life questionnaire (VascuQoL-25)

The VascuQoL-25 evaluates PAD-specific quality of life (QOL) and is divided into five subscales: pain, symptoms, activities, social, and emotional. Although designed to measure health-related QOL in PAD patients, all subscale scores and the composite score strongly correlate with functional status outcomes (*Morgan et al., 2001*; *Mehta et al., 2006*). In addition, the activity subscale was suggested to reflect physical functioning in patients with IC according to Wilson and Cleary's model for health-related QOL (*Wilson & Cleary, 1995*; *Conijn et al., 2015*), and was therefore considered as a valid comparator instrument. The VascuQoL-25 has also been shown to be responsive to changes in disease severity in PAD patients (*Mehta et al., 2006*; *de Vries et al., 2005*). The proportion of missing values was < 5% for all VascuQoL-25 items and were mean-imputed.

General Anxiety Disorder Scale (GAD-7)

The GAD-7 was shown to be a reliable and valid self-administered instrument with seven items for screening general anxiety by measuring symptom severity in the last two weeks (*Spitzer et al., 2006*; *Lowe et al., 2008*). Items are scored from zero to three on a 4-point scale from 'not at all' to 'nearly every day'. A study conducted in the German general population has found good psychometric properties for the GAD-7 (*Lowe et al., 2008*). Item-level missing data were not imputed.

Statistical analysis

The psychometric properties of the WELCH were assessed in accordance with the standards set out by the COSMIN group, which guide the development of rigorous methods to investigate psychometric properties of PROMs (*Mokkink et al., 2010*; *Mokkink et al., 2019*). When available, measurement properties were tested against criteria proposed for good measurement properties of health status questionnaires (*Terwee et al., 2007*), which were also used in a broad systematic review examining the psychometric validity of PROMs for measuring IC (*Conijn et al., 2015*).

Floor and ceiling effects were assessed by examining frequency distributions of each item and were considered to be present if > 15% of the study sample achieved the lowest or

highest possible score, respectively (*Terwee et al., 2007*). Feasibility of the WELCH was assessed based on the number of missing values in the study sample and per item before imputation. As a rule of thumb, multiple imputation is not considered necessary and single imputation deemed sufficient, if the proportions of missing data are $< 5\%$ (*Schafer, 1999*); therefore, the acceptable proportion of missing data for each item was set at $< 5\%$.

The *test-retest* reliability of the WELCH was assessed based on a group of 67 PAD patients at 12-month follow-up who were instructed to fill out the questionnaire again after two weeks under the same condition (*i.e.,* self-completed at home and returned *via* mail), with patients assumed to be stable during this time period without remembering their exact responses from two weeks earlier. To determine the level of consistency between these two time points (*i.e.,* stability of repeated measurements), the intraclass correlation coefficient (ICC) and the 95% confidence interval (CI) were calculated using a two-way mixed effects model for single measures with absolute reliability. Test-rest reliability of the WELCH was established when the ICC is $> .70$ (*Conijn et al., 2015*; *Terwee et al., 2007*).

Construct validity of the WELCH was verified with *convergent validity*. Pearson correlation coefficients, with bootstrapped CIs based on $n = 1,000$ samples, were determined between the WELCH and the comparator instruments at baseline and 12-month follow-up (*i.e.,* WIQ, VascuQoL-25 activity subscale), and were deemed satisfactory if there was a strong positive correlation $\geq .50$ (*Conijn et al., 2015*). *Divergent validity* was assessed by testing the association of the WELCH with anxiety, a construct known to be unrelated to symptomatic PAD (*Smolderen et al., 2009*); and was considered satisfactory if the correlation between the WELCH and the GAD-7 was weaker than with the comparator instruments at baseline and 12-month follow-up (*Conijn et al., 2015*). *Known-groups validity* was determined using a t-test with degrees of freedom adjusted for unequal variances to examine the extent to which the WELCH can significantly discriminate between PAD patients with poor to moderate (VascuQoL-25 score ≤ 4) and high QOL at baseline and 12-month follow-up, given that QOL and walking impairment are known to be associated in patients with IC (*Golledge et al., 2020*). The discriminatory ability of the WELCH was also assessed using a multiple linear regression to control for potential confounders between QOL and WELCH scores. The model was controlled for all significant variables reported in Table 1. The sample was assumed to be highly representative of the population of IC patients, making the introduction of collider bias unlikely. In the absence of defined quality criteria for health status questionnaires, known-groups validity was also assessed using Cohen's d effect sizes (small: $d = 0.2$, medium: $d = 0.5$, large: $d = 0.8$).

Responsiveness of the WELCH was examined by testing the ability to distinguish patients who have and have not changed after receiving the home-based exercise intervention (TeGeCoach), using the area under the receiver operating characteristics (ROC) curve (AUC) at various threshold settings for minimal clinically important differences (MCIDs) on the WIQ subscales (*Gardner, Montgomery & Wang, 2018*). MCIDs reflect the health status change that patients consider beneficial (*Jaeschke, Singer & Guyatt, 1989*). For the WIQ subscales, these were previously determined based on an anchor-based method assessing physical function quality of life following a 3-month (home or supervised) exercise intervention, with exercise protocols closely resembling the PAD-TeGeCoach

Table 1 Characteristics of subgroups used in the analyses (total sample at baseline, TeGeCoach group followed through to 12 months, TeGeCoach and routine care group at 12-month follow-up).

	Baseline	Followed through to 12 months	12-month follow-up*	
	Total ($n = 1,971$)	TeGeCoach	TeGeCoach	Routine care
N. of questionnaires received	1,696	530	588	645
Sex[a]				
Female	529 (31.2)	148 (27.9)	160 (27.2)	199 (30.9)
Male	1146 (67.6)	371 (70.0)	417 (70.9)	441 (68.4)
No information provided	21 (1.2)	11 (2.1)	11 (1.9)	5 (0.8)
Age (in years)[b]	66.3 (8.6)	67.0 (8.2)	67.1 (8.3)	67.3 (8.4)
Minimum–Maximum	35–81	35–81	35–81	38–81
BMI[b]	28.1 (5.0)	27.9 (5.4)	27.8 (5.3)	28.0 (4.7)
Minimum-Maximum	15.0–75.8	15.0–75.8	14.5–75.8	16.8–44.5
Education[b] *(multiple choices possible)*				
Apprenticeship	1166 (68.8)	365 (68.9)	365 (62.1)	431 (66.8)
College	562 (33.1)	177 (33.4)	177 (30.1)	224 (34.7)
University	289 (17.0)	105 (19.8)	105 (17.9)	104 (16.1)
Other	126 (7.4)	38 (7.2)	38 (6.5)	29 (4.5)
No education	67 (4.0)	22 (4.2)	22 (3.7)	14 (2.2)
Income[b]				
< 500 €	34 (2.0)	5 (0.9)	5 (0.9)	12 (1.9)
500€ to 1000€	135 (8.0)	33 (6.2)	33 (5.6)	41 (6.4)
1001€ to 1500€	215 (12.7)	58 (10.9)	58 (9.9)	69 (10.7)
1501€ to 2000€	282 (16.6)	85 (16.0)	85 (14.5)	114 (17.7)
2001€ to 2500€	306 (18.0)	108 (20.4)	108 (18.4)	103 (16.0)
2501€ to 3000€	242 (14.3)	79 (14.9)	79 (13.4)	95 (14.7)
3001€ to 3500€	147 (8.7)	42 (7.9)	42 (7.1)	67 (10.4)
3501€ and more	211 (12.4)	73 (13.8)	73 (12.4)	78 (12.1)
No information provided	124 (7.3)	47 (8.9)	105 (17.9)	66 (10.2)
Marital status[b]				
Single	113 (6.7)	29 (5.5)	29 (4.9)	36 (5.6)
Married	1,088 (64.2)	366 (69.1)	366 (62.4)	412 (63.9)
Divorced/separated	297 (17.5)	77 (14.5)	77 (13.1)	99 (15.3)
Widowed	167 (9.8)	46 (8.7)	46 (7.8)	61 (9.5)
No information provided	31 (1.8)	12 (2.3)	70 (11.9)	37 (5.7)
Number of children[a*]	1.7 (1.1)	1.8 (1.1)	1.8 (1.1)	1.7 (1.2)
Minimum–Maximum	0–11	0–6	0–6	0–11

(*continued on next page*)

Table 1 (*continued*)

	Baseline	Followed through to 12 months	12-month follow-up*	
	Total ($n = 1,971$)	**TeGeCoach**	**TeGeCoach**	**Routine care**
Profession[b] *(multiple choices possible)*				
Employed	462 (27.2)	143 (27.0)	143 (24.3)	141 (21.9)
Unemployed	77 (4.5)	15 (2.8)	15 (2.6)	21 (3.3)
Housewife/husband	61 (3.6)	14 (2.6)	14 (2.4)	32 (5.0)
Retired	1,057 (62.3)	351 (66.2)	351 (59.7)	410 (63.6)
Retired early	52 (3.1)	23 (4.3)	23 (3.9)	12 (1.9)
Permanently incapacitated for work	45 (2.7)	8 (1.5)	8 (1.4)	14 (2.2)
Diseases[a] *(multiple choices possible)*				
Myocardial infarction	217 (12.8)	79 (14.9)	85 (14.5)	82 (12.7)
Stroke	149 (8.8)	51 (9.6)	53 (9.0)	53 (8.2)
Metabolism disorder	965 (56.9)	314 (59.2)	344 (58.5)	383 (59.4)
Angina pectoris	224 (13.2)	66 (12.5)	71 (12.1)	90 (14.0)
Lung disease	271 (16.0)	71 (13.4)	79 (13.4)	117 (18.1)
Heart Failure	259 (15.3)	80 (15.1)	87 (14.8)	101 (15.7)
Hypertension	1,225 (72.2)	371 (70.0)	409 (69.6)	482 (74.7)
Diabetes	437 (25.8)	139 (26.2)	151 (25.7)	182 (28.2)
Cancer	155 (9.1)	51 (9.6)	55 (9.4)	64 (9.9)
Drugs[a] *(multiple choices possible)*				
Antihypertensive agents	1,253 (73.9)	397 (74.9)	440 (74.8)	489 (75.8)
Platelet function inhibitor	1,370 (80.8)	444 (83.8)	491 (83.5)	540 (83.7)
Statins	983 (58.0)	322 (60.8)	356 (60.5)	397 (61.6)
Revascularization[a]				
Yes	499 (29.4)	182 (34.3)	192 (32.7)	185 (28.7)
No	934 (55.1)	268 (50.6)	310 (52.7)	364 (56.4)
No information provided	263 (15.5)	80 (15.1)	86 (14.6))	96 (14.9)
Group heart rate training[a]				
Yes	221 (13.0)	79 (14.9)	85 (14.5)	90 (14.0)
No	1,438 (84.8)	440 (83.0)	492 (83.7)	538 (83.4)
No Information provided	37 (2.2)	11 (2.1)	11 (1.9)	17 (2.6)
Nationality[a]				
German	1,596 (94.1)	498 (94.0)	498 (84.7)	585 (90.7)
Other	41 (2.4)	11 (2.1)	11 (1.9)	11 (1.7)
No information provided	59 (3.5)	21 (4.0)	79 (13.4)	49 (7.6)

Notes.

[a]Categorical variables: *n* (%).

[b]Quantitative variables: M (SD).

*Information on *education, income, marital status, number of children, nationality* and *occupation* was collected at baseline only, and was not available from the 88 participants who completed only the 12-month follow-up questionnaire. These patients were included in *no information provided*.

intervention used in this study (*i.e.,* intermittent walking to near maximal claudication pain while using an activity monitor during exercise sessions) (*Gardner et al., 2014*; *Gardner et al., 2011*). An AUC of $\geq .70$ was considered to indicate adequate responsiveness (*Conijn et al., 2015*; *Terwee et al., 2007*). In addition, standardized effect sizes (d, baseline –12-month follow-up) were calculated for the WELCH and the convergent measures.

Analyses were performed using all available data at baseline and during 12-month follow-up. Statistical analyses were performed using SPSS version 25 (IBM Corporation, Armonk, New York, United States). Values of $p < .05$ (two-sided) were considered statistically significant.

RESULTS

Self-reported sociodemographic and clinical information of the PAD patients were collected at both time points and are presented in Table 1, grouped by time point and subgroups used in the analyses to allow tracking the pattern of missing data (see supplementary materials for an extended version of Table 1). Of those enrolled ($N = 1,971$), 1,696 patients returned their questionnaires at baseline (response rate: 86%). 551 patients were lost to 12-month follow-up, while 1,145 were followed up through 12-month follow-up. 88 patients returned their questionnaire only at 12-month follow-up, resulting in a sample size of 1,233 patients at 12-month follow-up (response rate: 63%). The response rates fall within the usual range of mail surveys (*Asch, Jedrziewski & Christakis, 1997*). Reasons for attrition were not identified, but may be attributed to the patient's right to withdraw at any time without having to give a reason and without penalty. The sample sizes, per analysis, using the RCT data are considered excellent for evaluating the psychometric properties of the WELCH (*Frost et al., 2007*).

Feasibility, and floor and ceiling effects

Score distributions and missing values per item before imputation are presented in Table 2. At baseline, the total amount of missing data was $< 5\%$ per item. A total of 1,611 (95.0%) filled out the WELCH completely at baseline, 79 patients (4.7%) filled it out partially, while only 6 WELCH questionnaires were returned completely empty (0.4%). The number of missing values at 12-month follow-up was similarly low irrespective of study group (Table 2), indicating excellent feasibility. In addition, the number of patients scoring the lowest or highest possible score was $< 15\%$ in all items, indicating that there were no floor or ceiling effects irrespective of study group.

Test-retest reliability

A group of 67 PAD patients filled out the WELCH twice within two weeks at 12-month follow-up. The ICC for the WELCH score was .81 (95% CI [.71–.88]), which indicates good test–retest reliability.

Construct validity

Convergent and divergent validity analyses are presented in Table 3. The findings indicate a good convergent validity of the WELCH, as there was a strong positive correlation with

Table 2 Score distributions and missing values of WELCH items at baseline and 12-month follow-up.

	Baseline						12-month follow-up					
	TeGeCoach ($n = 811$)		Routine care ($n = 885$)		Total ($n = 1,696$)		TeGeCoach ($n = 588$)		Routine care ($n = 645$)		Total ($n = 1,233$)	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Item 1												
Impossible	13	1.6	4	0.5	17	1.0	16	2.7	5	0.8	21	1.7
30 seconds	9	1.1	6	0.7	15	0.9	5	0.9	11	1.7	16	1.3
1 minute	27	3.3	25	2.8	52	3.1	10	1.7	21	3.3	31	2.5
3 minutes	98	12.1	112	12.7	210	12.4	43	7.3	78	12.1	121	9.8
10 minutes	239	29.5	240	27.1	479	28.2	118	20.1	160	24.8	278	22.5
30 minutes	204	25.2	234	26.4	438	25.8	133	22.6	155	24.0	288	23.4
1 hour	139	17.1	163	18.4	302	17.8	168	28.6	134	20.8	302	24.5
3 h or more	60	7.4	79	8.9	139	8.2	73	12.4	59	9.1	132	10.7
Total	789	97.3	863	97.5	1,652	97.4	566	96.3	623	96.6	1,189	96.4
NAs	22	2.7	22	2.5	44	2.6	22	3.7	22	3.4	44	3.6
Item 2												
Impossible	22	2.7	17	1.9	39	2.3	11	1.9	14	2.2	25	2.0
30 seconds	19	2.3	19	2.1	38	2.2	9	1.5	20	3.1	29	2.4
1 minute	60	7.4	77	8.7	137	8.1	32	5.4	55	8.5	87	7.1
3 minutes	199	24.5	192	21.7	391	23.1	86	14.6	129	20.0	215	17.4
10 minutes	249	30.7	262	29.6	511	30.1	153	26.0	168	26.0	321	26.0
30 minutes	134	16.5	169	19.1	303	17.9	134	22.8	128	19.8	262	21.2
1 hour	82	10.1	96	10.8	178	10.5	106	18.0	78	12.1	184	14.9
3 h or more	26	3.2	33	3.7	59	3.5	39	6.6	29	4.5	68	5.5
Total	791	97.5	865	97.7	1,656	97.6	570	96.6	621	96.3	1,191	96.6
NAs	20	2.5	20	2.3	40	2.4	18	3.1	24	3.7	42	3.4
Item 3												
Impossible	104	12.8	111	12.5	215	12.7	47	8.0	90	14.0	137	11.1
30 seconds	62	7.6	71	8.0	133	7.8	33	5.6	52	8.1	85	6.9
1 minute	145	17.9	143	16.2	288	17.0	72	12.2	90	14.0	162	13.1
3 minutes	216	26.6	217	24.5	433	25.5	125	21.3	144	22.3	269	21.8
10 minutes	149	18.4	194	21.9	343	20.2	139	23.6	131	20.3	270	21.9
30 minutes	78	9.6	79	8.9	157	9.3	86	14.6	70	10.9	156	12.7
1 hour	32	3.9	29	3.3	61	3.6	60	10.2	35	5.4	95	7.7
3 h or more	5	0.6	17	1.9	22	1.3	6	1.0	7	1.1	13	1.1
Total	791	97.5	861	97.3	1,652	97.4	568	96.6	619	96.0	1,187	96.3
NAs	20	2.5	24	2.7	44	2.6	20	3.4	26	4.0	46	3.7
Item 4												
Much slower	120	14.8	131	14.8	251	14.8	62	10.5	93	14.4	155	12.6
Moderately slow	320	39.5	362	40.9	682	40.2	182	31.0	245	38.0	427	34.6
A bit slower	231	28.5	250	28.2	481	28.4	186	31.6	179	27.8	365	29.6
At the same speed	107	13.2	112	12.7	219	12.9	125	21.3	90	14.0	215	17.4
Faster	23	2.8	26	2.9	49	2.9	23	3.9	17	2.6	40	3.2
Total	801	98.8	881	99.5	1,682	99.2	578	98.3	624	96.7	1,202	97.5
NAs	10	1.2	4	0.5	14	0.8	10	1.7	21	3.3	31	2.5

Table 3 Correlation between WELCH scores and other measures of walking impairment at baseline and 12-month follow-up.

	12-month follow-up											
	Baseline			TeGeCoach			Routine care			Total		
Correlation with WELCH score	***n***	**r**	**Bootstrapped 95%-CI**	***n***	**r**	**Bootstrapped 95%-CI**	***n***	**r**	**Bootstrapped 95%-CI**	***n***	**r**	**Bootstrapped 95%-CI**
WIQ walking distance	1564	.65	.62–.68	532	.71	.67–.74	578	.69	.64–.73	1110	.70	.68–.73
WIQ walking speed	1575	.68	.65–.71	531	.73	.69–.76	584	.71	.67–.75	1115	.72	.69–.75
WIQ stair climbing	1590	.56	.53–.59	535	.60	.55–.64	587	.60	.54–.64	1122	.60	.56–.63
WIQ total	1472	.70	.68–.73	493	.75	.72–.79	544	.73	.69–.76	1037	.74	.72–.77
VascuQoL Activity	1660	.61	.58–.64	571	.67	.63–.71	622	.64	.60–.68	1,193	.66	.63–.69
GAD-7	1629	−.14	−.19 to −.09	559	−.22	−.28 to −.14	603	−.21	−.28 to −.13	1162	−.22	−.27 to −.16

the WIQ distance subscale (baseline: $n = 1,564$, $r = 0.65$, 95% CI [.62–.68], $p < .001$; 12 months: $n = 1,110$, $r = .70$, 95% CI [.68–.73], $p < .001$); a strong positive correlation with the WIQ speed subscale ($n = 1,575$, $r = .68$, 95% CI [.65–.71], $p < .001$; 12 months: $n = 1,115$, $r = .72$, 95% CI [.69–.75], $p < .001$); a strong positive correlation with the WIQ stair climbing subscale ($n = 1,590$, $r = .56$, 95% CI [.53–.59], $p < .001$; 12 months: $n = 1,122$, $r = .60$, 95% CI [.56–.63], $p < .001$); a strong positive correlation with the WIQ total score ($n = 1,472$, $r = .70$, 95% CI [.68–.73], $p < .001$; 12 months: $n = 1,037$, $r = .74$, 95% CI [.72–.77], $p < .001$); and a strong positive correlation with the VascuQoL-25 activity scale ($n = 1,660$, $r = .61$, 95% CI [.58–.64], $p < .001$; 12 months: $n = 1,193$, $r = .66$, 95% CI [.63–.69], $p < .001$). Furthermore, in absolute terms, there was a weaker correlation between the WELCH and the GAD-7 (baseline: $n = 1,629$, r = −.14, 95% CI [−.19 to −.09], $p < .001$; 12 months: $n = 1,162$, r = −0.22, 95% CI [−.27 to −.16], $p < .001$), indicating adequate divergent validity. When separated by study group at 12 months of follow-up (TeGeCoach; routine care), the associations between the WELCH and the comparator instruments were nearly identical (see Table 3), demonstrating satisfactory construct validity regardless of treatment status.

Poor to moderate QOL (VascuQoL-25 < 4; $n = 383$; $M = 14.95$; SD = 12.20) has been reported by 23% of the sample at baseline. A significant mean score difference of 17.3 with a very large effect size ($d = 0.96$; 95% CI [0.84–1.01]) was identified between PAD patients with high ($n = 1,277$; $M = 32.23$; SD = 19.38) and those with poor to moderate QOL, t (1,001) = 20.91, $p < .001$, indicating excellent known-groups validity for the WELCH. In multiple linear regression analysis, a logarithmic transformation was performed to correct for heteroscedasticity. Health-related QOL remained a significant predictor of the WELCH score even after controlling for potential confounders, t (847) = 13.67, $p < .001$, which included age, BMI, income, comorbid diseases, medication, gender, education, revascularization and heart rate training. The partial r for predicting WELCH score from health-related quality of life (pr = .43) was not substantially different from the zero-order Pearson's r without controlling for confounders ($r = .47$). Similar results were found at 12-month follow-up irrespective of study group (not reported).

Responsiveness (TeGeCoach home-based exercise)

From baseline to 12-month follow-up, the WELCH [range: 0–100] improved by 6.61 points (SD = 17.04, 95% CI [5.12–8.10], $d = 0.39$) in the TeGeCoach group, from 28.86 (SD = 18.98) to 35.47 (SD = 22.29). During the same period, the WIQ distance, speed and stair climbing subscale scores [range: 0–100] improved in the TeGeCoach group by 10.65 (SD = 24.27, 95% CI [8.44–12.86], $d = 0.44$), 6.83 (SD = 19.55, 95% CI [5.05–8.61], $d = 0.35$) and 5.75 points (SD = 20.51, 95% CI [3.90–7.60], $d = 0.28$), respectively. The WIQ total score [range: 0–100] improved by 7.66 points (SD = 17.45, 95% CI [5.96–9.37], $d = 0.44$), and the VascuQOL [range: 0–7] by 0.32 points (SD = 0.81, 95% CI [0.25–0.39], $d = 0.40$).

Figure 2 presents the ROC curves generated for the WELCH for small (+5% change), moderate (+25% change) and large MCIDs (40% change) on the WIQ, and responsiveness statistics are reported in detail in Table 4. The AUC for small changes was .66 (SE = .02, 95% CI [.62–.71]) for the distance subscale, .64 (SE = .03, 95% CI [.59–.69]) for the speed

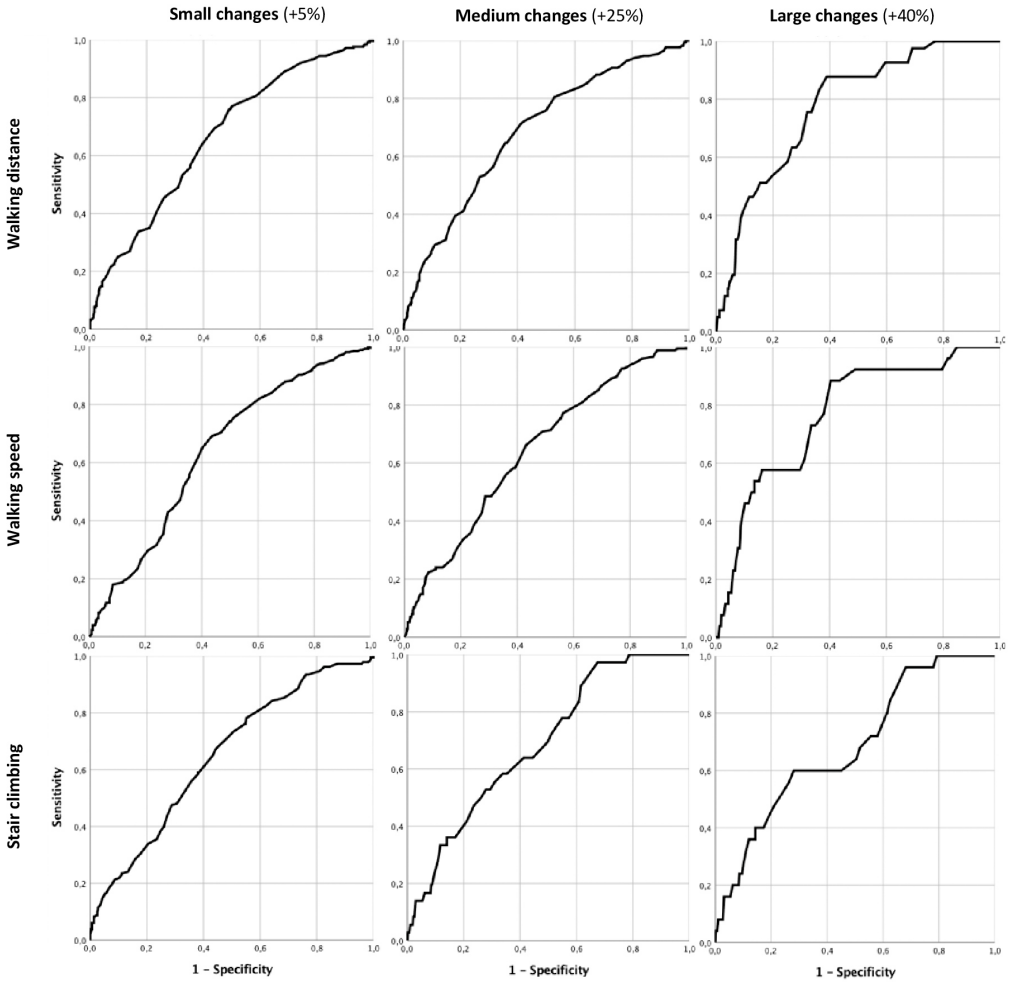

Figure 2 **WELCH ROC curves for small, moderate and large changes on the WIQ subscales.**
Full-size DOI: 10.7717/peerj.12039/fig-2

subscale and .65 (SE = .03, 95% CI [.60–.70]) for the stair climbing subscale. For moderate changes, the AUC was .69 (SE = .03, 95% CI [.64–.73]) for the distance subscale, .64 (SE = .03, 95% CI [.59–.69]) for the speed subscale and .69 (SE = .04, 95% CI [.61–.77]) for the stair climbing subscale. The AUC for large changes was .78 (SE = .03, 95% CI [.71–.84]) for the distance subscale, .77 (SE = .05, 95% CI [.68–.86]) for the speed subscale and .68 (SE = .05, 95% CI [.58–.79]) for the stair climbing subscale. Another ROC curve has been generated to test the ability of the WELCH to discriminate patients between study groups at 12-month follow-up (routine care *vs.* TeGeCoach). This showed an AUC of .63 (SE = .02, 95% CI [.59–.66]).

DISCUSSION

Further psychometric validation of PROMs that measure walking capacity in PAD patients is required. This study sought to validate the German version of the WELCH, which was

Table 4 WELCH responsiveness statistics at various thresholds reflecting small, moderate and large changes on the WIQ subscales.

WIQ subscale	Small (+5% change)			Moderate (+25% change)			Large (+40% change)		
	Walking distance	Walking speed	Stair climbing	Walking distance	Walking speed	Stair climbing	Walking distance	Walking speed	Stair climbing
Threshold [a]	≥ 5	≥ 2	≥ 12	≥ 15	≥ 11	≥ 35	≥ 42	≥ 37	≥ 41
AUC	0.66	0.64	0.65	0.69	0.64	0.69	0.78	0.77	0.68
SE	0.02	0.03	0.03	0.03	0.03	0.04	0.03	0.05	0.05
95% CI	0.62–0.71	0.59–0.69	0.60–0.70	0.64–0.73	0.59–0.69	0.61–0.77	0.71–0.84	0.68–0.86	0.58–0.79
n positive	249	256	183	170	175	36	41	26	25
n negative	257	250	323	336	331	470	465	480	481

Notes.
[a]Adopted from *Gardner, Montgomery & Wang (2018)*.

developed to address the limitations of existing PROMs for the measurement of walking impairment in PAD patients.

Consistent with previous findings (*Ouedraogo et al., 2013*), few missing values and > 95% completely filled out questionnaires largely support the excellent feasibility of the WELCH in PAD patients. The brief nature of the questionnaire with only four items, and that it can be easily completed without external support, makes it particularly attractive compared to other questionnaires, especially in settings where time pressure is high (*e.g.*, doctor's office). Furthermore, there were no floor or ceiling effects, which enables the WELCH to discriminate equally between symptomatic PAD patients across the entire IC severity spectrum.

In agreement with previous studies (*Cucato et al., 2016*; *Ouedraogo et al., 2011*), the WELCH has provided evidence for good psychometric properties in terms of test-retest reliability. This finding is directly related to the usefulness of the WELCH in repeated measurement designs ensuring that scores changes are due to real changes rather than irrelevant artefacts, making an important contribution to its psychometric validity and reliability.

In terms of construct validity, results were in line with previous studies (*Ouedraogo et al., 2013*; *Abraham et al., 2014b*; *Tew et al., 2014*), providing further evidence that the WELCH has good psychometric properties that make it suitable for use in assessing walking impairment living with intermittent claudication. As would be expected, the WELCH demonstrated satisfactory convergent validity, revealing a consistent pattern of moderate to strong correlations with the criterion measures. The associations between the WELCH and others PROMs indicate that the WELCH reflects similar but not identical constructs of walking impairment, with the WELCH showing the highest agreement with measures reflecting walking distance and walking speed (WIQ subscales). Notably, the correlation coefficients between the WELCH score and the WIQ subscales are fairly similar to those observed between the WELCH and treadmill maximum walking distance in previous studies (*Ouedraogo et al., 2013*; *Abraham et al., 2014b*; *Tew et al., 2014*), which further supports the validity of the WELCH for assessing walking impairment in symptomatic PAD patients. Simultaneously, the WELCH also shows a high correlation with health-related physical

functioning (VascuQoL-25 activity subscale), indicating that the WELCH also quantifies the subjective patient experience by reflecting walking limitations in daily life. Furthermore, the WELCH was able to very accurately discriminate between patients with poor and high levels of health-related QOL, demonstrating excellent known-groups validity. Although the relationship between QOL and walking impairment is already well known (*Golledge et al., 2020*), these results indicate that the WELCH also indirectly reflects aspects of QOL in symptomatic PAD patients, further supporting the WELCH's value as a patient-relevant outcome measure by addressing the impact of PAD on those living with the disease. Finally, as predicted from previous findings (*Smolderen et al., 2009*), the WELCH demonstrated good divergent validity in relation to anxiety symptoms (GAD-7), likewise supporting the validity of the instrument.

To date, only few PROMs for PAD patients have been studied in terms their responsiveness, which is a major shortcoming since PROMs are frequently used for measuring the effect of treatment in research and clinical practice (*Conijn et al., 2015*), raising doubts on the validity of results. Likewise, evidence on the responsiveness of the WELCH is sparse (*Henni et al., 2019*). In agreement with the construct validity results, the WELCH was found capable to detect large clinically important improvements observed in walking distance and speed following a home-based training regimen, suggesting that the WELCH may be considered responsive to exercise interventions, whereas small to moderate improvements did not generate sufficient change on the WELCH. These findings have direct implications for its use in therapy settings, as they show that the threshold for detecting clinically important effects is relatively high when using the WELCH. The ability to detect a restricted range of clinically meaningful changes (+40%) in response to exercise interventions may limit its utility in clinical settings, particularly since exercise interventions generally have small to moderate, yet clinically meaningful effects on walking impairment (*Golledge et al., 2019*; *Parmenter, Dieberg & Smart, 2015*). The WELCH may therefore be better suited to capture improvements after combined therapies of IC (*i.e.,* exercise therapy plus lower extremity revascularization), as greater improvements in walking performance are usually achieved than after either therapy alone (*Biswas et al., 2021*). The limited responsiveness found here is also comparable to the responsiveness of the WELCH after performing revascularization, where a moderate correlation with treadmill maximum walking distance was shown (*Henni et al., 2019*). In addition, the 12-month time interval between the measurements may have also reduced the WELCH's ability to detect improvements after exercise therapy, as the WELCHs responsiveness tends to decrease over time (*Henni et al., 2019*). Despite the promising results reported, the responsiveness of the WELCH in relation to other walking impairment measures (*i.e.,* other PROMs, functional testing), and whether it depends on the time interval between measurements (*i.e.,* short-term, long-term change), mode of intervention (*i.e.,* invasive, non-invasive) and degree of change (*i.e.,* small, medium, large intervention effects) still remains to be conclusively determined in further studies.

The present study is the first study to evaluate the psychometric properties of the WELCH in a German clinical population and has several strengths compared to previous validation studies. With a patient to item ratio of 400:1, this is the largest validation study

of the WELCH. Furthermore, this is the first study to assess the psychometric properties of a PROM for assessing IC based on the COSMIN checklist, which established guidelines for the psychometric validation of health status PROMs (*Terwee et al., 2007*). Although assessing psychometric properties of health status PROMs is common practice, the study quality in the field of PAD is often inadequate (*Conijn et al., 2015*), which underlines the importance of adopting universal quality criteria. The COSMIN checklist provided a rigorous methodological structure that helped in minimizing methodological bias. It would therefore be useful to use the COSMIN checklist to further evaluate the measurement properties of PROMs for PAD patients.

Several limitations of the study should be noted, including that the translation process did not rigorously comply with the Principles of Good Practice for the Translation and Cultural Adaptation Process for PROMs (*Wild et al., 2005*). Despite this shortcoming, the present study confirms the psychometric validity of the German version of the WELCH, suggesting that the translation and cultural adaptation process can be considered acceptable.

Furthermore, the comparator instruments used to test construct validity are not gold standards, which may have reduced the observed correlations. Notwithstanding this, the WELCH showed high correlations with the comparator instruments, as expected, with the strongest associations on the distance and speed subscales of the WIQ, supporting the validity of the WIQ in assessing walking impairment (*McDermott et al., 1998*; *Sagar et al., 2012*; *Tew et al., 2013*; *Nicolai et al., 2009*) and thus being well suited as a valid comparator instrument. To provide further evidence for the construct validity of the WELCH, it should also be tested against third-party assessments (*e.g.*, ratings by health professionals) and gold standard measurements (*e.g.*, treadmill testing) in future validation studies.

CONCLUSIONS

This article provides evidence that the German version of the WELCH questionnaire is a valid instrument for assessing walking impairment in patients with intermittent claudication. The WELCH, when used appropriately, enables the assessment of walking impairment in PAD patients, while compensating for the existing limitations of existing PROMs. In view of the excellent feasibility and good construct validity, its use can be recommended in clinical settings, as the medical team can quickly gain insight into the PAD patient's walking impairment condition without the need for cumbersome and time-consuming functional assessments. Nonetheless, despite its practicality, the WELCH should be treated with a degree of caution when used to evaluate the benefits of exercise treatments in clinical trials and practice. Alternatively, the WELCH merits consideration in vascular surgery to measure changes evoked by combined treatments (*i.e.,* exercise therapy plus lower extremity revascularization), which, however, remains to be investigated in future studies.

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Competing Interests

The authors declare there are no competing interests.

Author Contributions

- Farhad Rezvani conceived and designed the experiments, performed the experiments, analyzed the data, prepared figures and/or tables, authored or reviewed drafts of the paper, and approved the final draft.
- Martin Härter and Jörg Dirmaier conceived and designed the experiments, authored or reviewed drafts of the paper, and approved the final draft.

Human Ethics

The following information was supplied relating to ethical approvals (i.e., approving body and any reference numbers):

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Data Availability

The following information was supplied regarding data availability:

The measurements for the first (t0) and second (t1) time points are available in the Supplementary File.

Supplemental Information

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RESEARCH ARTICLE

Effects of telephone-based health coaching on patient-reported outcomes and health behavior change: A randomized controlled trial

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Data Availability Statement: Data are owned by a third party, the statutory health insurance KKH and only available upon formal request. Public deposition of the data would breach ethical and legal compliance. Interested researchers could contact Mr. Frank Freudenstein (Frank.Freudenstein@kkh.de) to request the data. In order to fulfill the legal requirements to obtain that kind of data, researchers must obtain a permission for a specific research question from the German Federal (Social) Insurance Office. Additionally,

Abstract

Objective

Telephone based health coaching (TBHC) seems to be a promising approach to foster self-management in patients with chronic conditions. The aim of this study was to evaluate the effectiveness of a TBHC on patient-reported outcomes and health behavior for people living with chronic conditions in Germany.

Methods

Patients insured at a statutory health insurance were randomized to an intervention group (IG; TBHC) and a control group (CG; usual care), using a stratified random allocation before giving informed consent (Zelen's single-consent design). The TBHC was based on motivational interviewing, goal setting, and shared decision-making and carried out by trained nurses. All outcomes were assessed yearly for three years. We used mixed effects models utilizing all available data in a modified intention-to-treat sample for the main analysis. Participants and study centers were included as random effects. All models were adjusted for age, education and campaign affiliation.

Results

Of the 10,815 invited patients, 4,283 returned their questionnaires at baseline. The mean age was 67.23 years (SD = 9.3); 55.5% were female. According to the model, TBHC was statistically significant superior to CG regarding 6 of 19 outcomes: physical activity in hours per week ($p = .030$) and in metabolic rate per week ($p = .048$), BMI ($p = .009$) (although mainly at baseline), measuring blood pressure ($p < .001$), patient activation ($p < .001$), and health literacy ($p < .001$). Regarding stages of change ($p = .005$), the IG group also showed statistically different results than the CG group, however the conclusion remains inconclusive. Within-group contrasts indicating changes from baseline to follow-ups and significant

researchers must conclude a contract with the statutory health insurance KKH regarding data access. Moreover, the study has to be approved by the data protection officer both at the statutory health insurance and the research institute as well as the local ethics committee. The authors had no special access privileges to the third-party data, other researchers would be able to access the data in the same way as the authors, as described in the Data Availability Statement.

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between-group comparisons regarding these changes supported the findings. Standardized effect sizes were small. TBHC did not show any effect on mental QoL, health status, alcohol, smoking, adherence, measuring blood sugar, foot monitoring, anxiety, depression and distress. Campaign-specific subgroup effects were detected for 'foot monitoring by a physician' and 'blood sugar measurement'.

Conclusion

TBHC interventions might have small effects on some patient reported and behavioral outcomes.

Practice implications

Future research should focus on analyzing which intervention components are effective and who profits most from TBHC interventions.

Registration

German Clinical Trials Register (Deutsches Register Klinischer Studien; DRKS): DRKS00000584

1. Introduction

Due to better medical treatment and changes in demographics, an ageing population will result in increasing numbers of people living with chronic conditions. In 2010, 15% of Europe's population was older than 65 years; prognoses expect an increase to 25% in 2050 [1]. In Europe, chronic conditions account for 80% of the mortality; particularly diseases of the circulatory system account for nearly 50% [1, 2]. In addition to those patients affected by one chronic condition (24.3%), the proportion of multimorbid patients is very high: 13.8% had two and 11.7% had more than three chronic conditions [3], resulting in a reduction in life expectancy by about 1.8 years with each additional chronic condition for a 67-year old individual [4]. Besides accounting for most part of the health care expenditures and lost work productivity [5, 6], chronic conditions also have a large impact on the individual living with it. Cardiovascular diseases for example are responsible for the most lost "disability-adjusted life-years" (DALYs) in low- and middle-income countries in Europe, and the third most lost DALYs in high-income countries [1, 7].

However, an existing chronic condition and its impact on a person's life may be modifiable in several ways, such as adopting better health behaviors and a better self-management. Studies show that the consumption of alcohol and tobacco, as well as high blood pressure are the three most important risk factors predicting a higher disease burden [1]. Therefore, current treatment guidelines, like the NICE guideline for managing diabetes [8], as well as the disease management program (DMP) guidelines for diabetes, breast cancer, asthma, and coronary heart disease in Germany [9], include self-management trainings and lifestyle change as a part of the medical treatment of many chronic conditions. Also in the US, the enhancement of self-management abilities and patient empowerment are major goals, as stated in the "Strategic Framework on Multiple Chronic Conditions" of the US Department of Health and Human Services [10].

Meta-analyses show that self-management interventions can improve quality of life (QoL) as well as disease-specific outcomes and decrease health care costs [11–13]. Besides self-management courses in group settings [14], one promising approach to improve self- and disease-management in people living with chronic conditions is telephone-based health coaching (TBHC), which is more accessible to people living in rural areas or having limited mobility. However, evidence regarding the effectiveness of TBHC is still inconclusive: Reviews conclude that TBHC may have beneficial effects on some clinical, behavioral, and psychosocial outcomes [10, 15, 16], but the heterogeneity, for example in duration and delivery method (e.g. calls, video calls, short messages, automated messages), of the TBHC interventions included, as well as the narrative review methods, make it difficult to draw clear conclusions.

Studies reporting the effect on patient-reported outcomes, like QoL, mental status, and distress are rare and have not been thoroughly summed up. A systematic review about the effectiveness of TBHC for chronic conditions found that results regarding psychosocial outcomes were quite inconclusive [15]. Most studies reported no effect of TBHC on "overall QoL" [17–22], but there were effects on "physical QoL" [19, 22–24]. Although not the focus of most of the studies, the effects of TBHC on anxiety of people living with chronic conditions have been quite positive [25, 26]. On the contrary, effects of TBHC on depression were mixed, but more likely to show no effect in favor of TBHC compared to controls [17, 19, 25, 27, 28].

Change of health behavior is a key focus in many TBHC interventions. Nevertheless, a review of current research we conducted showed no difference between a TBHC intervention group (IG) and a control group (CG) regarding most health behavior outcomes, like exercise [23, 29–37], self-monitoring [29, 34, 35, 38], alcohol [28, 39, 40], and smoking [17, 25, 27, 28, 32, 41]. Yet, there are promising results in favor of TBHC for diet change [24, 25, 31, 33–35, 38, 42].

Most existing studies were conducted in the United Stated, Australia, and the United Kingdom, which leads to different health systems and quite diverse populations, especially in countries with huge rural areas. There is limited data on TBHC in Europe; in particular there is no study on TBHC outcomes in Germany besides the present study [43, 44] and its pilot study [45]. The evaluation of health economic outcomes of this study showed no effect of the TBHC on the time until and probability of rehospitalization, number of daily defined medication doses (medication), as well as frequency and duration of inability to work. Nevertheless, there was a reduction of hospitalization in participants with heart failure, and a reduction of mortality in participants with chronic somatic conditions [44].

1.1 Objectives

The aim of this study was to evaluate the effects of a TBHC for people living with chronic conditions on 1) QoL, 2) health behaviors, (e.g. treatment or medication adherence, smoking, and alcohol consumption), as well as 3) psychosocial outcomes, (e.g. depression, anxiety, health literacy, patient activation and stages of change) compared to a CG of patients receiving usual care.

2. Materials and methods

The methods, including design, randomization process and all measures have been described elsewhere [43, 44]. The primary outcome of this study was "time from enrolment until hospital readmission within two years" which was assessed using routine data of the statutory health insurance data set. Together with further health economic outcomes (e.g. health related costs, inability to work, and mortality) the corresponding results are presented and discussed elsewhere [44]. Here we report findings on patient-reported secondary outcomes of the study.

2.1 Study design

In this 4-year (June 2010 to October 2014) prospective, pragmatic randomized controlled trial (RCT) we compared participants receiving a TBHC intervention with patients in usual care. Using Zelen's single-consent design, patients were randomized into IG or CG before giving informed consent [46] due to ethical reasons within the statutory health insurance. If patients declined TBHC, they received usual care. In addition to baseline measure (T_0) there were three follow-up measures at 12 months (T_1), 24 months (T_2), and 36 months (T_3). A study protocol reporting rationale, study design and statistical analysis procedures has been published a priori [43].

The study complied with the Helsinki Declaration 2008. The ethics approval was granted by the Hamburg Medical Chamber Ethics Committee on the 12.05.2011 (process number: PV3567). The study was registered in the German Clinical Trials Register (DRKS00000584). The trial was registered nine months late due to unexpected delays in the course of contract negotiations with the funding institution (Kaufmännische Krankenkasse Hannover: KKH) and resulting problems with timely recruitment of scientific staff. Nevertheless, registration was completed before any data were analyzed. The authors confirm that all ongoing and related trials for this intervention are registered. The consort checklist can be found in S1 Table.

2.2 Sample

The sample consisted of patients insured at the statutory health insurance KKH, which met the inclusion criteria within the recruitment period.

2.2.1 Inclusion criteria and exclusion criteria. Study participants were adults ($\geq$ 18 years), insured at KKH, and diagnosed with at least one chronic condition. Based on the diagnosed condition, eligible persons were grouped into different campaigns: The "chronic campaign" was utilized for type 2 diabetes, hypertension, and coronary artery disease; the "heart failure campaign" for heart failure patients, and the "mental health campaign" for chronic depression and schizophrenia. For the "chronic campaign" there were two different identification ways: For 'chronic campaign 1' patients were identified by a previous hospital stay, for 'chronic campaign 2' patients were identified by a risk score. If an insurant has more than one chronic conditions diagnosis, he is grouped in the most specific campaign in following order: "mental health campaign", "heart failure campaign", "chronic campaign". Insurees were excluded if they were not able to understand German, had hearing impairment, or were not able to use a phone [43].

2.2.2 Procedures. Successive recruitment took place between June 2010 and October 2011, with the follow-ups exactly 1, 2 and 3 years later. The members of the randomized IG received an invitation to take part in the TBHC and an acquisition call by the health insurance nurses. After sending back the informed consent for taking part in the intervention to the health insurance, they were included in the study as "TBHC participants". In case they did not send back the required confirmation they were grouped as "TBHC decliners". The randomized CG did not receive an invitation. To avoid bias also decliners received questionnaires, but due to economic reasons, decliners group and CG were randomly limited to 3,000 patients. All included patients received the consent form for the study with the baseline questionnaire, which had to be sent back to the research institute for taking part in the study. Patient reported data were collected by questionnaires sent to the insured persons' home by the statutory health insurance.

2.2.3 Randomization. All eligible persons were blindly randomized by a computer algorithm at the statutory health insurance's headquarters to either IG or CG. Inclusion and randomization process took place gradually over a period of 14 months. We used a stratified random allocation design based on sociodemographic variables available in routine data. The randomization process was carried out by the statutory health insurance.

2.2.4 Blinding. Blinding of study participants and coaches was not possible, as the coaching is provided one-to-one. However, the coaches did not know who did answer the questionnaires and who did not. The questionnaires were pseudonomyzed, to enable an aggregation of data from different sources.

2.2.5 Sample size calculation. The a priori power calculation showed that an overall minimum of 1,670 patients were needed at T_2 to be able to detect a small standardized mean difference (Cohen's d of 0.2) in group comparisons in order to achieve a power of at least 95% at a type I error rate of $\alpha = 5\%$ in a two-sided test accounting for the unbalanced group allocation [47]. Based on experiences in the pilot study showing low response and high drop-out rates [45], we targeted to invite 12,000 patients to participate, but achieved 10,815.

2.3 Intervention

The intervention is described following the TIDieR checklist [48] in S2 Table. The TBHC concept was originally developed by Health Dialog Inc. [49, 50], adapted to the German health care system and, subsequently, widely implemented by the health insurance KKH. A pilot study indicated that the intervention was well accepted by the participants [45]. Important components and counselling strategies were motivational interviewing (MI) to increase willingness to change and confidence to implement changed behaviors in daily life, individual and collaborative goal setting, and shared decision-making (SDM) [49, 50]. SDM focused on shared information on advantages and disadvantages of health behaviors and a joint decision. The set goals were recorded by the coach and followed-up in the upcoming calls. The intervention was tailored to important chronic conditions that require similar self-management strategies in the three campaigns "chronic campaign", "heart failure campaign", and "mental health campaign". Although patients were identified for the 'chronic campaign' in two different ways, the intervention was the same.

The intervention was conducted by 20 nurses and one ecotrophologist located in two call centers (Munich and Halle/Saale). The coaches were trained in TBHC with MI and SDM components by experts directly trained by Health Dialog. They were supervised two to four times per year by two experienced supervisors from the project group (MH,IBB).

The minimum call frequency was defined as one telephone contact every six weeks with a maximum intervention duration of one year. Specific intervention manuals for the coaches regarding different situations (e.g. for smoking cessation), available topics, and accessible information materials provided support for the coaches. Also, the coaches were assisted by an online health platform (www.netdoktor.de) providing evidence-based and up-to-date health information. NetDoktor is a health portal written and edited by health professionals, certified by HONcode (www.hon.ch) and related to the afgis criteria (www.afgis.de), two quality certifications for reliable online health information. Data on the coaching process, individual goal setting, medication, and clinical parameters (e.g. Hb_{A1c} and blood pressure) were recorded by the coach in an electronic documentation system. Written patient information for specific conditions, medication plans, and weight-control tables could be sent to the TBHC participants. Additionally, participants in the heart failure campaign got a booster call, in which the coaches checked whether participants maintained health behaviors (e.g., weighing and medication adherence).

The CG received no coaching.

2.4 Measures

We assessed changes in QoL with the subscales "mental QoL" and "physical QoL" of the "Short Form 12 Health Survey" (SF-12) [51] and the health status with the visual analogue scale of the "EuroQol- 5 Dimension" (EQ-5D) [52].

Health behaviors (alcohol consumption, medication adherence, exercise) were assessed with the "Alcohol Consumption Questions of the Alcohol Use Disorders Identification Test" (AUDIT-C) [53], the "Medication Adherence Report Scale" (MARS-D) [54], and the "Freiburg Questionnaire for Physical Activity" (FFKA) [55]. The FFKA calculates the activity in hours per week and metabolic rate per week. We used self-developed, ordinally scaled instruments for the assessment of the rate of measuring blood pressure (1 = not until now, 2 = not regularly, 3 = weekly, 4 = mostly once a day, 5 = twice a day or more), measuring blood sugar (1 = not until now, 2 = not regularly, 3 = mostly once a day in the morning, 4 = twice a day or more when eating), foot monitoring by themselves (1 = not until now, 2 = not regularly, 3 = once a week, 4 = daily), foot monitoring by their physician (1 = unnecessary, 2 = once in the last year, 3 = twice or more in the last year).

Other **psychosocial outcomes** included patient activation with the German version of the "Patient Activation Measure" (PAM) [56], health literacy with the "Functional Communicative Critical Health Literacy" (FCCHL) [57], and the process of behavior change with an adaptation of the "Stages of Change across 10 Health Risk Behaviors for older Adults" (SOC) [58]. Changes in depression and anxiety were assessed with the "Hospital Anxiety and Depression Scale" (HADS) [59]. Additionally, we assessed socio-demographic factors like age, nationality, sex, marital status, number of children, net income, years of school, level of education and occupation, as well as clinical parameters with self-developed, ordinally scaled items. All outcomes and times of assessment can be found in Table 1.

2.5 Statistical methods

We applied three different analyses to minimize participation bias. We followed an intention-to-treat approach including available data from all patients randomized to IG (TBHC participants and TBHC decliners) in one analysis to avoid bias (intention-to-treat 1, ITT-1). Thus, as the majority of the study participants invited to the IG declined participation in the allocated intervention, we ran two additional analyses: one comparing the TBHC participants only (i.e. removing decliners) with the CG (intention-to-treat 2, ITT-2) and finally, in the as-treated (AT) analysis we compared TBHC participants with a minimum of 5 calls to the CG (S1 Fig). We defined the ITT-2 analysis as our main outcome. Decliners were not added to the CG group to prevent a larger bias in ITT-2 and AT.

Chi-square tests (for categorical outcomes) and ANOVA tests (for dimensional outcomes) were used to compare groups at baseline.

Mixed models with maximum likelihood estimation were used to test the impact of health coaching on the course of outcomes from baseline across the three follow-ups compared to routine care. In all models, intervention group (IG and CG), time (t_0, t_1, t_2, t_3) and the interaction between group and time ('time x group') were set as fixed effects. Participants and study centers were included as random effects. Due to group differences, models were adjusted for the campaign they were in ("chronic campaign" ('chronic campaign 1', 'chronic campaign 2'), "heart failure campaign", "mental health campaign") and some sociodemographic variables (ITT-1: education; ITT-2: education, age; AT: education). In contrast to the health economic publication [44] we decided to subdivide the chronic campaign into its two smaller subgroups, which differed regarding their inclusion criteria, to avoid a possible bias and detect potential group differences.

The effect of health coaching was estimated based on the interaction between group and time. For group comparisons we calculated standardized between-group effect sizes (Cohen's d) by dividing the estimated marginal means difference (EMM difference) of the groups by the observed standard deviation of the CG group. Post hoc interaction contrasts between group

Table 1. Outcomes, measures and times of assessment.

Outcome	Measure	Score
Quality of life		
Mental QoL	SF-12 Mental subscale	0–100, Mean = 50 (SD = 10)
Physical QoL	SF-12 Physical subscale	0–100, Mean = 50 (SD = 10)
Health status	EQ-5D-Visual Analog Scale	0–100
Health behaviors		
Alcohol consumption	AUDIT-C	0–12
Medication adherence	MARS-D	5–25
Smoking	Self-developed	Yes / No
Measuring blood pressure	Self-developed	Ordinal scale
Measuring blood sugar	Self-developed	Ordinal scale
Foot monitoring self	Self-developed	Ordinal scale
Foot monitoring by physician	Self-developed	Ordinal scale
Physical activity	FFKA	Hours per week, metabolic rate per week
Body Mass Index (BMI)	Self-reported (height, weight)	
Clinical parameters		
Blood pressure	Self-developed	Ordinal scale
Hb_{A1c}	Self-developed	Ordinal scale
Cholesterol	Self-developed	Ordinal scale
NYHA status	Self-developed	Ordinal scale
Psychosocial outcomes		
Patient activation	PAM	12–52
Stages of change	SOC	9–45
Health literacy	FCCHL	14–56
Anxiety	HADS-A anxiety subscale	0–21
Depression	HADS-D depression subscale	0–21
Total score	HADS-T distress; total score	0–42

QoL = quality of life; SF-12 = Short Form 12 Health Survey; EQ-5D = EuroQol- 5 Dimension; AUDIT-C = Alcohol Use Disorders Identification Test; MARS-D = Medication Adherence Report Scale; FFKA = Freiburg Questionnaire for Physical Activity; PAM = Patient Activation Measure; SOC = Stages of Change; FCCHL = Functional Communicative Critical Health Literacy; HADS = Hospital Anxiety and Depression Scale; all outcomes were assessed atT_0, T_1, T_2, T_3; T_0 = Baseline; T_1 = 12 months after baseline; T_2 = 24 months after baseline; T_3 = 36 months after baseline.

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and time, i.e. the difference between the two groups in the amount of change from baseline (t_0) to post-intervention measurements (t_1, t_2, t_3), indicative of treatment effects, were determined.

Additionally, we tested whether campaigns moderate the effectiveness of the health coaching intervention, including the interaction between group, time and campaign (along with all lower level interactions) as a fixed effect in the analysis.

Across all tests, we considered results with $p < 0.05$ as statistically significant. Mixed model analyses were performed with R version 9.2 [60] using the lmer command from the lme4 package. Differences between the groups at baseline, imputation of missing values, as well as observed values were conducted with IBM SPSS 23 [61].

Although stated otherwise in the study protocol [43], we preferred the mixed model approach over the ANCOVA, as it utilizes data across all measurement points simultaneously and is more robust against missing values. Also, we did not adjust for multiple comparisons given the explorative nature of this study. As the Bonferroni correction increases the type II

error in favor for decreasing type I error, we decided to follow Perneger (1998) to describe the results openly and discuss them carefully [62].

2.6 Missing values

In order to calculate sum scores, it was necessary to impute missing values on item level. First, to check whether the missing values were missing at random, we applied Littles MCAR test [63]. It showed that missing values could not be considered to be missing completely at random at all times (t_0, t_1, t_2, t_3). Therefore, we decided to use the expectation-maximization algorithm for imputing missing values on single item level across each scale at each time point, as it is assumed to be unbiased and efficient even though missing mechanisms may be unclear [64]. Also, we decided to impute values just for those patients that provided more than 70% valid responses in accordance with Wirtz (2004) [65]. If there were data missing due to lost to follow-up, there was no imputation done since mixed model analyses provide unbiased estimates under the assumption that data are missing at random conditional on the variables in the model [66]. Therefore, we did not use last observation carried forward as initially planned [43].

3.Results

3.1 Participant flow

10,815 patients were eligible for TBHC, with 7,582 allocated to IG (70%) and 3,233 allocated to CG (30%). Unfortunately, there are no data on how many people were excluded based on which eligibility criterion. 3,229 people (42.6%) of the IG received the allocated intervention (TBHC participants), whereas 4,353 (57.4%) declined participation (TBHC decliners). 1,767 (54.7%) of the TBHC participants provided baseline data, 45.3% did not respond. 1,353 (31.1%) of the TBHC decliners were randomly excluded and did not receive a questionnaire, of the remaining N = 3,000, 1,294 (43.1%) sent back the baseline questionnaire and 1,706 (56.9%) did not respond. Of the CG 233 patients (7.2%) were randomly excluded due to economic reasons, with 1,222 (40.7%) of the remaining N = 3,000 providing baseline data, and 2,011 (67.0%) not sending back the questionnaire. At t_2, of those providing baseline data, 1,134 (64.2%) of the TBHC participants, 685 (52.9%) of the TBHC decliners, and 722 patients (59.1%) of the CG also provided t_2 data. Three years after randomization 932 (52.7%) of the TBHC participants, 576 (44.5%) of the decliners and 608 (49.8%) of the CG provided baseline and t_3 follow-up data.

As the analysis will include all patients that responded at baseline, the sample will be as follows: 4,283 patients in ITT-1 (IG: N = 3,061; CG: N = 1,222), 2,989 patients in ITT-2 (IG: N = 1,767; CG: N = 1,222), and 2,665 patients in AT (IG: N = 1,443; CG: N = 1,222). The detailed participant flow is provided in Fig 1.

3.2 Baseline characteristics

Of the 4,283 patients that returned their questionnaires at baseline, 41.3% belonged to the participants, 30.2% declined participation, and 28.5% belonged to the CG. The mean age was 67.3 years (SD = 9.3). More than half were female (55.5%), and most of them were married (66.3%). They had an average of two children and a median household net income of 1,501 to 2,000 €. Patients went to school for an average of 9.6 years (SD = 2.0) and most of them completed an apprenticeship. The majority was retired (Table 2).

There were statistically significant differences between the IG and the CG for the primary and the sensitivity analysis (ITT-1, ITT-2, and AT). The IG had significantly more children

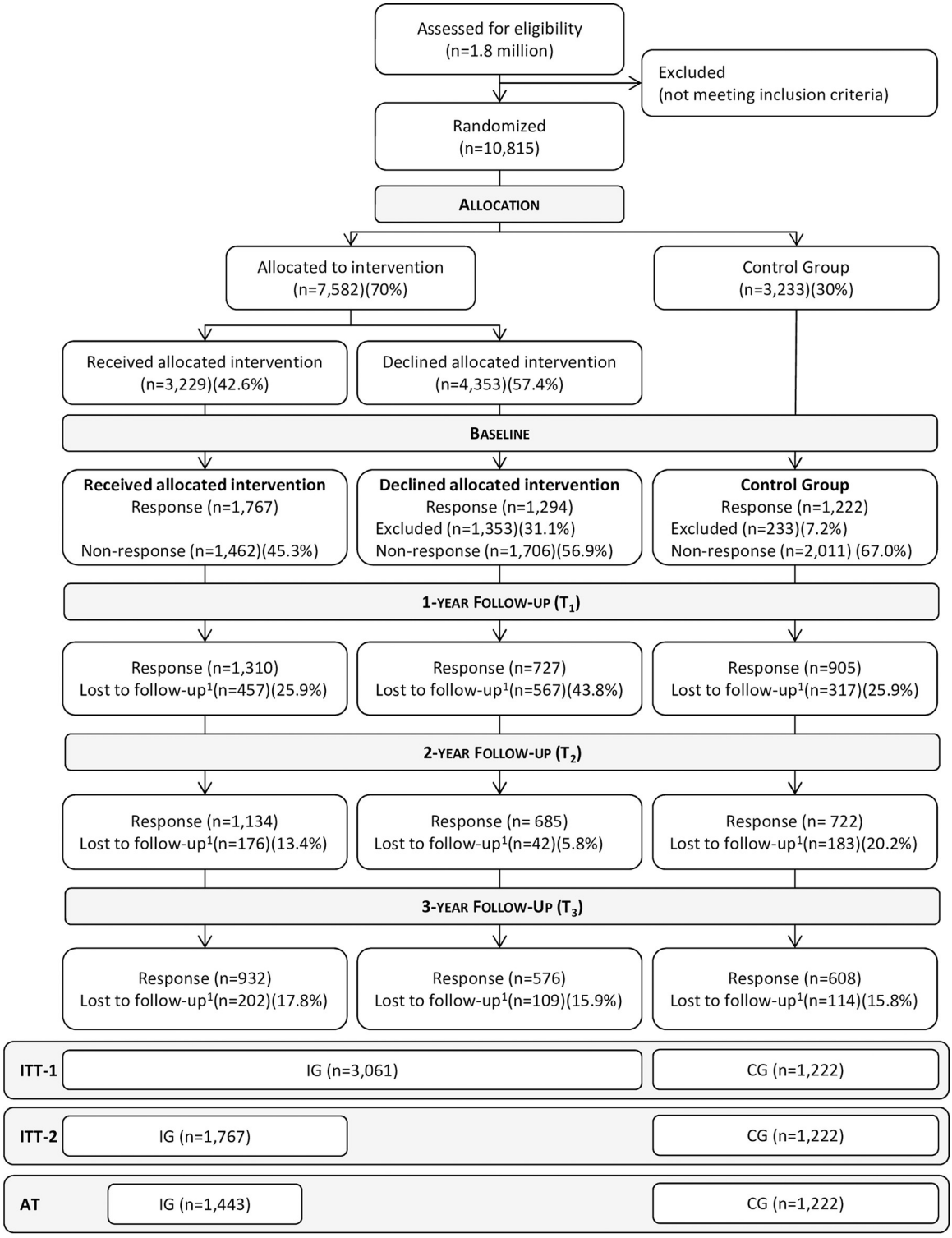

Fig 1. CONSORT participant flow chart. [1] = due to non-response / can include death; ITT-1 = intention-to-treat analysis 1 (n = 4,283); ITT-2 = intention-to-treat analysis 2 (n = 2,989); AT = as treated analysis (n = 2,665).

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Table 2. Sociodemographic baseline characteristics.

	All	IG			CG	Difference between groups (Sign. (p))		
		ITT-1	ITT-2	AT		ITT-1	ITT-2	AT
Number (n)	**4,283**	**3,061**	**1,767**	**1,443**	**1,222**	**4,283**	**2,989**	**2,665**
Age (Mean (SD))	67.28 (9.336)	66.9 (9.260)	66.29 (9.559)	66.60 (9.156)	67.28 (9.523)	.238	.006**	.063
Sex (% female)	55.5%	54.7%	54.4%	55.9%	57.5%	.097	.089	.411
Marital status (n (%))						.743	.127	.052
Married	66.3%	66.2%	66.0%	65.7%	66.5%			
Number of children (Mean (SD))	1.98 (1.053)	2.03 (1.020)	2.06 (1.035)	2.03 (.999)	1.85 (1.116)	< .001**	< .001**	< .001**
Net income[A] (n (%))						.724	.628	.239
< 500 €	2.9%	2.8%	2.7%	2.1%	3.2%			
500–1000 €	16.9%	16.3%	16.0%	16.1%	18.1%			
1001–1500 €	27.7%	27.0%	27.9%	28.7%	25.2%			
1501–2000 €	22.5%	22.4%	22.5%	22.9%	22.7%			
2001–2500 €	16.3%	16.2%	16.5%	16.7%	16.7%			
2501–3000 €	6.8%	7.0%	7.3%	7.1%	6.4%			
3001–3500 €	3.8%	3.7%	3.6%	3.6%	4.0%			
> 3501 €	3.8%	3.9%	3.6%	2.8%	3.7%			
Years of school (Mean (SD))	9.6 (1.988)	9.64 (1.962)	9.61 (1.926)	9.59 (1.906)	9.69 (2.050)	.427	.279	.190
Education (n (%))						< .001**	< .001**	< .001**
Apprenticeship	63.9%	68.4%	70.6%	70.8%	54.5%			
Technical college	14.1%	11.3%	11.5%	11.2%	19.9%			
University	6.0%	5.0%	4.4%	4.5%	8.2%			
Other	6.9%	6.7%	6.8%	6.5%	7.2%			
None	9.1%	8.5%	6.8%	7.0%	10.2%			
Occupation (n (%))						.451	.862	.495
Occupied	10.5%	10.4%	11.4%	11.2%	10.6%			
Unemployed	3.7%	3.6%	3.8%	3.1%	4.0%			
Homemaker	3.4%	3.3%	3.5%	3.6%	3.5%			
Retired	73.9%	74.5%	72.3%	72.6%	72.5%			
Early retirement	5.3%	5.2%	5.7%	6.4%	5.3%			
Incapacitated for work	3.3%	2.9%	3.3%	3.2%	4.2%			
Campaign						.438	.177	.188
Chronic C. 1	23.2%	23.2%	21.0%	24.9%	22.2%			
Chronic C. 2	63.1%	63.2%	63.6%	58.3%	63.7%			
Heart Failure C.	9.3%	9.3%	10.9%	11.9%	9.4%			
Mental health C.	4.4%	4.3%	4.5%	4.9%	4.7%			

IG = intervention group; CG = control group; ITT-1 = intention-to-treat analysis 1; ITT-2 = intention-to-treat analysis 2; AT = as treated analysis.

[A] = per month

** = significant difference between the groups $p < .01$

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than the CG although we considered the difference as only statistically but not clinically significant. Nevertheless, there was a difference between the groups regarding their level of education that was both statistically and clinically significant ($p < .001$). Participants more likely completed an apprenticeship than decliners and patients in the CG more often had a university degree.

In addition to the sociodemographic characteristics, the IG and CG showed further statistically significant baseline differences. For the ITT-1 analysis, there were differences in the

physical subscale of the SF-12 (p = .016), and the reported health status (EQ5D-VAS) (p = .028), each with the IG reporting a slightly higher quality of life. Also, there were significant differences in the ITT-1 analysis for medical adherence (p = .006) with the IG being slightly more adherent, the BMI (p = .007), patient activation (p = .007), for health literacy (p = .004) and distress (p = .019). For the ITT-2 analysis, there were just differences regarding the BMI (p< .001) with the IG reporting a higher BMI than the CG. For the AT analysis, there are difference in the baseline values for the reported alcohol consumption (p = .030), with the IG drinking a bit less, medication adherence (p = .041), with the IG being slightly more adherent, and the BMI (p = .001) with the IG reporting a higher BMI (Table 3). All in all it can be subsumed, that the differences might be statistically significant, but the clinical significance is questionable.

3.3 Outcomes

In the main analysis, the ITT-2, a mixed model analysis was used to determine the group effect over all times of measurement ('time x group') controlling for level of education and age

Table 3. Clinical baseline characteristics.

	All	IG			CG	Difference between groups (Sign. (p))		
		ITT-1	ITT-2	AT		ITT-1	ITT-2	AT
Number (N)	4283	3061	1767	1443	1222	4283	2989	2665
Quality of life								
SF-12 Mental Subscale	41.52 (6.22)	41.43 (6.20)	41.43 (6.13)	41.47 (6.12)	41.77 (6.30)	.140	.173	.256
SF-12 Physical Subscale	36.48 (11.27)	36.76 (11.26)	36.02 (10.74)	35.90 (10.63)	35.77 (11.28)	.016*	.557	.772
Health status (EQ5D-VAS)	55.43 (20.41)	55.87 (20.20)	54.82 (19.89)	54.93 (19.59)	54.32 (20.91)	.028*	.516	.449
Health behaviors								
Alcohol consumption (AUDIT-C)	2.17 (2.00)	2.14 (1.98)	2.14 (2.01)	2.06 (1.99)	2.25 (2.02)	.130	.192	.030*
Smoking (%)	15.5%	15.3%	15.8%	14.9%	16.2%	.510	.798	.416
Physical activity (hours per week)	8.38 (10.01)	8.54 (10.24)	8.27 (9.87)	8.33 (10.09)	7.98 (9.41)	.103	.421	.367
Physical activity (metabolic rate per week)	4231 (5117)	4301 (5278)	4155 (5033)	4169 (5121)	4055 (4687)	.157	.585	.552
BMI (kg/m^2)	28.86 (5.48)	29.01 (5.53)	29.28 (5.72)	29.27 (5.71)	28.50 (5.36)	.007**	< .001**	.001**
Medication adherence (MARS-D)	24.09 (1.66)	24.14 (1.62)	24.09 (1.59)	24.11 (1.57)	23.98 (1.75)	.006**	.089	.041*
Measuring blood pressure	3.64 (1.42)	3.62 (1.42)	3.61 (1.41)	3.60 (1.41)	3.70 (1.42)	.141	.101	.081
Measuring blood sugar	1.80 (1.11)	1.81 (1.11)	1.79 (1.11)	1.79 (1.11)	1.78 (1.12)	.397	.752	.723
Foot monitoring self	2.56 (1.13)	2.55 (1.12)	2.54 (1.11)	2.52 (1.11)	2.59 (1.14)	.302	.235	.201
Foot monitoring by physician	1.80 (0.82)	1.79 (0.82)	1.82 (0.82)	1.83 (0.82)	1.80 (0.81)	.173	.571	.387
Psychosocial Outcomes								
Patient Activation (PAM)	39.12 (5.32)	39.27 (5.30)	38.91 (5.20)	38.90 (5.15)	38.77 (5.38)	.007**	.481	.531
Health Literacy (FCCHL)	32.67 (6.85)	32.85 (6.83)	32.41 (6.57)	32.45 (6.53)	32.24 (6.88)	.011*	.511	.433
Stages of Change (SOC)	12.80 (5.61)	12.76 (5.60)	12.85 (5.43)	12.68 (5.33)	12.90 (5.64)	.473	.817	.318
Anxiety (HADS-A)	10.16 (1.54)	10.13 (1.55)	10.21 (1.54)	10.23 (1.52)	10.23 (1.52)	.051	.700	.963
Depression (HADS-D)	8.53 (1.72)	8.50 (1.70)	8.48 (1.70)	8.46 (1.70)	8.548 (1.79)	.208	.121	.084
Distress (HADS-T)	18.69 (2.20)	18.64 (2.19)	18.69 (2.20)	18.69 (2.19)	18.81 (2.24)	.019*	.139	.165

IG = intervention group; CG = control group; ITT-1 = intention-to-treat analysis 1; ITT-2 = intention-to-treat analysis 2; AT = as treated analysis; Means (SD) provided unless specified otherwise.

* = significant difference between the groups $p < .05$

** = significant difference between the groups $p < .01$

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(Table 4). The estimated marginal means, their standard errors and the contrasts between baseline and t_1, t_2 and t_3 for ITT-2 are presented in Table 5, accompanied by the differences in the contrasts between the groups, showing the differences in differences.

3.3.1 Quality of life. Overall, groups did not statistically significant differ regarding the course of **mental** (p = .963) and **physical quality of life** (p = .441) from baseline to three years (SF-12; interaction effect 'time x group'). Also, there was no significant difference between the groups over time concerning the **health status** reported with the visual analogue scale of the EQ5D (p = .147).

3.3.2 Health behaviors. For health behaviors, there was no difference between the groups over time ('time x group') regarding **alcohol consumption** (p = .238), **smoking** (p = .531), **medication adherence** (p = .939), **measuring blood sugar** (p = .619), **foot monitoring by themselves** (p = .352), and **foot monitoring by a physician** (p = .720). Nevertheless, there was a significant 'time x group' interaction effect regarding the **physical activity** in *hours per week* (p = .030), although the 'time x group' interaction contrasts (adjusted group contrasts) between the groups were all non-significant. There was also a significant 'time x group' interaction effect regarding **physical activity** measured *in metabolic rate per week* (p = .048), which did not result in any significant difference in contrasts between the groups at any follow-up.

Table 4. Mixed model analysis (ITT-1, ITT-2, AT), overall effects ('time x group') adjusted for education and age.

	ITT-2[A] (main analysis)	ITT-1[B]	AT[B]
	Sign. (p)	Sign. (p)	Sign. (p)
Quality of life			
SF-12 Mental Subscale	0.963	0.91	0.82
SF-12 Physical Subscale	0.441	0.56	0.41
Health status (EQ5D-VAS)	0.147	0.48	0.29
Health behaviors			
Alcohol consumption (AUDIT-C)	0.238	0.47	0.40
Smoking	0.531	0.61	0.87
Physical activity (hours per week)	**0.030***	**0.01***	**0.03***
Physical activity (metabolic rate per week)	**0.048***	**0.01***	**0.04***
Body Mass Index (BMI; kg/m^2)	**0.009****	0.59	**0.01****
Adherence (MARS-D)	0.939	0.89	0.98
Measuring blood pressure	<**0.001*****	<**0.01****	< **.0001****
Measuring blood sugar	0.619	0.93	0.78
Foot monitoring self	0.352	0.27	0.38
Foot monitoring by physician	0.720	0.60	0.57
Psychosocial outcomes			
Patient activation (PAM)	<**0.001*****	0.56	< **0.01****
Health literacy (FCCHL)	<**0.001*****	0.08	< **.0001****
Stages of Change (SOC)	**0.005****	**0.02***	< **0.01****
Anxiety (HADS-A)	0.646	0.77	0.55
Depression (HADS-D)	0.758	0.51	0.86
Distress (HADS-T)	0.815	0.73	0.92

* = significant p≤.05

** = significant p≤.01

[A] = adjusted for education and age

[B] = adjusted for education

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Table 5. Estimated marginal means, their standard errors and contrasts between baseline (t_0) and t_1, t_2, t_3 for ITT-2 (intervention group and control group); differences in contrasts between the groups.

			Intervention group						Control group						Differences in differences		
					Difference to baseline		Signifi-cance	Effect size			Difference to baseline		Signifi-cance	Effect size	Differences in contrasts between the groups		Signifi-cance
			n	EMM (SE)	Contrasts (adjusted EMM differences)	95%-CI	(p)	Cohen's d	n	EMM (SE)	Contrasts (adjusted EMM differences)	95%-CI	(p)	Cohen's d	Contrasts (adjusted group contrasts)	95%-CI	(p)
Quality of life	SF-12 Mental Subscale	t_0	1539	42.63 (0.86)					1033	42.97 (0.86)							
		t_1	1101	43.08 (0.88)	0.45	(-0.27;1.17)	0.22	0.07	760	42.83 (0.88)	-0.15	(-094;0.65)	0.72	-0.02	0.60	-0.48;1.67	0.27
		t_2	945	42.95 (0.89)	0.33	(-0.43;1.08)	0.40	0.05	602	42.79 (0.90)	-0.19	(-1.05;0.67)	0.67	-0.03	0.51	-0.63;1.65	0.38
		t_3	787	42.63 (0.90)	0.01	(-0.80;0.82)	0.99	0.00	514	42.63 (0.91)	-0.35	(-1.26;0.57)	0.46	-0.06	0.35	-0.87;1.58	0.57
	SF-12 Physical Subscale	t_0	1539	34.08 (0.99)					1033	33.67 (1.00)							
		t_1	1101	34.97 (1.00)	0.89	(0.21;1.46)	< **.01****	0.08	760	34.69 (1.00)	1.02	(0.38;1.65)	< **.01****	0.09	0.13	-0.98;0.72	0.77
		t_2	945	35.03 (1.00)	0.94	(0.35;1.54)	< **.01****	0.09	602	34.38 (1.01)	0.71	(0.03;1.39)	**0.04***	0.06	0.23	-0.67;1.19	0.62
		t_3	787	34.72 (1.01)	0.63	(-0.01;1.28)	**0.05***	0.06	514	33.72 (1.02)	0.05	(-0.67;0.78)	0.89	0.00	0.58	-0.39;1.55	0.24
	Health status (EQ5D-VAS)	t_0	1714	53.46 (1.45)					1171	53.11 (1.45)							
		t_1	1191	55.74 (1.48)	2.28	(1.12;3.44)	**.0001****	0.11	832	53.47 (1.48)	0.36	(-0.93;1.64)	0.59	0.02	1.92	(0.19;3.66)	**0.03***
		t_2	1042	55.71 (1.49)	2.25	(1.03;3.47)	< **.001****	0.11	655	53.80 (1.51)	0.69	(-0.70;2.09)	0.33	0.03	1.56	(0.30;3.41)	0.10
		t_3	848	54.72 (1.52)	1.26	(-0.06;2.59)	0.06	0.06	565	53.17 (1.53)	0.06	(-1.41;1.54)	0.93	0.00	1.20	(0.78;3.18)	0.24
Health behaviors	Alcohol consumption (AUDIT-C)	t_0	1477	1.93 (0.16)					1046	2.07 (0.16)							
		t_1	1180	1.69 (0.16)	-0.25	(-0.34;-0.16)	< **.0001****	-0.12	824	1.90 (0.16)	-0.17	(-0.26;-0.07)	< **.001****	-0.08	-0.08	(-0.21;0.05)	0.23
		t_2	824	1.81 (0.17)	-0.12	(-0.22;-0.02)	**0.02***	-0.06	539	2.00 (0.17)	-0.07	(-0.18;0.04)	0.20	-0.03	-0.05	(-0.20;0.10)	0.52
		t_3	802	1.58 (0.17)	-0.35	(-0.45;-0.25)	< **.0001****	-0.17	544	1.87 (0.17)	-0.20	(-0.31;-0.08)	< **.001****	-0.10	-0.15	(-0.31;0.00)	0.05
	Smoking	t_0	1740	1.82 (0.02)					1201	1.81 (0.02)							
		t_1	1220	1.84 (0.02)	0.01	(0.00;0.03)	**0.03***	0.03	841	1.83 (0.02)	0.02	(0.00;0.03)	**0.01****	0.05	-0.01	(.02;0.02)	0.68
		t_2	995	1.85 (0.02)	0.03	(0.01;0.04)	**.0001****	0.08	622	1.83 (0.02)	0.02	(0.00;0.04)	**0.01****	0.05	0.01	(-0.01;0.03)	0.43
		t_3	821	1.83 (0.02)	0.01	(-0.01;0.02)	0.42	0.03	547	1.83 (0.02)	0.02	(-0.00;0.03)	0.07	0.05	-0.01	(-0.03;0.01)	0.41
	Physical activity (hours per week)	t_0	1767	6.87 (0.59)					1222	6.95 (0.59)							
		t_1	1251	6.61 (0.61)	-0.27	(-0.85;0.31)	0.37	-0.03	858	7.43 (0.61)	0.48	(-0.17;1.12)	0.15	0.05	-0.74	(-1.61;0.12)	0.10
		t_2	1081	6.81 (0.62)	-0.06	(-0.67;0.55)	0.85	-0.01	676	6.87 (0.63)	-0.08	(-0.78;0.62)	0.81	-0.01	0.03	(-0.90;0.96)	0.95
		t_3	870	6.94 (0.63)	0.07	(-0.60;0.73)	0.84	0.01	580	6.21 (0.64)	-0.75	(-1.49;-0.01)	< **0.05***	-0.08	0.81	(-0.18;1.81)	0.11
	Physical activity (metabolic rate per week)	t_0	1767	3288 (346)					1222	3323 (346)							
		t_1	1251	3363 (354)	75.69	(-237;389)	0.64	0.02	858	3801 (356)	478.84	(133;825)	< **0.01****	0.10	-403.15	(-876;63)	0.09
		t_2	1081	3468 (358)	180.64	(-148;509)	0.28	0.04	676	3452 (364)	129.31	(-247;505)	0.50	0.03	51.33	(-448;550)	0.84
		t_3	870	3360 (365)	72.83	(-285;430)	0.69	0.01	580	3024 (370)	-298.13	(-696;100)	0.14	-0.06	370.96	(-164;906)	0.17
	Body Mass Index (BMI)	t_0	1647	27.90 (0.43)					1151	27.27 (0.43)							
		t_1	1154	27.75 (0.43)	-0.15	(-0.31;0.01)	0.07	-0.03	797	27.43 (0.43)	0.15	(-0.09;0.33)	0.10	0.03	-0.30	(-0.55;-0.06)	**0.02***
		t_2	1030	27.74 (0.43)	-0.16	(-0.33;0.01)	0.07	-0.03	654	27.53 (0.43)	0.26	(0.06;0.45)	**0.01****	0.05	-0.41	(-0.67;-0.16)	**0.002***
		t_3	827	27.69 (0.43)	-0.21	(-0.40;-0.03)	**0.02***	-0.04	554	27.36 (0.43)	0.09	(-0.11;0.30)	0.38	0.02	-0.31	(-0.58;-0.03)	**0.03***
	Adherence (MARS-D)	t_0	1683	24.01 (0.12)					1152	23.88 (0.12)							
		t_1	1189	24.03 (0.12)	0.02	(-0.08;0.11)	0.74	0.01	824	23.90 (0.12)	0.03	(-0.08;0.13)	0.64	0.02	-0.01	(-0.15;0.16)	0.90
		t_2	996	24.05 (0.12)	0.04	(-0.06;0.15)	0.40	0.03	630	23.95 (0.12)	0.07	(-0.05;0.19)	0.25	0.04	-0.02	(-0.18;0.13)	0.75
		t_3	834	24.08 (0.12)	0.07	(-0.04;0.18)	0.19	0.04	547	23.92 (0.12)	0.04	(-0.08;0.17)	0.50	0.02	0.31	(-0.13;0.20)	0.71
	Measuring blood pressure	t_0	1678	2.63 (0.07)					1146	2.47 (0.07)							
		t_1	1143	2.81 (0.07)	0.18	(0.11;0.24)	< **.0001****	0.15	799	2.46 (0.07)	-0.01	(-0.09;0.06)	0.73	-0.01	0.19	(0.09;029)	< **.001****
		t_2	1006	2.70 (0.07)	0.07	0.00;0.14)	**0.04***	0.06	621	2.43 (0.07)	-0.04	(-0.12;0.04)	0.29	-0.04	0.11	(0.01;0.22)	**0.03***
		t_3	815	2.66 (0.07)	0.03	(-0.04;0.11)	0.41	0.03	549	2.50 (0.07)	0.03	(-0.06;0.11)	0.52	0.03	0.00	(-0.10;0.12)	0.93
	Measuring blood sugar	t_0	1576	1.52 (0.06)					1093	1.51 (0.06)							
		t_1	1112	1.55 (0.06)	0.03	(-0.01;0.01)	0.09	0.03	781	1.51 (0.06)	0.00	(-0.04;0.04)	0.97	0.00	0.03	(-0.02;0.09)	0.27
		t_2	981	1.56 (0.06)	0.04	(0.00;0.08)	**0.03***	0.04	617	1.52 (0.06)	0.01	(-0.04;0.05)	0.68	0.01	0.03	(-0.02;0.09)	0.25
		t_3	758	1.58 (0.03)	0.06	(0.02;0.11)	<**0.01****	0.05	506	1.56 (0.06)	0.05	(0.00;0.10)	**0.05***	0.04	0.02	(-0.05;0.08)	0.61
	Foot monitoring self	t_0	1684	2.48 (0.08)					1150	2.45 (0.08)							
		t_1	1162	2.51 (0.08)	0.04	(-03;0.10)	0.32	0.03	807	2.43 (0.08)	-0.03	(-0.10;0.05)	0.52	-0.03	0.06	(-0.04;0.16)	0.25
		t_2	1027	2.53 (0.08)	0.05	(-0.02;0.12)	0.20	0.04	635	2.43 (0.08)	-0.02	(-0.11;0.06)	0.56	-0.02	0.07	(-0.04;0.18)	0.20
		t_3	821	2.60 (0.08)	0.12	(0.04;0.20)	< **.01****	0.10	545	2.48 (0.08)	0.02	(-0.06;0.11)	0.59	0.02	0.10	(-0.02;0.21)	0.10
	Foot monitoring by physician	t_0	1499	1.66 (0.04)					1028	1.64 (0.04)							
		t_1	1076	1.66 (0.05)	0.00	(-0.05;0.05)	0.97	0.00	721	1.60 (0.05)	-0.04	(-0.09;0.02)	0.22	-0.05	0.04	(-0.04;0.11)	0.38
		t_2	920	1.68 (0.05)	0.02	(-0.03;0.07)	0.46	0.02	550	1.63 (0.05)	-0.01	(-0.07;0.06)	0.84	-0.01	0.03	(-0.06;0.11)	0.53
		t_3	749	1.69 (0.5)	0.03	(-0.03;0.09)	0.29	0.04	471	1.62 (0.05)	-0.01	(-0.08;0.05)	0.66	-0.01	0.05	(-0.04;0.13)	0.30

(*Continued*)

Table 5. (Continued)

			Intervention group						Control group						Differences in differences		
					Difference to baseline		Signifi-cance	Effect size			Difference to baseline		Signifi-cance	Effect size	Differences in contrasts between the groups		Signifi-cance
			n	EMM (SE)	Contrasts (adjusted EMM differences)	95%-CI	(p)	Cohen's d	n	EMM (SE)	Contrasts (adjusted EMM differences)	95%-CI	(p)	Cohen's d	Contrasts (adjusted group contrasts)	95%-CI	(p)
Psychosocial outcomes	Patient activation (PAM)	t_0	1671	38.40 (0.31)					1156	38.47 (0.30)							
		t_1	1189	39.11 (0.31)	0.71	(0.39;1.03)	< **.0001****	0.14	818	38.23 (0.32)	-0.24	(-0.60;0.11)	0.18	-0.04	0.95	(0.48;1.43)	< **.0001****
		t_2	1038	38.99 (0.32)	0.59	(0.25;0.93)	< **.001****	0.11	642	38.37 (0.33)	-0.10	(-0.49;0.29)	0.61	-0.02	0.69	(0.18;1.20)	**0.01***
		t_3	843	38.57 (0.33)	0.17	(-0.20;0.53)	0.37	0.03	559	38.27 (0.33)	-0.20	(-0.60;0.21)	0.34	-0.04	0.37	(0.18;0.91)	0.19
	Health literacy (FCCHL)	t_0	1684	32.59 (0.35)					1156	32.71 (0.35)							
		t_1	1187	33.45 (0.36)	0.86	(0.47;1.24)	< **.0001****	0.13	812	32.54 (0.36)	-0.16	(-0.59;0.27)	0.46	-0.02	1.02	(0.44;1.60)	< **.001****
		t_2	1009	33.51 (0.37)	0.92	(0.51;1.33)	< **.0001****	0.14	639	32.03 (0.38)	-0.67	(-1.14;-0.21)	< **.01****	-0.10	1.60	(0.97;2.22)	< **.0001****
		t_3	812	33.48 (0.38)	0.89	(0.44;1.33)	**.0001****	0.14	554	32.07 (0.38)	-0.63	(-1.13;-0.14)	**0.01****	-0.09	1.52	(0.86;2.19)	< **.001****
	Stages of Change (SOC)	t_0	1723	13.33 (0.32)					1192	13.52 (0.31)							
		t_1	1220	12.75 (0.32)	-0.58	(-0.87;-0.29)	**.0001****	-0.11	847	13.58 (0.32)	0.06	(-0.26;0.37)	0.72	0.01	-0.64	(-1.07;-0.21)	< **.01****
		t_2	1057	12.70 (0.33)	-0.63	(-0.93;-0.33)	< **.0001****	-0.12	661	13.52 (0.33)	0.00	(-0.34;0.35)	1.00	0.00	-0.63	(-1.08;-0.17)	< **.01****
		t_3	860	12.67 (0.33)	-0.66	(-098;-0.33)	**.0001****	-0.12	565	13.56 (0.34)	0.04	(-0.32;0.41)	0.82	0.01	-0.70	(-1.19;-0.21)	< **.01****
	Anxiety (HADS-A)	t_0	1744	10.32 (0.14)					1205	10.30 (0.14)							
		t_1	1243	10.30 (0.15)	-0.02	(-0.12;0.09)	0.78	-0.01	848	10.37 (0.15)	0.07	(-0.04;0.19)	0.22	0.05	-0.09	(-0.25;0.07)	0.27
		t_2	1072	10.35 (0.15)	0.03	(-0.08;0.14)	0.54	0.02	669	10.37 (0.15)	0.07	(-0.06;0.19)	0.30	0.05	-0.03	(-0.20;0.14)	0.71
		t_3	862	10.48 (0.15)	0.16	(0.04;0.28)	<**0.01****	0.10	576	10.44 (0.15)	0.14	(0.01;0.28)	**0.03***	0.09	0.02	(-0.16;0.20)	0.85
	Depression (HADS-D)	t_0	1744	8.43 (0.09)					1205	8.56 (0.09)							
		t_1	1243	8.57 (0.09)	0.15	(0.03;0.26)	**0.01****	0.09	848	8.63 (0.09)	0.07	(-0.05;0.20)	0.26	0.04	0.07	(-0.10;0.24)	0.40
		t_2	1072	8.51 (0.09)	0.09	(-0.03;0.21)	0.16	0.05	669	8.60 (0.09)	0.04	(-0.09;0.18)	0.54	0.02	0.04	(-0.14;0.22)	0.64
		t_3	862	8.49 (0.09)	0.06	(-0.07;0.19)	0.33	0.04	576	8.53 (0.10)	-0.03	(-0.17;0.11)	0.68	-0.02	0.09	(-0.10;0.29)	0.34
	Distress (HADS-T)	t_0	1744	18.74 (0.17)					1205	18.86 (0.17)							
		t_1	1243	18.87 (0.17)	0.13	(-0.02;0.22)	0.09	0.06	848	19.00 (0.17)	0.14	(-0.02;0.21)	0.09	0.06	-0.01	(-0.24;0.21)	0.90
		t_2	1072	18.86 (0.17)	0.12	(-0.04;0.28)	0.14	0.05	669	18.97 (0.18)	0.11	(-0.07;0.29)	0.24	0.05	0.01	(-0.23;0.25)	0.94
		t_3	862	18.97 (0.18)	0.23	(0.05;0.40)	**0.01****	0.10	576	18.97 (0.18)	0.12	(-0.08;0.31)	0.24	0.05	0.11	(-0.15;0.37)	0.40

EMM = Estimated Marginal Means.

* = significant difference $p < .05$

** = significant difference $p < .01$

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Furthermore, there was a significant 'time x group' interaction effect on the **BMI** ($p = .009$). The 'time x group' interaction contrasts (adjusted group contrasts) were significant at t_1 between IG (adjusted EMM Diff = -0.15) and CG (adjusted EMM Diff = 0.15) by -0.30 BMI points ($p = .02$), at t_2 between IG (adjusted EMM Diff = -0.16) and CG (adjusted EMM Diff = 0.26) by -0.41 BMI points ($p = .002$), and at t_3 between IG (adjusted EMM Diff = -0.21) and CG (adjusted EMM Diff = 0.09) by -0.31 BMI points ($p = .03$). Also, there was a significant 'time x group' interaction effect on **measuring blood pressure** ($p < .001$). The between-group differences in differences ('time x group' interaction contrasts) were statistically significant ($p < .001$) in the changes from baseline at t_1 between IG (adjusted EMM Diff = 0.18) and CG (adjusted EMM Diff = -0.01) with an adjusted group contrast of .19 and at t_2 ($p = .03$) with an adjusted group contrast of .11 (IG: adjusted EMM Diff = 0.07; CG: adjusted EMM Diff = -0.04).

3.3.3 Psychosocial outcomes. For psychosocial outcomes, there were several significant 'time x group' interaction effects: For instance, there is an overall effect on **patient activation** ($p< .001$), resulting in significant 'time x group' interaction contrasts in the changes from baseline to t_1 ($p < .0001$) with an adjusted group contrast of 0.95 (IG: adjusted EMM Diff = 0.71; CG: adjusted EMM Diff = -0.24), and also in the changes from baseline to t_2 ($p = .01$) with an adjusted group contrast of .69 (IG: adjusted EMM Diff = 0.59; CG: adjusted EMM Diff = -0.10). Also, there was a significant overall 'time x group' effect for **health literacy** ($p < .001$), with significant 'time x group' interaction contrasts (adjusted group contrasts) in the changes from baseline to t_1 of 1.02 ($p < .001$; IG: adjusted EMM Diff = 0.86; CG: adjusted EMM Diff = -0.16)), to t_2 of 1.60 ($p < .0001$, IG: adjusted EMM Diff = 0.92; CG: adjusted EMM Diff = -0.67)) and to t_3 of 1.52 ($p < .001$; IG: adjusted EMM Diff = 0.89; CG: adjusted EMM Diff = -0.63)). Regarding **stages of change** there is a significant 'time x group' effect ($p = .005$). The 'time x group' interaction contrasts were significant for the change from t_0 to t_1 with an adjusted group contrast of -0.64 ($p < .01$) between IG (adjusted EMM Diff = -0.58) and CG (adjusted EMM Diff = 0.06), from t_0 to t_2 with an adjusted group contrast of -0.63 ($p < .0$; IG: adjusted EMM Diff = -0.63; CG: adjusted EMM Diff = 0.00) and from t_0 to t_3 with an adjusted group contrast of -0.70 ($p < .01$; IG: adjusted EMM Diff = -0.66; CG: adjusted EMM Diff = 0.04). Regarding **anxiety** ($p = .646$), **depression** ($p = .758$) and **mental distress** ($p = .815$) there were no significant differences between the groups over the time of three years.

A closer look at the changes from baseline (contrasts (adjusted EMM differences)) for both groups may give a more detailed impression of the different courses over time for each outcome (Table 5). There are statistically significant within-group changes from baseline in both groups. Nevertheless, the effect size of all contrasts were below .2 indicating a small effect size.

The detailed results for ITT-2 including the estimated marginal means (EMM), the standard error (SE), the adjusted EMM differences between t_0 and each follow-up (including 95% confidence interval (CI)), the significance (p) of the adjusted EMM difference, as well as the effect size (Cohen's d) for each time of measurement for each group, as well as the between-group differences in the within-group changes (adjusted group contrasts), its 95% CI and significance (p) can be found in Table 5. The observed means and standard deviations for all analyses (ITT-1, ITT-2, AT) across all time points can be found in S3 Table.

Estimated marginal means, their standard errors and estimated marginal differences by time (t_0, t_1, t_2, t_3), adjusted for education for ITT-1 and AT can be found in S4 and S5 Tables.

The **ITT-1** analysis comparing the IG including those declining the TBHC to the CG controlling for level of education showed statistically significant differences in physical activity in hours per week ($F_{3,\ 6431.5} = 3.66$; $p = .01$), physical activity measured in metabolic rate per week ($F_{3,\ 6493.0} = 3.77$; $p = .01$), measuring blood pressure ($F_{3,\ 5728.3} = 3.89$; $p< .01$) and stages of change ($F_{3,\ 5955.5} = 3.37$; $p = .02$) (Table 4).

Additionally, we employed an **as-treated** approach (AT) comparing those participants that received five or more calls to the CG (Table 4). Controlling for level of education, there were statistically significant 'time x group' interaction effects in physical activity in hours per week ($F_{3, 4427.0} = 3.11$; p = .03), physical activity measured in metabolic rate per week ($F_{3, 4459.1} = 2.76$; p = .04), body mass index ($F_{3, 3827.2} = 4.12$; p = .01), measuring blood pressure ($F_{3, 3997.1} = 7.65$ p< .0001). Following psychosocial outcomes showed significant interaction effects: Patient activation ($F_{3, 4121.0} = 5.11$; p< .01), health literacy ($F_{3, 4038.2} = 9.69$; p< .0001), and stages of change ($F_{3, 4169.9} = 5.08$; p< .01).

3.3.4 Moderator analyses. We conducted moderator analyses to examine whether intervention effects vary among campaigns ("heart failure campaign" (N = 397), "chronic campaign 1" (N = 993), "chronic campaign 2" (N = 2698), and "mental health campaign" (N = 190)). We found campaign-specific intervention effects for foot monitoring by physician (p = .036) and blood sugar measurements (p = .001). Detailed results of the subgroup analyses can be found in Table 6. The estimated marginal means for "measuring blood sugar" and "foot monitoring by physician" can be found in S6 Table.

4. Discussion

4.1 Principal findings

The aim of this randomized controlled trial was to evaluate the effectiveness of a TBHC intervention for people living with chronic conditions on a variety of patient reported outcomes

Table 6. Mixed model analysis (ITT-2), overall effects ('time x group x campaign') adjusted for education and age.

	Df	F	Sign. (p)
Quality of life			
SF-12 Mental Subscale	12, 4414.8	1.00	0.443
SF-12 Physical Subscale	12, 3919.7	0.62	0.827
Health status (EQ5D-VAS)	12, 4440.9	0.67	0.782
Health behaviors			
Alcohol consumption (AUDIT-C)	12, 3755.1	0.97	0.476
Smoking	12, 4111.5	1.49	0.118
Physical activity (hours per week)	12, 4735.9	1.16	0.303
Physical activity (metabolic rate per week)	12, 4765.0	1.03	0.415
Body Mass Index (BMI; kg/m^2)	12, 4046.3	1.07	0.380
Adherence (MARS-D)	12, 4327.8	1.72	0.057
Measuring blood pressure	12, 4259.8	0.97	0.476
Measuring blood sugar	12, 3821.8	2.67	**0.001****
Foot monitoring self	12, 4381.9	1.69	0.063
Foot monitoring by physician	12, 3849.3	1.85	**0.036***
Psychosocial outcomes			
Patient activation (PAM)	12, 4386.8	1.11	0.351
Health literacy (FCCHL)	12, 4308.6	1.26	0.234
Stages of Change (SOC)	12, 4445.8	0.89	0.562
Anxiety (HADS-A)	12, 4776.8	0.74	0.715
Depression (HADS-D)	12, 4704.0	0.87	0.574
Distress (HADS-T)	12, 4769.8	0.81	0.646

Df = degrees of freedom; F = F Value.

* = significant p < .05

** = significant p < .01

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such as QoL, health behaviors, and psychosocial outcomes. We compared the effectiveness of a TBHC intervention for people living with chronic conditions, insured at a German statutory health insurance, to a usual care group.

In the a modified intention-to-treat analysis, comparing TBHC participants and CG (ITT-2), seven out of 19 outcomes showed significant overall intervention effects ('time x group') after controlling for education and age. Patients in the IG group differed significantly from patients in the CG group regarding their physical activity (hours per week and metabolic rate per week) and their BMI, which can be attributed to the central focus of the TBHC to promote exercise, to improve nutrition, and to provide information about these topics (see S2 Table 'TIDIER Checklist'). With regard to blood pressure measurement, TBHC was found to result in more frequent blood pressure measurements, although the overall frequency of measuring blood pressure is significantly lower in the CG at all times. One explanation for this finding is that this is one of the main foci of the TBHC, including the use of a "blood pressure log book" for recording blood pressure measurements. Furthermore, it was found that TBHC results in greater (patient) activation, like taking charge over their health, and better health literacy. This suggests that the MI technique used by the health coaches is an effective counselling method that enhances motivation and thus acts as a catalyst to accelerate health behavior change. Nonetheless, in contrast to these findings, it was found that patients in the TBHC group were less motivated to change according to the stages of change (no willingness to change, considering change, preparation, taking action and maintenance) over time compared to patients in the CG whose willingness did not change. One explanation for this finding might be that participants receiving TBHC are more satisfied with their own health behavior and therefore see no reason to change. These findings are supported by a closer look at the contrasts comparing each follow-up to the baseline. The IG remains rather stable regarding their physical activity, whereas the CG shows a significant decrease in active hours per week. Nevertheless, comparing the groups regarding their differences from baseline there is no significant difference between the groups. With regards to the BMI the IG shows a continuous drop over the years, while the CG shows an increase in BMI (especially at the 2 years follow-up). This difference from baseline is also statistically different between the groups at all times. Concerning the overall frequency of measuring blood pressure and the patient activation the IG reveals a short- (t_1) and mid-term (t_2) increase that does not remain until t_3. The change from baseline is also statistically significant between the groups for t_1 and t_2. The significant improvement in health literacy in the IG remains stable over all follow-ups, whereas the CG shows a significant decline of health literacy at t_2 and t_3, which is also statistically significant in the post hoc interaction contrasts. The decrease of the stages of change in the IG remains stable over all follow-ups, while there is no statistically significant change in the CG. The difference in difference analysis also supports this finding by showing statistically significant group differences in change over all times. These inconsistent findings warrant further investigation in future clinical trials.

Finally, the absence of significant effects requires some comment. There were no effects on QoL (mental, physical QoL and health status), alcohol consumption, smoking, medication adherence, the amount of measuring blood sugar and foot monitoring (by the participants or a physician), anxiety, depression and mental distress. One plausible explanation for the absence of significant effects could be that a change in QoL, health status, anxiety and depression depends on too many other complex and multifaceted factors to be merely influenced by TBHC and the engagement in the desired health behaviors alone such as regular exercise and a healthy diet. The change of addictive behaviors like smoking or alcohol consumption might be too challenging for a broad telephone intervention that focuses on more than one health behavior. The absent effect on medication adherence might be due to problem of the high

ceiling effects of the MARS-D and possible effects of social desirability as the TBHC was conducted by their health insurance.

There were just two moderator effects between the study group and the campaigns on 'blood sugar measurement' and 'foot monitoring by a physician', suggesting limited variation in the treatment effects across campaigns.

The results of the AT analysis were very similar with slightly higher effect sizes. Therefore, we cannot state a dose-effect based on these analyses. There is future research needed to provide valid information on this.

4.2 Results in relation to similar studies

Our findings are in line with previous results that report no effect of TBHC on QoL [17, 21, 28, 67, 68], health status [26, 28] or health behaviors such as alcohol consumption [28, 39, 40] and smoking [17, 25, 27, 28, 32, 41]. Likewise, the lack of effects on depression and distress is comparable with the findings of similar studies [17, 19, 25, 27, 28]. Regarding patient activation, findings are consistent with previous studies showing a positive effect of TBHC on patient activation [21, 69].

In contrast with earlier findings in the literature, our findings do not confirm previous research reporting TBHC effects on anxiety [25, 26], which can be attributed to a different focus of our TBHC intervention (S2 Table). However, we found an effect of TBHC on the frequency of blood pressure measurements, physical activity and the BMI of participants, while most studies do not show effects on these parameters (blood pressure measurement [29, 34, 35, 38], physical activity [23, 29–37], BMI [29–31, 38–40, 70–72]), although there are also studies that have similar results (blood pressure measurement [35, 38, 70], physical activity [25, 28, 30, 37, 38, 41, 70, 72, 73], BMI [17, 25, 74]). However, as our findings are exploratory, we can only assume why we see these effects. One possible reason could be that our intervention is more tailored to the needs of the patients, be it their condition, their leisure time activities or their delegation of responsibility regarding their condition. As we also found that the activation and health literacy is higher in the IG than in the CG, especially in the first year, it is possible that empowering the patient to take responsibility for their health actions is a good way to moderate effects on exercise, diet and BMI.

Furthermore, we tested outcomes that were not used so far. Health literacy has not been assessed in the evaluation of a TBHC so far, therefore our findings may be the first to indicate that TBHC could be an effective measure to promote participants' health literacy. For the Transtheoretical Model of Change and its stages of change there have only been longitudinal, non-randomized studies that concluded, contrary to our findings no effects of TBHC [27, 32, 75].

Overall, these inconsistent findings indicate that the effectiveness of TBHC remains inconclusive given the spectrum of heterogeneous studies, although the effects of the TBHC intervention on psychosocial outcomes are partly in line with the known literature. That said, the data presented in this paper significantly adds knowledge to the existing body of literature regarding the effectiveness of TBHC. Despite some international and nationwide studies like Birmingham OwnHealth [76, 77], TERVA [78], the DIAL study [24] and the Connection Program [79], there have not been many studies with such a large sample available for the assessment of patient reported outcomes.

4.3 Strengths and weaknesses

As this study included 4,283 patients in the analyses, a main strength is the large sample size. There are few studies in this field that include as many patients in the evaluation of patient reported data. The drop-out over this amount of time of 50.6% is as expected as it is

comparable to the pilot study [45]. We tried handle missing values conservatively: EM-imputation for item-level missings to compute scores for those that provide 70% of the scores data on the one hand, and the statistical analyses with mixed model analysis which is quite robust against missing values on the other hand.

The randomization process based on Zelen's single-consent design before informed consent ensures that patients participating in the intervention are clearly willing to take part in the intervention. Also, the participation rate is higher than in classic RCT designs leading to larger sample sizes [80]. Nevertheless, an intention-to-treat analysis, in this case ITT-1, is necessary to avoid selection bias in Zelen's design. Therefore, the thorough statistical evaluation can be considered a strength of this study.

For good scientific practice a study protocol was published [15], and it was registered in the German Clinical Trials Register (GCTR). The inclusion of more than one of the most important chronic conditions, like diabetes mellitus type II and chronic heart diseases, increases generalizability. Also, this study provides high treatment fidelity, as it is manual-based; the coaches received regular supervision and the quality of the intervention was assessed regularly. A further strength is that this study was conducted in real routine health care. Therefore, generalizability and external validity are high. Also, the analysis of three yearly follow-ups enables the readers to assess the long-term effectiveness of this intervention.

Nevertheless, this study has some limitations. Although we employed an intention-to-treat approach (ITT-1) to avoid the participation bias, one could argue that this is not a flawless ITT, as we do not have complete data of all patients that were randomized, but of those, that replied at least at baseline [81]. Therefore, the results must be interpreted with caution. It is possible that there are differences between those taking part and those who dropped out on the one hand and between those taking part in the intervention and those who declined the intervention on the other hand. As stated earlier, eligible insurants decided whether to participate after randomization—this could be a crucial cause for potential bias. 57.4% of the randomized potential participants decided to decline participation. A comparison between those groups showed that participants were significantly less educated than decliners or CG. Therefore, we tried to control for this bias by adjusting the model by education and age as a fixed effects. Nevertheless, there is a possibility of other differences between the groups, as we did not assess all possible confounding variables. Additionally, we did not assess whether the patients have an immigrant background, which could also lead to some participation and group differences. Also, we lacked the insurants' clinical and physician data. Therefore, the severity of the patients' condition could not be considered. In addition, no data were available on the routine health care that has taken place alongside the intervention and during follow-up. Therefore, it was not possible to ascertain how much of a poorly controlled disease status is lack of adequate treatment. Another limitation could be that the chronic campaign was heterogeneous with different diagnoses, like diabetes mellitus type II, coronary artery disease etc. in need for different coaching targets. To prevent an even higher bias within the chronic campaign we divided it into two smaller subgroups that differed regarding their inclusion criteria. Therefore, the campaigns are slightly different to the manuscript reporting the health economic outcome [44].

Also, the questionnaires were sent out by the health insurance. Therefore, it is possible that there is a bias due to social desirability, despite making clear the pseudonomyzation. Also, patient reported outcomes are prone to social desirability bias and inaccurate reporting. Additionally, effect sizes of all statistically significant EMM differences (despite for health literacy and measuring blood pressure) were very small. Also, the clinical significance needs to be questioned as all statistically significant effects were practically very small and we did not adjust for multiple testing (Bonferroni).

Generalizability of the findings might also be limited, since those insured at this health insurance have a slightly higher socioeconomic status than at other health insurances due to historic reasons. Nevertheless, in Germany nearly all citizens are insured for health care as mandatory members of the public health insurance (86.2%) or private health insurances (10.6%) [82].

5.Conclusion and practice implications

Based on previous research and the results of our study, TBHC interventions might have small effects on some patient reported outcomes. It would be interesting to find out, which intervention components actually have an effect. So maybe a more disease specific approach could make it easier to distinguish between effective and ineffective components without disease specific variables diluting the results. Also, future research should focus on who exactly profits most from TBHC interventions and whether there are any differences regarding disease, multimorbidity or gender.

Supporting information

S1 Table. CONSORT checklist.
(PDF)

S2 Table. TIDieR checklist.
(PDF)

S3 Table. Observed means and standard deviations for all outcomes and measurement times.
(PDF)

S4 Table. Model-predicted (ITT-1) estimated marginal means, their standard errors and estimated marginal differences by time (t_0, t_1, t_2, t_3), adjusted for education.
(PDF)

S5 Table. Model-predicted (AT) estimated marginal means, their standard errors and estimated marginal differences by time (t_0, t_1, t_2, t_3), adjusted for education.
(PDF)

S6 Table. Model-predicted (time x group x campaign; ITT-2) estimated marginal means, their standard errors and estimated marginal differences by time (t_0, t_1, t_2, t_3), adjusted for education and age for "measuring blood sugar" and "foot monitoring by physician".
(PDF)

S1 File. Published study protocol.
(PDF)

S2 File. Study protocol for ethics committee.
(PDF)

S3 File. Ethics approval document.
(PDF)

S1 Fig. Analysis principles.
(TIFF)

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Publication 4: Telephone health coaching with exercise monitoring using wearable activity trackers (TeGeCoach) for improving walking impairment in peripheral artery disease: study protocol for a randomised controlled trial and economic evaluation

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Telephone health coaching with exercise monitoring using wearable activity trackers (TeGeCoach) for improving walking impairment in peripheral artery disease: study protocol for a randomised controlled trial and economic evaluation

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ABSTRACT

Introduction Peripheral artery disease (PAD) is the third most prevalent cardiovascular disease worldwide, with smoking and diabetes being the strongest risk factors. The most prominent symptom is leg pain while walking, known as intermittent claudication. To improve mobility, first-line treatment for intermittent claudication is supervised exercise programmes, but these remain largely unavailable and economically impractical, which has led to the development of structured home-based exercise programmes. This trial aims to determine the effectiveness and cost advantage of TeGeCoach, a 12-month long home-based exercise programme, compared with usual care of PAD. It is hypothesised that TeGeCoach improves walking impairment and lowers the need of health care resources that are spent on patients with PAD.

Methods and analysis The investigators conduct a prospective, pragmatic randomised controlled clinical trial in a health insurance setting. 1760 patients diagnosed with PAD at Fontaine stage II are randomly assigned to either TeGeCoach or care-as-usual. TeGeCoach consists of telemonitored intermittent walking exercise with medical supervision by a physician and telephone health coaching. Participants allocated to the usual care group receive information leaflets and can access supervised exercise programmes, physical therapy and a variety of programmes for promoting a healthy lifestyle. The primary outcome is patient reported walking ability based on the Walking Impairment Questionnaire. Secondary outcome measures include quality of life, health literacy and health behaviour. Claims data are used to collect total health care costs, healthcare resource use and (severe) adverse events. Outcomes are measured at baseline, 12 and 24 months.

Ethics and dissemination Ethical approval has been obtained from the Medical Association Hamburg. Findings are disseminated through peer-reviewed journals, reports to the funding body, conference presentations and media press releases. Data from this trial are made available to the public and researchers upon reasonable request.

Strengths and limitations of this study

- To our knowledge, this pragmatic clinical trial conducted in a health insurance-based setting is the first to investigate the clinical effectiveness of a structured home-based exercise programme in patients with peripheral artery disease.
- Collecting data on healthcare costs and utilisation allows a comprehensive economic evaluation of a structured home-based exercise programme in patients with peripheral artery disease.
- An initial 1 hour baseline assessment based on remote activity monitoring data determines the current walking impairment in order to create a training plan tailored to varying fitness levels; however, the validity of this assessment method has not been established yet.
- Since a potentially high attrition may endanger the internal validity of the results, a linear mixed model without any ad hoc imputation is used in order to deal adequately with missing values arising from study dropouts.
- The heterogeneity of intervention delivery given the pragmatic trial approach ensures the generalisability of the results applicable to the real-world clinical practice, which yet may lead to a dilution of the treatment effect.

TRIAL REGISTRATION NUMBER

NCT03496948 (www.clinicaltrials.gov), Pre-results.

INTRODUCTION

Peripheral artery disease (PAD) is the third most prevalent atherosclerotic cardiovascular disease with over 200 million people affected worldwide and has become one of the leading causes of disability and death.[1 2] It is characterised by the progressive narrowing of the peripheral arteries resulting in the reduction of blood supply, eventually leading to functional impairment and mobility loss.[3] If not intervened sufficiently early, the atherosclerotic processes can lead to ulcer formation and gangrenous necrosis (ie, critical limb ischaemia),[4] and may affect other vascular beds with potentially fatal consequences.[5 6] PAD is markedly more prevalent in the elderly population, estimating that 5.4% and 18.6% of individuals aged from 45 to 49 and 85 to 89 years are affected, respectively.[1 2] The amount of people with PAD has risen rapidly in recent years, with a sharp increase by nearly 25% between 2000 and 2010 in the general population.[2] Likewise, in Germany, the amount of PAD-related hospitalisations increased by 20.7% between 2005 and 2009, from 400 928 to 483 961. Meanwhile, hospital reimbursement costs for the treatment of PAD have grown nationwide from €2.14 billion in 2007 to €2.6 billion in 2009, a 21% increase within 2 years.[7] Major risk factors are tobacco smoking and diabetes, followed by high cholesterol, hypertension, history of cardiovascular disease (ie, coronary heart disease, stroke) and chronic kidney disease.[1 2 8 9]

The most common clinical manifestation is leg pain while walking, known as *intermittent claudication* (IC), which reflects impaired haemodynamics and vascular dysfunction.[10 11] IC is associated with diminished mental health and lower quality of life, thus reducing symptom burden is the cornerstone of the comprehensive care for patients with PAD.[12–15] Besides pharmacotherapy, risk factor management and surgical revascularisation procedures, exercise-based interventions provide substantial mental and physical health benefits for patients with IC.[16–19] Accordingly, formal *supervised exercise programmes* (SEPs) are shown to be effective in the treatment of PAD with IC and are recommended as first-line therapy with the highest level of evidence in a variety of published clinical guidelines.[20–22] SEPs involve the use of intermittent walking exercise and are minimum 3-month commitments, with at least three sessions per week (30–60 min per session) provided in a clinical setting (eg, hospital outpatient setting, outpatient facility or a physician's office). Although SEPs commonly form part of usual care, its use is hampered by low uptake and adherence rates, possibly due to copayment requirements and lack of reimbursement, lack of available local training centres and the burden of travelling.[23 24] These obstacles highlight the need for innovative models of care, which have led to the emergence of structured *home-based* exercise programmes (HEPs) where SEPs are not available or impractical to deliver.[25] According to clinical practice guidelines, structured HEPs can serve as a useful alternative to SEPs[20 22] as they improve walking impairment[26] and are preferred by patients over SEPs.[27] Structured HEPs are performed independently by the patient but follow an exercise regimen similar to that of SEPs, with a duration of 3–6 months. Protocols of structured HEPs show considerable variation with regard to programme duration, form of exercise, exercise frequency and duration, and intervention components used (for an overview, see Hageman *et al*).[28] To achieve benefits, structured HEPs include psychological behaviour change techniques (eg, goal setting, barrier identification and motivational interviewing), regular follow-ups with a healthcare professional or coach (eg, face-to-face and phone), activity monitoring and feedback (eg, wearable activity trackers and logbooks), patient education or any combination thereof.[28] Although inferior to SEPs,[24 28–30] structured HEPs have been shown to improve performance-based,[31–40] patient-reported[31–38 40] and cardiorespiratory fitness[39] outcomes with high adherence,[31 37] whereas unstructured exercise giving merely 'go home and walk' advice to patients with symptomatic PAD has proven ineffective.[41]

Given the promising results demonstrating the *efficacy* of structured HEPs in previous explanatory trials, pragmatic trials (ie, with high external validity) are urgently warranted to establish the *effectiveness* of structured HEPs with the goal to inform clinical practice and to shape healthcare policies.[42] In response to the lack of effectiveness trials, while drawing on best available evidence and experience with previous telecoaching studies,[43] three German statutory health insurance funds (*KKH Kaufmännische Krankenkasse, TK Techniker Krankenkasse* and *mhplus Krankenkasse*) launch TeGeCoach, a 12-month long-structured HEP that involves telemonitored intermittent walking exercise using wearable activity trackers with medical supervision by a physician, and motivational interviewing-based telephone health coaching. TeGeCoach provides a streamlined, structured HEP approach based on current evidence using several components that have been shown to be beneficial; telephone health coaching have been shown to be a cost efficient and effective tool in the management of other chronic diseases,[44–46] supporting physical activity and dietary behaviour change.[47] Therefore, structured HEPs involving telephone health coaching may also offer great potential for patients with PAD, although the frequency of coaching conversations may play a critical role in whether telephone health coaching is beneficial.[48] With regard to the mode of exercise, intermittent walking exercise has been proven to be effective in patients with IC, which involves repeated bouts of exercise to maximally tolerable claudication pain alternated with recovery breaks.[49] Likewise, the use of activity trackers alone or as an intervention modality are considered a convenient way for facilitating physical activity[50 51] with long-term health benefits,[52] while remote activity monitoring (eg, by a coach) may

improve walking impairment and significantly lower the costs of healthcare in PAD patients.[53] Among older adults, the use of activity trackers is well accepted and may be effective to encourage physical activity,[54 55] with behavioural change techniques such as social support and motivating feedback facilitating their (long-term) use.[56 57] Furthermore, adding some kinds of counselling to the use of wearable activity tracker (eg, activity monitor-based counselling) could allow the health coach to deliver behaviour change techniques and to support sustained exercise. For example, using an activity tracker with regular feedback combined with access to SEPs has proven to improve functional walking performance and quality of life in PAD patients.[58] Similarly, telephone health coaching combined with activity monitoring was found to increase physical activity and reduce sedentary behaviour in elderly people.[59]

The aim of this study is to explore the effectiveness of TeGeCoach, a structured HEP for patients with PAD. A randomised controlled trial of 1760 patients with PAD is conducted to determine whether TeGeCoach improves patient-reported walking impairment while lowering healthcare costs at 12-month and 24-month follow-up, compared with the usual care of PAD (care-as-usual, CAU). It is hypothesised that TeGeCoach improves walking impairment and lowers the costs of healthcare that are spent on patients with PAD. Given the size and remote nature of the study (ie, no personal contact to research staff), as well as the pragmatic trial approach (ie, measurement of outcomes should be patient relevant and should not interfere with the usual care),[60] it was opted to use only patient-reported outcome measures (PROMs), while collecting healthcare utilisation and costs from claims data. PROMs emphasise the patient perspective by collecting information that are directly relevant to the patients; with growing interest in comparative effectiveness research, PROMs are commonly used in clinical trials to measure treatment effects.[61] If effective, TeGeCoach could be widely integrated into PAD usual care with the potential to provide health benefits for patients with PAD while reducing healthcare costs.

METHODS

Trial design

This is a two-arm, parallel-group, open-label, pragmatic, randomised, controlled superiority trial embedded within three German statutory health insurance funds (*KKH Kaufmännische Krankenkasse, TK Techniker Krankenkasse* and *mhplus Krankenkasse*). It is designed to compare the effects of TeGeCoach (intervention arm) to the CAU, conducted in a health insurance system-based setting (figure 1). Trial initiation was in 4/2018 and ends in 2/2021. The recruitment period was 9 months (4/2018 to 12/2018; table 1). The study is conducted in full compliance with Good Clinical Practice quality standards and in accordance with the Declaration of Helsinki of 2008. It is expected that final results are reported after study completion in 2021.

This study protocol is reported in accordance with the CONsolidated Standards Of Reporting Trials (CONSORT) statement;[62] the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement;[63] the SPIRIT Patient-Reported Outcome (PRO) extension[64] and the Template for Intervention Description and Replication checklist.[65]

Patient and public involvement statement

This research was planned without patient involvement. Patients were not invited to comment on the study design and were not consulted to develop patient relevant outcomes. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy.

Participants

Participants have to meet the following criteria: registered with one of the participating statutory health insurance funds (*KKH Kaufmännische Krankenkasse, TK Techniker Krankenkasse* and *mhplus Krankenkasse*); aged between 35 and 80; German-speaking; access to a telephone (landline or mobile) and a primary or secondary diagnosis of PAD at Fontaine stage IIa (>200 m, Fontaine stage IIa) or IIb (<200 m, Fontaine stage IIb) within the last 36 months (corresponding ICD-10-German Modification codes I70.21, I70.22 and I73.9). Participants should have no primary or secondary diagnosis of PAD at Fontaine stage I (asymptomatic) within the last 12 months, and no diagnosis of Fontaine stage III (ischaemic rest pain) or IV (ulcer, gangrene) within the last 36 months to increase diagnostic accuracy (corresponding ICD-10-German Modification codes I70.23, I70.24 and I73.25).

Exclusion criteria for participants are immobility that goes beyond claudication (Fontaine stage III or IV; inability to carry out intervention); (chronic) physical conditions that interfere with the intervention (eg, COPD); cognitive disorders (inability to carry out intervention); severe and persistent mental disorders (adherence reasons); suicidality (safety reasons); life-threatening illnesses (safety reasons); active or recent participation in any other PAD intervention trial; ongoing hospitalisation; (self-reported) alcoholism and/or other drug dependency (adherence reasons) and heart failure-graded NYHA classes III and IV (inability to carry out intervention and competing risks).

Recruitment

Participants

Recruitment of participants is managed by three statutory health insurance funds in Germany: *KKH Kaufmännische Krankenkasse, TK Techniker Krankenkasse* and *mhplus Krankenkasse.* Eligible participants are retrospectively identified using ICD-10-GM diagnosis codes from inpatient and outpatient encounters, which are routinely collected for reimbursement purposes (claims data). Due to the high

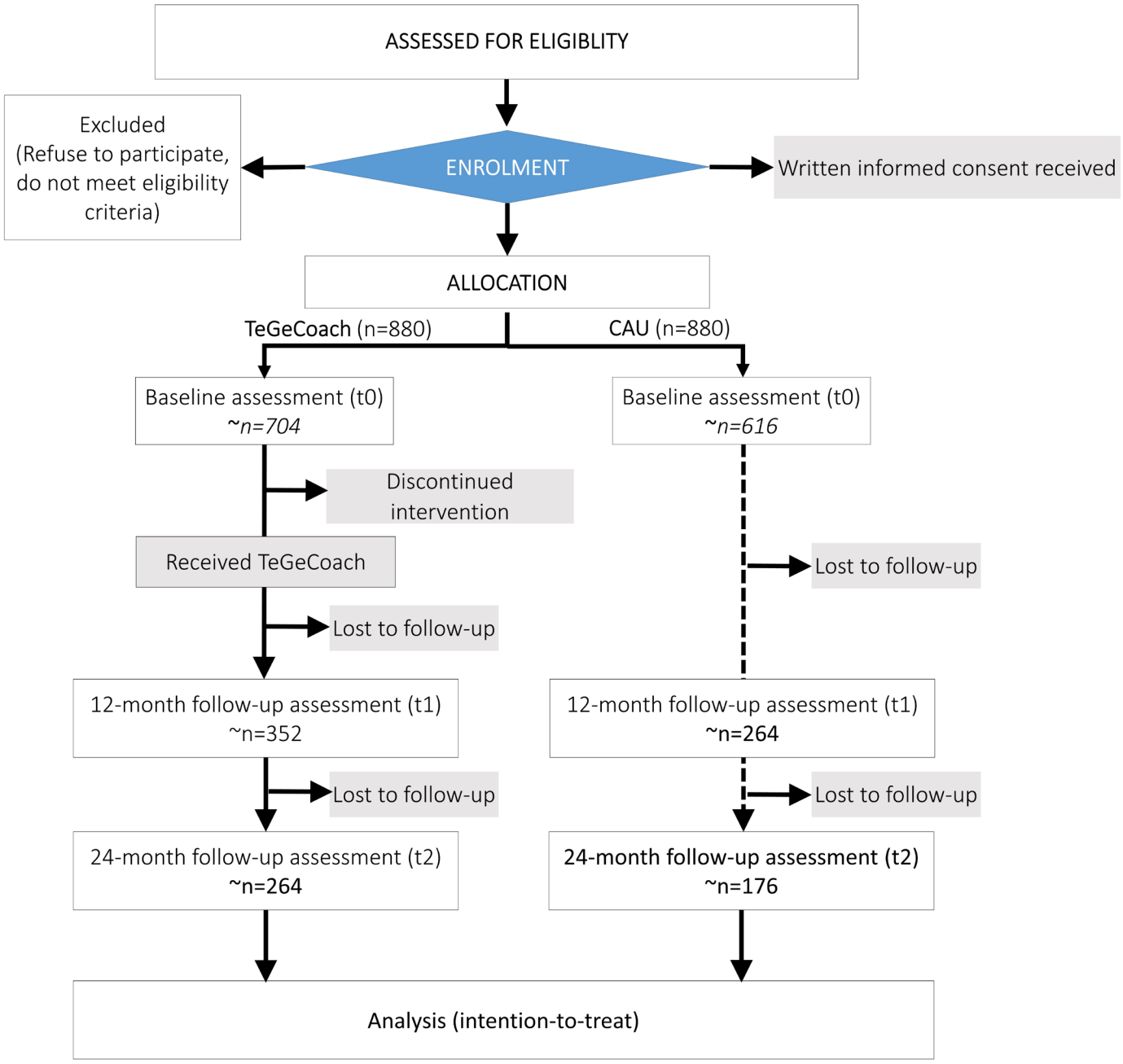

Figure 1 Prospective flow chart of the study design. CAU, usual care of PAD; PAD, peripheral artery disease; TeGeCoach, telemonitored intermittent walking exercise with medical supervision by a physician and telephone health coaching.

number of diagnostic errors and poor coding habits in outpatient settings, exclusion criteria are only checked using inpatient diagnosis codes.

An iterative recruitment process was developed, as substantial challenges to the recruitment of clinical trials have been shown in the PAD population.[66] Eligible participants are contacted by their health insurance fund to explain the purpose of the study and to confirm their PAD diagnosis by questioning them about their symptoms. Eligible participants receive a study information letter that is supplemented with consent and permission forms (ie, authorisation for release of medical reports by the contracted physician to the health coach). If interested to participate, they are asked to sign all documents and send them back to their health insurance fund. Eligible non-responders who are still interested in the study but have not given written consent are followed up by phone to be reminded of the trial. Once the written consent has been received, a query is submitted to the data warehouse of the respective health insurance fund which automatically assigns a pseudonym to the participant. No participant will be enrolled without full, written informed consent.

Physicians

Each participant allocated to TeGeCoach must be medically supervised by a physician, which is a prerequisite for receiving the TeGeCoach intervention; participants can elect their preferred physician prior to programme start,

Table 1 Trial registration data

Data category	Information
Primary registry and trial identifying number	ClinicalTrials.gov (NCT03496948)
Date of registration in primary registry	23 March 2018
Source(s) of monetary or material support	Innovation Fund, Federal Joint Committee (G-BA)
Trial sponsor	KKH Kaufmännische Krankenkasse
Contact for public queries	FB (frank.bienert@kkh.de), KKH Kaufmännische Krankenkasse
Contact for scientific queries	FR (f.rezvani@uke.de), University Medical Center Hamburg-Eppendorf
Public title	TeGeCoach—a home-based exercise programme using telephone health coaching with telemonitoring for patients with peripheral artery disease
Scientific title	Telephone health coaching with exercise monitoring using wearable activity trackers (TeGeCoach) for improving walking impairment in peripheral artery disease: study protocol for a randomised controlled trial
Countries of recruitment	Germany
Health condition(s) or problem(s) studied	Peripheral artery disease (PAD)
Intervention(s)	Active comparator: telemonitored intermittent walking exercise with medical supervision by a physician and telephone health coaching (TeGeCoach) Active comparator: care-as-usual (CAU)
Key inclusion and exclusion criteria	Ages eligible for study: ≥35 years and ≤80 years Sexes eligible for study: both Accepts healthy volunteers: no *Inclusion criteria*: ≥35 years and ≤80 years, insured at one of the participating statutory health insurance funds, access to a telephone, primary or secondary diagnosis of PAD at Fontaine stage IIa/b within the last 36 months, no primary or secondary diagnosis of PAD at Fontaine stage I within the last 12 months, no diagnosis of Fontaine stage III/IV within the last 36 months *Exclusion criteria*: immobility that goes beyond claudication, inability to carry out intervention (chronic) physical conditions that interfere with the intervention, cognitive disorders, severe and persistent mental disorders, suicidality, life-threatening illnesses, active or recent participation in any other PAD intervention trial, ongoing hospitalisation, alcoholism and/or other drug dependency, heart failure graded NYHA classes III and IV
Study type	Interventional Allocation: randomised Intervention model: parallel assignment masking: analysis blinding Primary purpose: prevention
Date of first enrolment	April 2018
Target sample size	1760
Recruitment status	Completed
Primary outcome(s)	*PROM*: walking impairment *Time points*: baseline, 12 and 24 months
Key secondary outcomes	*PROMs*: generic health-related quality of life, PAD-specific quality of life, depression, generalised anxiety disorder, alcohol use, nicotine dependence, health literacy, patient activation *Claims data*: total healthcare costs, healthcare resource use, (severe) adverse events *Time points*: baseline, 12 and 24 months

NYHA, New York Heart Association; PROM, patient-reported outcome measures.

or are alternatively referred to an already contracted physician by their health coach. To encourage physicians to participate, they enter into an integrated care contract with the respective health insurance fund that provides financial incentives for the delivery of special medical services throughout the intervention.[67] The enrolment and reimbursement of contracted physicians is coordinated by medicalnetworks (Kassel, Germany), a

company that is specialised on the management of integrated care programmes within the §140a volume V of the German Social Security Code. If the physician of choice refuses to participate, the participant is referred to a nearby contracted physician who has already entered into the integrated care contract. Once enrolled, the health coach contacts the contracted physician to discuss their tasks during the course of the study. Due to recruitment barriers, it is possible that no suitable physician can be found for the patient by the end of the recruitment phase. For safety reasons, participants for whom no physician can be appointed do not receive TeGeCoach.

Treatment allocation and blinding

Participants are allocated in a 1:1 ratio to either the TeGeCoach or CAU group, stratified by health coaching centre using a permuted block method within each stratum. In order to prevent selection bias and to eliminate any predictability (allocation concealment), participants are randomly allocated via Sealed Envelope (London, UK), a secure internet-based randomisation service including concealment, stratification and blocking for each health coaching site.

Blinding of care providers (health coaches and contracted physicians) and participants is not possible because of obvious differences between the TeGeCoach intervention and CAU. However, as supported by the CONSORT guidelines, blinding of the analysis is achieved by engaging an independent data analyst and by withholding information about how the groups were coded before analytical decisions have been completed.[68]

Interventions

TeGeCoach

TeGeCoach is a 12-month long-structured HEP that is designed to inspire healthy habits in patients with PAD based on the transtheoretical model of behaviour change. The main strategies used to improve health outcomes include patient-centred motivational interviewing, shared decision making and active listening, aiming to help patients to enhance their individual motivation for exercise and receive the support needed to improve their condition.

Telemonitored intermittent walking exercise

Patients are instructed to continuously wear an activity tracker device (ie, from getting up to going to bed; not while showering, bathing and swimming). Two different brands of activity tracker are used that record the number of steps (*KKH Krankenkasse* and *mhplus Krankenkasse*: AS 95 Pulse by Beurer; *TK Techniker Krankenkasse*: Mi Band 2 by Xiaomi). The data from the activity tracker are transmitted automatically to the health coaching platform once per day over the internet using a SIM card modem (econnect, IEM GmbH). A 60-min baseline assessment is initially taken to evaluate the patient's individual walking capacity whereby patients are instructed to walk at a brisk pace (defined as >50 steps/min) until maximal tolerable claudication pain is reached, followed by breaks and continued walking when the pain subsides (intermittent walking). The net brisk walking time (>50 steps/min) during the 60 min baseline assessment is used to assign patients to one of three intermittent walking plans of increasing duration; the patient is assigned to level A (15-min exercise, including breaks) if he/she is able to walk less than 15 min during the baseline assessment, level B (30-min exercise, including breaks) if he/she is able to walk 15–30 min, and level C (60-min exercise, including breaks) if he/she is able to walk 30–60 min. Patients are instructed to walk intermittently at a brisk pace (>50 steps/min) on at least 5 days per week. The assignment to one of the training levels is not conclusive; the coach regularly reviews, and if necessary, adjusts the walking plan after every coaching session. The goal is to progressively increase walking intervals and shortening breaks until painless walking exercise (or bearable pain) without breaks needed has been achieved by the patient, suggesting to switch to the next training level. In addition to exercise sessions, the health coach also sees the absolute number of steps per day as a measure of overall physical activity. To ensure patient safety, the contracted physician initially reviews the proposed exercise plan, checks if any contraindications to exercise exist and whether all important comorbidities such as high blood pressure, diabetes and coronary heart disease are sufficiently treated. Furthermore, they receive three health reports from the health coach during the course of the programme, which are important for the joint exchange of information to provide collaborative care.

Telephone health coaching

Over the course of 12 months, patients regularly receive health information leaflets and have up to nine structured 30–60 min phone calls with their health coach. During these structured phone calls, the health coach and the patient jointly discuss the progress towards exercise goals and review the activity tracker data to check whether the patient adheres to the walking plan. For this purpose, exercise sessions (ie, intermittent walking represented as changes between walking and break intervals) are visualised and automatically identified as an exercise session by the health coaching platform. Additional phone calls are warranted when no data have been received, no steps were taken or when coaches are alerted that the amount of exercise days has fallen below an individual threshold. During these calls, barriers like lack of motivation, exercise intolerance or technical issues are discussed and how they can be overcome through behavioural support. Along with the walking exercise, patient-tailored topics of interest that are relevant to the management of PAD are discussed in order to improve health literacy, to facilitate patient empowerment and to adopt a proactive stance in dealing with their disease. The health coaching curriculum includes knowledge of PAD, PAD medication, comorbidities of PAD and other related health topics (eg, tobacco use and nutrition). The

health coaches use an electronic documentation system to monitor the coaching process (*KKH Kaufmännische Krankenkasse* and *mhplus Krankenkasse*: Picama Managed Care, Trustner GmbH; *TK Techniker Krankenkasse*: Philips GmbH Market DACH). The telephone health coaching is carried out by three health coaching centres that are located throughout Germany, each affiliated to one of the three statutory health insurance funds (Health Coaching Center of *KKH Kaufmännische Krankenkasse*, Telemedical Center at Robert-Bosch-Hospital on behalf of *TK Techniker Krankenkasse*, Health Coaching Center of *mhplus Krankenkasse*) and are staffed with licensed health workers (eg, nurses, physical therapists and medical assistants). To ensure high-quality health coaching, health coaches are regularly supervised by a team of experts and receive 51 hours of training, including 19 hours of programme training, 7 hours of medical training, 8 hours of group supervision and 1 hour of individual supervision. Compliance to coaching guidelines are continuously monitored and reviewed. In addition to the structured TeGeCoach intervention, participants have regular access to CAU as described below.

After 12 months, there is an additional 12 months of unstructured follow-up in which patients have no interaction with their health coach but still have access to their activity tracker device, which they may continue to use to self-monitor their physical activity.

Care as usual

Patients allocated to CAU receive usual medical care through the regular statutory healthcare system. Additionally, participants receive PAD patient information leaflets from their statutory health insurance fund, with each health insurance fund providing its own leaflets. These leaflets provide information about course offerings of the respective health insurance fund to encourage regular exercise and to promote lifestyle changes, including SEPs (vascular and cardio exercise), physical therapy, nutritional assistance programmes, smoking cessation programmes, weight loss programmes, as well as patient education programmes for obesity and diabetes. It is thereby ensured that participants allocated to CAU receive genuine usual care as supplied in everyday practice.

Outcome measures

Outcome measures are listed in table 2 along with timing of assessment; the effectiveness of TeGeCoach is measured based on PROMs, claims data and activity tracker data. PROMs are collected at baseline (t0), at 12 (t1) and 24 (t2) months.

Primary outcomes

- *PROM:* walking impairment (WIQ).[69–72]

Secondary outcomes

- *PROMs:* generic health-related quality of life (EQ5D-5L and SF-12 questionnaires);[73–76] PAD-specific quality of life (VascuQoL-25 questionnaire);[77 78] depression (PHQ-9 questionnaire);[79] generalised anxiety disorder (GAD-7 questionnaire);[80 81] alcohol use (AUDIT-C questionnaire);[82–84] nicotine dependence (FTND);[85] health literacy (HLQ);[86 87] patient activation (PAM-13 questionnaire).[88 89]
- *Claims data:* Total healthcare costs, that is, inpatient hospital care costs; outpatient (ambulatory) services and primary care costs, costs for drugs and other medical supplies, sick pay costs; healthcare resource use, that is, time period until hospitalisation, probability of hospitalisation, number and duration of inpatient hospitalisation, outpatient medical treatment, drug dose; (severe) adverse events, that is, death, amputation and revascularisation (see online supplementary file).

Table 2 Participant timeline: time schedule of enrolment (eligibility screen, informed consent, pseudonymisation and allocation), study arms (TeGeCoach or CAU) and measurements (questionnaires and claims data)

	Study period			
	Enrolment	Allocation	Postallocation	
Time point*	t1	t0	t1	t2
Enrolment				
Eligibility screening (claims data)	X			
Informed consent	X			
Pseudonymisation		X		
Allocation		X		
Study arms				
TeGeCoach (intervention)		♦———♦--------♦		
CAU (control)		---------->		
Measurements				
Intervention and control arm				
PROMs (questionnaires)†		X	X	X
Cost and medical outcomes (claims data)‡		♦———♦———♦		
Intervention arm only				
ZAPA questionnaire			X	
Walking exercise parameters (activity tracker data)§		♦———♦		

*t1, ~1 month before patient in; t0, baseline; t1, 12-month follow-up; t2, 24-month follow-up.
†WIQ, EQ5D-5L, SF-12, VascuQoL-25, PHQ-9, GHD-7, AUDIT-C, FTND, HLQ, PAM-13.
‡Healthcare costs, healthcare resource use (severe) adverse events.
§Exercise adherence, amount of steps/net walking time (>50 steps/min) per day/week.
AUDIT-C, Alcohol Use Disorders Identification Test; CAU, care-as-usual; EQ5D-5L, ; FTND, ; GAD-7, Generalized Anxiety Disorder-7; HLQ, Health Literacy Questionnaire; PAM-13, Patient Activation Measure; PHQ-9, Patient Health Questionnaire-9; PROMs, patient-reported outcome measures; SF-12, 12-Item Short Form Health Survey; VascuQoL-25, 25-item Vascular Quality of Life Questionnaire; WIQ, Walking Impairment Questionnaire; ZAPA, Satisfaction with Outpatient Care with Focus on Patient Participation .

Additional outcomes (intervention arm only)

- *PROM*: patient satisfaction (ZAPA questionnaire).[90]
- *Activity tracker data*: exercise adherence, for example, number of alerts and corresponding phone calls made when step frequency or the duration of exercise sessions fall below an individual threshold range;

amount of steps/net walking time (>50 steps/min) per day/week.

Sample size

To find a 'meaningful' effect that is clinically relevant, practicable and economically feasible, the sample size is calculated based on the distribution-based minimal clinically relevant difference (MCID) for small changes on the WIQ following 3 months of a structured HEP that have been determined in previous studies (WIQ speed MCID: 6%; WIQ distance MCID: 5%; WIQ stair climbing MCID: 5%).[91] As TeGeCoach is more intensive and longer, a small-to-moderate group difference was estimated (f=0.15), while accounting for the inherited heterogeneity of this pragmatic trial that could lead to a dilution of the treatment effect. Assuming a response rate of 30% (TeGeCoach) and 20% (CAU) from baseline 24-month follow-up (t2),[43 92] a sample size of 1760 (880 per group) is required to have 176 and 264 participants at t2 in the CAU and intervention arm, respectively, which is sufficient to detect the estimated small-to-moderate effect with 80% power and a 5% level of significance (Gpower V.3.1.9.2).

Data collection and management

Data management and storage are carried out in compliance with the General Data Protection Regulation in the European Union and Good Scientific Practice guidelines by the German Research Foundation.[93] To ensure confidentiality, all data are collected, processed, analysed and stored in deidentified form by replacing personally identifying information of each participant with a unique patient identification number (ie, by pseudonymisation), which allows to combine data from multiple sources and to merge longitudinal data. Linkage to an identity (depseudonymization) is not possible without a separately stored pseudonymisation key, which is protected by technical and organisational measures.

At each study point, the data coordinators of the health insurance funds send out a set of paper-based questionnaires (PROMs) to the participants. Participants are asked to send them back to the Department of Medical Psychology at the University Medical Center Hamburg-Eppendorf. To maximise response rates, participants who have not send their questionnaire back in time receive a postal reminder after 2–4 weeks. All participants are followed up at t1 and t2, irrespective of whether questionnaires have been returned at previous study points. Questionnaire data are entered into an electronic database, with only authorised personnel being allowed to retrieve, enter or change data. For data quality and monitoring purposes, validation checks regarding out of range data, illogical and invalid responses and data entry errors are performed.

Claims data are routinely collected for the purpose of billing and contains information on all contacts with the healthcare system including ICD codes, operations and procedure key codes (the German equivalent to the American procedure coding system), medication prescriptions and amount of sick leaves. After study completion, the health insurance funds assemble and pseudonymise the claims data and send it to the study team (University Medical Center Hamburg-Eppendorf). No individual insurance information can be identified from this data.

Activity tracker data are automatically uploaded to the electronic documentation system via SIM card modem (econnect, IEM GmbH) once per day. The statutory health insurance funds share the activity tracker data with the study team in pseudonymised form.

All data are stored for a maximum of 10 years, securely locked in cabinets and saved on password-protected computers in areas with restricted access. Personally identifiable information of participants and pseudonymisation keys are only accessible to the data coordinators at each health insurance fund. The pseudonymisation keys are deleted 2 years after study completion so that virtually from this point all data are fully anonymised. Regarding dissemination, all publicly available data are fully anonymised and do not disclose identities. Participants have the right to be informed about their data. If a participant decides to withdraw from the trial prematurely, the data already collected may be used, unless revoking their informed consent. Deletion of the data cannot be requested if the data have already been anonymised.

Statistical analysis

Analyses are by intention-to-treat in accordance with the CONSORT guidelines, that is, participants who do not adhere to or withdraw from the prescribed TeGeCoach intervention and for whom no doctor could be appointed (see the 'Recruitment' section) are included in the analyses as randomised. For questionnaire data, changes from baseline to follow-up measurements are compared between study arms using linear mixed models.[94] Single imputation using the Expected-Maximisation algorithm are applied for item-level missing data. Scale-level imputation of missing data is not necessary since this is fully handled by estimating mixed models with full information maximum likelihood.[95 96] In order to take correlation between the observations into account, models are adjusted for participant and health coaching centre characteristics. For claims data, changes over time between groups are compared between study arms using random-effects regression models (difference-in-differences method) after eliminating differences in observable baseline characteristics between groups with the use of entropy balancing.[97] Entropy balancing allows a better balancing compared with conventional processes such as propensity matching. Tests of treatment effects are conducted at a two-sided significance level of 0.05. In order to check the robustness of the results, subgroup analyses are performed to determine the influence of baseline characteristics (eg, degree of walking impairment), health insurance fund (ie, *KKH Kaufmännische Krankenkasse, TK Techniker Krankenkasse* and *mhplus Krankenkasse*) and type of analysis (ie, intention-to-treat and per-protocol).

Data monitoring and harms

This trial is not monitored by a data monitoring committee, and no interim analyses are performed as TeGeCoach is a low risk, non-invasive intervention with no identifiable risks. Over the course of the intervention, participants allocated to TeGeCoach are medically monitored by their treating physician while having regular access to the usual care of PAD. The risks from the use of wearable activity trackers is low; all devices have been certified and conform to health, safety and environmental protection standards for products sold within the European Union (CE certificate).

Ethics and dissemination

The informed consent forms and all other documents that are handed out to the participants have been reviewed and approved by the ethical review bodies (Medical Association Hamburg; reference number: PV5708). The ethics committee will be informed in case of any amendments made to the study protocol or informed consent forms.

Findings are disseminated widely through peer-reviewed manuscripts published in scientific journals, reports to the funding body, international conference presentations and media press releases. Furthermore, the study team realises the value of open science and feels committed to information exchange through data being accessible to the research community. Therefore, in an attempt to tackle the problem of hidden data, deidentified participant data from this trial are made available to the public and the medical research community on reasonable request to the corresponding author.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval Ethical approval has been obtained at the ethics committee of the Medical Association Hamburg (Ärztekammer Hamburg; reference number: PV5708).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement None.

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Publication 5: Telephone health coaching with remote exercise monitoring (TeGeCoach) in peripheral artery disease: A pragmatic, multicenter randomized controlled trial

Rezvani F, Heider D, König HH, Herbarth L, Steinisch P, Schuhmann F, Böbinger H, Krack G, Korth T, Thomsen L, Chase DP, Schreiber R, Alscher MD, Finger B, Härter M, Dirmaier J (2024) Telephone health coaching with remote exercise monitoring (TeGeCoach) in peripheral artery disease: A pragmatic, multicenter randomized controlled trial. Deutsches Ärzteblatt International 121: 323-30 https://doi.org/10.3238/arztebl.m2024.0008

Abstract

Background: Supervised exercise programs are commonly employed to treat intermittent claudication (IC). In order to reduce participation barriers for patients, home-based training programs have been developed. This study examines the effects of a home-based training program (TeGeCoach) on self-reported walking ability in patients with IC.

Methods: A pragmatic, multicenter, randomized controlled trial was conducted (Registration: NCT03496948). 1,982 participants from three statutory health insurances with confirmed diagnosis of IC received either telephone health coaching with remote exercise monitoring (TeGeCoach; n = 994) or routine care (n = 988). The primary outcome was the change in the Walking Impairment Questionnaire (WIQ) after 12 and 24 months in the Intention-To-Treat population. Secondary outcomes included health-related quality of life, depression and anxiety symptoms, health literacy, patient activation, alcohol use, and nicotine dependence.

Results: There was a significant difference between arms in favor of TeGeCoach in the WIQ ($P<0.0001$), with a difference of 6.30 points at 12 months (Bonferroni-corrected 95% CI [4.02; 8.59], $p<0.0001$, Cohen's $d = 0.26$) and 4.55 points at 24 months ([2.20; 6.91], $d = 0.19$). These findings were further supported by several secondary outcomes showing at least small effects ($d > 0.20$) in favor of TeGeCoach at 12 months, including physical health-related quality of life and patient activation. The average daily step count did not show an increase in the TeGeCoach group.

Discussion: Significant reductions in symptom burden support the use of a home-based exercise program for treating intermittent claudication and expands the opportunity to provide guideline-based exercise for patients with IC. Future studies should investigate the effect of home-based exercise programs on clinical parameters, for example, using the 6-minute walk test.

Introduction

Peripheral artery disease (PAD) affects over 200 million people worldwide [1] and poses substantial challenges for healthcare systems [2]. PAD is characterized by progressive occlusion of the arteries of the legs, usually caused by atherosclerotic plaques [3]. Approximately 10–30% of patients experience intermittent claudication (IC) [4, 5], which is characterized by exercise-induced limb pain that subsides with rest.

Supervised exercise programs (SEPs) have been shown to be effective for the treatment of IC [6] and are recommended by clinical guidelines [7, 8]. However, SEPs face barriers to widespread adoption such as limited availability, reimbursement, and patient adherence [9-11]. Consequently, home-based exercise programs (HEPs) have emerged as viable alternatives that require fewer resources than conventional SEPs. Evidence from systematic reviews of randomized trials highlight the benefits of HEPs for the treatment of IC [6, 12-15], including those employing activity trackers for self- and telemonitoring [16, 17]. However, more high-quality evidence is needed to guide their application in clinical practice.

This pragmatic trial aimed to evaluate the effectiveness of a HEP that incorporates telemedicine-supported exercise, telephone health coaching, and medical supervision (TeGeCoach) into routine clinical practice. The primary outcome is self-reported walking ability measured by the Walking Impairment Questionnaire (WIQ), with secondary outcomes including quality of life, mental health, health literacy, patient activation, and health risk behaviors.

Methods

Design

The TeGeCoach trial was a parallel-group, open-label, randomized, controlled superiority trial involving 1,982 participants in collaboration with three statutory health insurance funds (SHIs): Kaufmännische Krankenkasse (KKH), Techniker Krankenkasse (TK), and mhplus Betriebskrankenkasse (MH). The SHIs managed the recruitment and implementation of the intervention. Ethical approval was obtained from the Ethics Committee of the Medical Association of Hamburg (reference no. PV5708). The trial was registered on ClinicalTrials.gov

(NCT03496948), and the trial protocol was published in a peer-reviewed journal (18). For additional details about the methods see eMethods.

Participants

Eligible patients, aged 35-80 years, who spoke German and had access to a telephone, were recruited using SHI claims data (ICD-10-GM codes). They were required to have a physician-confirmed diagnosis of PAD at IC stage (Fontaine stage IIa or IIb) within the past 36 months. Exclusions included patients with asymptomatic PAD in the last 12 months (Fontaine Stage I), or rest pain in the last 36 months (Fontaine Stage III or IV). Patients with medical conditions that hinder using the intervention or those participating in other PAD studies were also excluded. Written informed consent was obtained from all enrolled patients.

Intervention

TeGeCoach

The TeGeCoach intervention involved participants receiving telephone health coaching based on the transtheoretical model of behavioral change using motivational interviewing, goal setting and health education. The program included five educational modules delivered across nine phone sessions by licensed health coaches at three telemedicine centers in Germany (eMethods, eTable 1).

On a minimum of five days per week, participants were directed to engage in intermittent walking exercise at an intensity that elicits maximal tolerable claudication. Exercise levels were initially determined based on baseline capacity, with the goal of gradually increasing exercise duration to advance to the next level (15 min per daily exercise session for Group A, 30 min for Group B, and 60 min for Group C). The use of activity trackers enabled remote monitoring of exercise training and daily activity, complemented by medical supervision from a physician (see eMethods). After 12 months, participants had no further interaction with their coach but could continue self-monitoring using their activity tracker. Participants also had regular access to usual care.

Usual care

The comparator was usual medical care under the statutory healthcare system.

Table 1. Baseline characteristics in the ITT and mITT populations (TeGeCoach, usual care)

	TeGeCoach *ITT* (n = 806)	TeGeCoach *mITT* (n = 590)	Usual care (n = 879)
Sociodemographic characteristics			
Statutory health insurance fund †			
KKH	287 (35.6%)	167 (28.3%)	294 (33.4%)
TK	496 (61.5%)	406 (68.8%)	562 (63.9)
mhplus	23 (2.9%)	17 (2.9%)	23 (2.6)
Gender †			
Female	250 (31.0%)	171 (29.0%)	284 (32.3%)
Male	556 (69.0%)	419 (71.0%)	595 (67.7%)
Age (in years) *	66.6 ± 8.6	66.5 ± 8.4	66.4 ± 8.7
Body Mass Index *	28.1 ± 5.4	27.9 ± 5.0	28.1 ± 4.8
Education † *(multiple answers possible)*			
Apprenticeship	549 (68.1%)	418 (70.8%)	610 (69.4)
Technical college	263 (32.6%)	196 (33.2%)	296 (33.7)
University	140 (17.4%)	103 (17.5%)	149 (17.0)
Other	67 (8.3%)	45 (7.6%)	57 (6.5)
None	44 (5.5%)	25 (4.2%)	23 (2.6)
Marital status †			
Single	53 (6.6%)	38 (6.4%)	60 (6.8%)
Married	522 (64.8%)	393 (66.6%)	560 (63.7%)
Divorced/separated	139 (17.2%)	92 (15.6%)	156 (17.7%)
Widowed	76 (9.4%)	55 (9.3%)	89 (10.1%)
No information provided	16 (2.0%)	12 (2.0%)	14 (1.6%)
Number of children *	1.8 ± 1.1	1.8 ± 1.1	1.6 ± 1.1
Clinical characteristics			
Comorbidities/Diseases † *(multiple answers possible)*			
Myocardial infarction	114 (14.1%)	77 (13.1%)	103 (11.7%)
Stroke	75 (9.3%)	52 (8.8%)	73 (8.3%)
High cholesterol	455 (56.5%)	344 (58.3%)	509 (57.9%)
Angina pectoris	107 (13.3%)	70 (11.9%)	117 (13.3%)
Lung disease	122 (15.1%)	86 (14.6%)	147 (16.7%)
Heart Failure	127 (15.8%)	83 (14.1%)	131 (14.9%)
Hypertension	568 (70.5%)	416 (70.5%)	653 (74.3%)
Diabetes mellitus	214 (26.6%)	148 (25.1%)	223 (25.4%)
Cancer	78 (9.7%)	52 (8.8%)	77 (8.8%)
Drugs † *(multiple answers possible)*			
Antihypertensive agents	596 (73.9%)	436 (73.9%)	654 (74.4%)
Platelet function inhibitor	651 (80.8%)	492 (83.4%)	715 (81.3%)
Statins	469(58.2%)	361 (61.2%)	511 (58.1%)
Previous revascularization †			
Yes	255 (31.6%)	200 (33.9%)	242 (27.5%)
No	420 (52.1%)	293 (49.7%)	510 (58.0%)
No information provided	131 (16.3%)	97 (16.4%)	127 (14.4%)
Previous group heart rate training †			
Yes	111 (13.8%)	83 (14.1%)	110 (12.5%)
No	679 (84.2%)	493 (83.6%)	752 (85.6%)
No information provided	16 (2.0%)	14 (2.4%)	17 (1.9%)

Footnote:
* Quantitative variables: Mean ± SD
† Categorical variables: n (%)

Outcomes

Participants completed paper-based questionnaires at baseline, 12 and 24 months. The primary outcome was walking ability using the WIQ (19), a validated tool for measuring walking distance, speed, and stair climbing. WIQ scores are responsive to the effects of exercise therapy (20, 21), and correlate with objective measures walking ability (22-24) and the ankle-brachial index (25). Secondary outcomes included health-related quality of life, depression and anxiety symptoms, health literacy, patient activation, alcohol use, nicotine dependence, and program satisfaction (assessed only in the TeGeCoach arm). A detailed description of secondary outcomes can be found in the study protocol (18). The health economic analysis of TeGeCoach has been published separately (26).

Intervention access and use

For safety reasons, participants in the TeGeCoach arm needed to be supervised by a physician close to their home. They had the option of choosing their own physician or being assigned a physician provided by their health coaches. Participants without a physician referral had no access to TeGeCoach, although they remained in the study (i.e., included in the effectiveness cohort).

Owing to the pragmatic study design, the degree of program penetration was calculated based on the proportion of participants successfully referred to a physician, as not all patients could be assigned to a suitable physician located in proximity to their residence. Coaching fidelity was assessed as the number of coaching sessions completed per participant. Exercise activity in the TeGeCoach arm was measured using logs from wearable activity trackers, including the longest daily exercise session and the median number of steps taken per day. Patient ratings of intervention satisfaction are summarized descriptively in the eResults.

Statistical methods

The trial aimed to detect a small-to-moderate group difference ($f = 0.15$) with 80% power and a significance level of 5%, necessitating a minimum of 1,760 participants (880 per arm) due to expected attrition rates of 70% (TeGeCoach arm) and 80% (usual care arm).

Primary and secondary outcomes were analyzed in the intention-to-treat (ITT) population, including all participants who provided questionnaire data at baseline (i.e., effectiveness cohort). Linear mixed models were used to compare changes between arms, fitted with restricted maximum likelihood estimation (REML) to account for missing data using the *lme4* package in R (27). The fixed effects of time, SHI, and the interaction between the study group and time were specified, with participant-level random intercepts. Outcomes were also analyzed in a modified ITT population (assigned to a physician and with access to TeGeCoach) and per-protocol (PP) population (completed nine coaching calls). Statistical tests were conducted at a two-sided significance level of 5%, and post-hoc contrasts in the primary analyses were adjusted using Bonferroni-correction for two comparisons. Secondary outcomes were not adjusted for multiple testing and should be interpreted as exploratory. Effect sizes were calculated using Cohen's d, dividing the model estimates by the pooled standard deviation at baseline.

Results

The participant flow throughout the trial (04/2018 - 02/2021) is shown in eFigure 1. Further details on the intervention delivery, including graphical representations of activity parameters and the use of course and programs from usual care, are shown in the eResults.

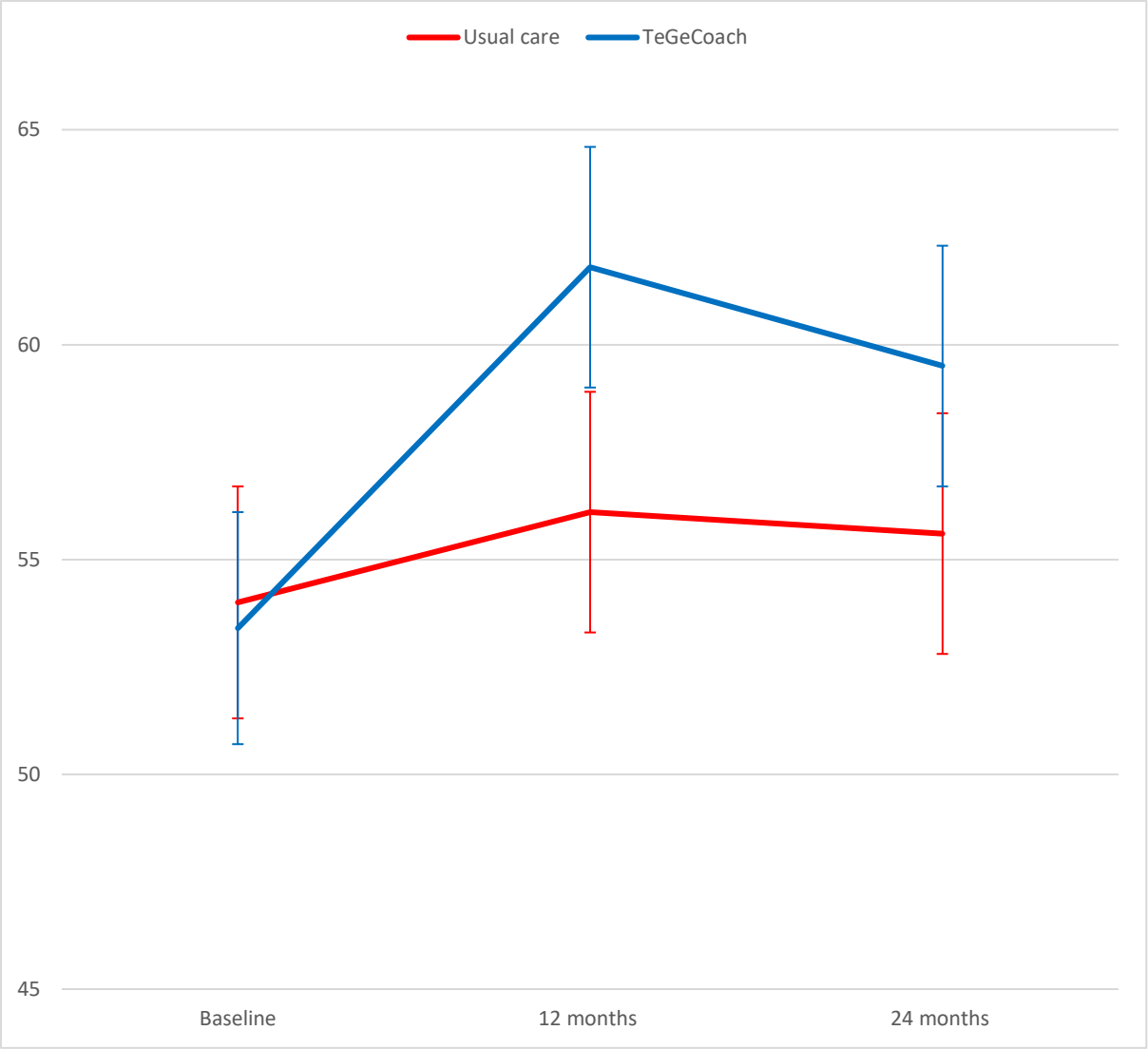
Treatment effectiveness

The ITT population included 806 participants in the TeGeCoach arm and 879 participants in the usual care arm who provided baseline data, accounting for 85% of the randomized sample (effectiveness cohort). In the effectiveness cohort, the program penetration rate in the TeGeCoach arm was 73.2% (n=590). Baseline characteristics were well-balanced between the two arms, except for revascularizations, which were slightly more frequent in the TeGeCoach arm (31.6 vs. 27.5%, Table 1). However, the number of patients undergoing revascularization during the study period was low and similar between groups (eTable 3).

Figure 1 shows the estimated means in both arms at baseline, 12 and 24 months for the primary outcome, the WIQ total score. In the TeGeCoach arm, walking impairment improved by 8.40 points at 12 months (95% CI [6.93; 9.86]) and 6.18 points at 24 months (95% CI [4.64; 7.71) from baseline. In the usual care arm, walking impairment improved by 2.09 points at 12 months (95%

CI [0.73; 3.45]) and 1.62 points at 24 months (95% CI [0.25; 2.99]) from baseline. The difference in change between arms was in favor of TeGeCoach and statistically significant ($F = 15.02$, $p < .0001$). Specifically, the difference was 6.30 points at 12 months (two-test Bonferroni-corrected 95% CI [4.02; 8.59], $p < .0001$, $d = 0.26$) and 4.55 points at 24 months (two-test Bonferroni-corrected 95% CI [2.20; 6.91], $p < .0001$, $d = 0.19$).

Figure 1. Estimated marginal means and 95% confidence intervals for the WIQ total in the ITT population



These results were supported by the WIQ subscales of walking distance and speed and several secondary outcomes that showed at least small effects ($d > 0.20$) in favor of TeGeCoach, including measures of physical health-related quality of life and patient activation (Table 2). Treatment effects were more pronounced in the modified ITT and PP populations (eTables 4 and 5) and remained largely consistent when adjusted for self-reported revascularizations (eTables 6-

8). Moderation analyses showed no significant differences by gender, age, BMI or revascularization status (eTable 9). Subgroup analyses revealed some variations in treatment effects based on the initially assigned exercise level (eTable 10).

Table 2. Treatment effects on secondary outcomes in the ITT population

	12 months		24 months	
	Difference [95% CI]	ES	Difference [95% CI]	ES
WIQ subscales				
WIQ - walking distance	8.87 [6.21; 11.52]	**0.30**	5.62 [2.88; 8.35]	0.19
WIQ - walking speed	5.73 [3.47; 7.98]	**0.22**	4.95 [2.63; 7.28]	0.19
WIQ - stair climbing	4.48 [2.19; 6.77]	0.17	3.21 [0.85; 5.57]	0.12
Secondary outcomes				
SF-12 - physical component	1.95 [1.02; 2.87]	**0.20**	1.31 [0.36; 2.27]	0.13
SF-12 - mental component	0.63 [-0.47; 1.73]	0.06	0.51 [-0.62; 1.64)]	0.05
VascuQoL-25 - pain	0.30 [0.19; 0.42]	**0.24**	0.20 [0.08; 0.32]	0.16
VascuQoL-25 - symptoms	0.25 [0.16; 0.35]	**0.24**	0.16 [0.06; 0.26]	0.15
VascuQoL-25 - activities	0.31 [0.21; 0.42]	**0.27**	0.14 [0.03; 0.25]	0.12
VascuQoL-25 - social	0.29 [0.15; 0.42]	0.19	0.12 [-0.02; 0.26]	0.08
VascuQoL-25 - emotional	0.24 [0.13; 0.36]	0.18	0.09 [-0.02; 0.21]	0.07
PHQ-9 - depression symptoms	-0.67 [-1.07; -0.28]	-0.14	-0.26 [-0.66; 0.15]	-0.05
GAD-7 - anxiety symptoms	-0.41 [-0.76; -0.07]	-0.10	-0.16 [-0.52; 0.20]	-0.04
HLQ - sufficient information to manage health	0.06 [0.00; 0.11]	0.10	0.00 [-0.06; 0.06]	0.01
HLQ - actively managing health	0.01 [-0.05; 0.06]	0.01	-0.02 [-0.08; 0.03]	-0.04
HLQ - ability to engage with healthcare providers	0.02 [-0.03; 0.07]	0.05	-0.03 [-0.08; 0.02]	-0.07
HLQ - navigating the healthcare system	0.01 [-0.05; 0.06]	0.02	-0.04 [-0.10; 0.02]	-0.10
PAM-13 - patient activation	1.18 [0.63; 1.72]	**0.24**	0.47 [-0.09; 1.03]	0.10
AUDIT-C - alcohol use	0.06 [-0.09; 0.20]	0.03	-0.02 [-0.17; 0.13]	-0.01
FTND - tobacco dependence [a]	-0.19 [-0.47; 0.09]	-0.09	-0.22 [-0.51; 0.07]	-0.10

[a] Analysis only in the smoker subgroup (TeGeCoach: n=316; CAU: n=350)

Note:
AUDIT-C = Alcohol Use Disorders Identification Test, CI = Confidence Interval, ES = Effect Size, FTND = Fagerström Test for Nicotine Dependence, GAD-7 = Generalized Anxiety Disorder Assessment, HLQ = Health Literacy Questionnaire, PAM-13 = Patient Activation Measure-13, PHQ-9 = Patient Health Questionnaire-9, SF-12 = 12-item Short Form Survey, VascuQoL-25 = Vascular Quality of Life Questionnaire-25, WIQ = Walking Impairment Questionnaire

Effects d ≥0.20 are highlighted in **bold;** a positive effect size indicates a higher change from baseline to follow-up in the intervention group

Discussion

The results support the effectiveness of TeGeCoach in improving walking ability (WIQ) among patients with PAD and IC. The intervention demonstrated both immediate and long-term improvements in pain-free walking distance, aligning with the primary treatment goal and outcome measure for exercise interventions targeting IC (28). Additionally, the lower 95% CI limits exceeded

the minimum clinically important difference (MCID) on the WIQ distance and speed subscales following exercise interventions (29). This indicates that the improvements were viewed as clinically meaningful by patients. This is an interesting finding considering that patients despite objective clinical improvements often perceive no change or even perceive a decline in their walking ability following exercise interventions (20).

Furthermore, TeGeCoach had positive effects ($d > 0.20$) on measures of quality of life (SF-12 and VascuQoL-25) and patient activation (PAM-13). However, it is important to note that there was no noticeable improvement in daily steps, indicating that an improvement in pain-free walking distance and duration does not necessarily translate to increased daily activity. This observation is in line with results from previous studies that either found minimal correlation between physical exercise capacity and daily activity (30) or no significant effects of walking exercise on daily steps in patients with IC (31, 32).

Comparing TeGeCoach with other HEPs provides insights into its mechanism responsible for improving walking ability. Two previous HEP trials, which also employed activity trackers, found negligible to moderate effects on the WIQ distance ($d = 0.16$ and 0.50) and speed ($d = 0.05$ and 0.45) subscales when compared to non-exercise controls (31, 33). HEPs similar to TeGeCoach that have proven effective in improving walking ability typically incorporate behavioral change techniques such as self and remote monitoring with wearable activity trackers, goal setting, education counselling, and feedback components (16, 17, 34). Additionally, effective HEPs involve high-intensity interval walking exercises up to the point of moderate to maximum claudication pain, usually scheduled at least three times a week (35). Furthermore, the inclusion of telephone health coaching informed by motivational interviewing likely reinforced the benefits of exercise by further promoting behavior change and, consequently, increasing physical activity (36).

The primary strength of the current trial is its unique scope and size, with the largest sample size, longest program duration, and longest available follow-up among HEP studies involving patients with PAD and IC. Using a pragmatic study design, this study is also the first to demonstrate the effectiveness of a telemedicine-delivered HEP implemented in a primary healthcare setting, highlighting its great potential for translation into clinical practice. By enabling patients to exercise at their own convenience, TeGeCoach has the potential to improve adherence and long-term engagement with exercise therapy. Furthermore, TeGeCoach can be easily disseminated to a large number of patients, ensuring access to effective exercise therapy regardless of their geographical

location. Additionally, health care costs and utilization of health care services, including hospitalizations, were similar between study groups, underlining the potential for future program implementation (26).

It is important to also acknowledge some limitations. Although self-reported walking ability is an important outcome measure, future research should include objective clinical measures of walking performance (e.g. Six-Minute Walk Test). However, the WIQ, used as primary outcome, has demonstrated responsiveness to exercise therapy (20, 21), and is commonly employed as secondary outcome in exercise trials (33). Furthermore, the low enrollment rate (3.1%) represents a significant limitation to the study's external validity, which is likely due to the impersonal recruitment approach in which potential participants received invitations via mail from their SHI. Due to the pragmatic, health-insurance based approach, patients were not personally recruited by research or medical staff (e.g., study nurses, physicians) and did not exclusively target individuals motivated and interested in participating in an exercise program, in contrast to other HEP studies involving physician or self-referrals via advertisements (33, 37), but was offered to the whole cohort of patients with PAD and IC insured with one of the participating SHIs.

Another reason that may have been discouraging to participate in the study was the high level of effort required to actively participate in the intervention (i.e., coaching calls, regular exercise sessions). This highlights the challenges of motivating patients with PAD and IC to partake in exercise programs (38) and their reluctance to experience exercise-induced pain (11). Additionally, individuals who were invited to participate cited various barriers, including technology concerns, privacy concerns regarding monitoring, lack of awareness of having PAD, and the presence of other medical conditions. Future studies could adopt a more personal approach, with the study team discussing participation with eligible patients in person and addressing their concerns.

Another concern is the significant number of patients unable to access TeGeCoach due to a lack of suitable physicians. This underscores the complexities associated with implementing exercise-based interventions for PAD patients in primary care settings, which involve administrative demands. Further research is needed to evaluate the real-world applicability of TeGeCoach.

Lastly, the COVID-19 pandemic may have had impact on study outcomes pandemic. However, the pandemic only emerged after the intervention had concluded for all participants (i.e., after the 12-month outcomes). While it may have influenced the 24-month outcomes, it is important to

emphasize that both groups were equally affected, with patients able to exercise independently at any time.

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Summary

German Version

Patient:innenberichtete Endpunkte (patient-reported outcome measures; PROMs) ermöglichen es, die Perspektive von Patient:innen mit peripherer arterieller Verschlusskrankheit (pAVK) in die Forschung und die klinische Praxis einzubeziehen. Das Potenzial von PROMs wird jedoch noch nicht voll ausgeschöpft. Das Ziel dieser Dissertation war es, PROMs im Bereich der pAVK aus verschiedenen Perspektiven zu untersuchen.

Zunächst wurden die Zusammenhänge zwischen mehreren patient:innenberichteten, pAVK-relevanten Konstrukten untersucht. Die Ergebnisse bestätigten das Vorliegen einer komplexen Beziehung zwischen Gehbeeinträchtigung, psychischer Belastung, riskantem Gesundheitsverhalten und gesundheitsbezogener Lebensqualität und geben somit Aufschluss über mögliche Behandlungsziele der pAVK.

Zweitens wurde die deutsche Version des Fragebogens "Walking Estimated-Limitation Calculated by History" (WELCH) - ein PROM zur Beurteilung der Gehbeeinträchtigung bei pAVK - psychometrisch validiert. Die Ergebnisse zeigten, dass der WELCH ein valides und reliables Instrument zur Beurteilung der Gehbeeinträchtigung bei Patient:innen mit pAVK ist. Aufgrund seiner guten psychometrischen Eigenschaften und seiner Kürze wird das WELCH als ein geeignetes Instrument zur Beurteilung der Gehbehinderung bei pAVK-Patient:innen betrachtet.

Drittens wurde im Rahmen von zwei randomisierten kontrollierten Studien die Wirkung von telefonischem Gesundheitscoaching auf PROMs untersucht. Die erste Studie ergab, dass ein telefonisches Gesundheitscoaching für chronische Erkrankungen zu kleine, aber signifikanten Veränderungen in mehreren PROMs führte, darunter Patient:innenaktivierung und Gesundheitskompetenz. Die zweite Studie zeigte, dass ein häusliches Trainingsprogramm mit telefonischem Gesundheitscoaching und Fernüberwachung des Trainings für pAVK-Patient:innen zu signifikanten Verbesserungen der patient:innenberichteten Gehbeeinträchtigung, der gesundheitsbezogenen Lebensqualität und der Patient:innenaktivierung führte. Die Ergebnisse verdeutlichen, dass PROMs ein besseres Verständnis der tatsächlichen Auswirkungen einer Behandlung auf das Leben der Patient:innen ermöglichen.

Insgesamt unterstreichen die Ergebnisse dieser Dissertation die Bedeutung des Einsatzes von PROMs in allen Phasen der Behandlung der pAVK - von der Festlegung der Behandlungsziele bis zur Messung der Behandlungseffekte. Die Verwendung von PROMs in der pAVK-Forschung und in der klinischen Praxis bedeutet eine zunehmende Berücksichtigung der Perspektiven von Patient:innen. Dies kann dazu beitragen, die klinische Entscheidungsfindung zu unterstützen und letztlich die Patient:innenversorgung und den Gesundheitszustand der Patient:innen zu verbessern.

English Version

Patient-reported outcome measures (PROMs) are gaining recognition as useful tools for assessing the impact of peripheral artery disease (PAD) on patients' lives, but their full potential is yet to be realized. The aim of this dissertation was to examine PROMs in the field of PAD from different angles.

First, cross-sectional associations between several constructs relevant to PAD measured by PROMs were assessed. A theory-based path model was used to examine the complex relationship between walking disability, mental distress, risky health behaviors, and health-related quality of life. These results highlight the need for a comprehensive treatment strategy to enhance PAD patients' overall health.

Second, the German version of the 'Walking Estimated-Limitation Calculated by History' (WELCH) questionnaire – a PROM for the assessment of walking impairment in PAD – was psychometrically validated. The results indicated that the WELCH is a valid and reliable instrument for assessing walking impairment in patients with PAD. Given its good psychometric properties and brevity, the WELCH is considered suitable for assessing walking impairment in PAD patients.

Third, the effect of telephone health coaching on PROMs was investigated through two randomized controlled trials. The first trial found that a telephone-based health coaching program for chronic conditions had small but significant effects on several PROMs, including patient activation and health literacy. The second trial showed that a home-based exercise program with telephone health coaching and remote exercise monitoring resulted in significant improvements in patient-reported walking disability, health-related quality of life, and patient activation in PAD patients. The findings highlight the usefulness of PROMs in evaluating the effects of interventions on patients' lives.

Overall, this dissertation emphasizes the importance of using PROMs at all stages of PAD management – from the identification of treatment targets to the measurement of treatment effects. The use of PROMs in PAD research and clinical signifies a shift towards placing more emphasis on patient-centered outcomes, which can help to guide clinical decision-making and ultimately improve patient care and health outcomes.

Statement of Contribution

1. Rezvani F, Härter M, Dirmaier J (2021) Measuring walking impairment in patients with intermittent claudication: psychometric properties of the Walking Estimated-Limitation Calculated by History (WELCH) questionnaire. PeerJ 9:e12039. https://doi.org/10.7717/peerj.12039

   Farhad Rezvani, Martin Härter and Jörg Dirmaier jointly conceived and designed the experiments, authored or reviewed drafts of the paper, and approved the final draft. Farhad Rezvani exclusively performed the experiments, analyzed the data, and prepared the figures and tables.

2. Rezvani F, Pelt M, Härter M, Dirmaier J (2022) Effects of walking impairment on mental health burden, health risk behavior and quality of life in patients with intermittent claudication: A cross-sectional path analysis. PLoS ONE 17(9): e0273747. https://doi.org/10.1371/journal.pone.0273747

   Farhad Rezvani designed the methodology of the study. Farhad Rezvani and Mara Pelt jointly conducted the formal analysis and wrote the original draft of the manuscript. Farhad Rezvani, Martin Härter and Jörg Dirmaier were responsible for the review and editing process of the manuscript.

3. Dwinger S, Rezvani F, Kriston L, Herbarth L, Härter M, Dirmaier J (2020) Effects of telephone-based health coaching on patient- reported outcomes and health behavior change: A randomized controlled trial. PLoS ONE 15(9): e0236861. https://doi.org/10.1371/journal.pone.0236861

   Farhad Rezvani contributed to the development of the methodology. He curated the data together with Sarah Dwinger and Levente Kriston. Farhad Rezvani, Sarah Dwinger, Levente Kriston, Martin Härter, and Jörg Dirmaier jointly conducted the formal analysis. Additionally, Farhad Rezvani contributed to the review and editing process of the manuscript.

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Farhad Rezvani contributed to the conceptualization and development of the study. Furthemore, Farhad Rezvani assisted in the actual conduct of the study by working out study procedures and preparing study materials. Lastly, with support from Jörg Dirmaier, Farhad Rezvani wrote the initial draft of the manuscript.

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   Farhad Rezvani, Jörg Dirmaier, Martin Härter, Hans-Helmut König, and Lutz Herbarth developed the study design. Farhad Rezvani exclusively analyzed and interpreted the data, drafted the manuscript and was responsible for the decision to submit the manuscript.

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Curriculum Vitae

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