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mHealth tools for patient empowerment and chronic disease management

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mHealth tools for patient empowerment and chronic disease management

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Table of contents

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Editorial: mHealth tools for patient empowerment and chronic disease management

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Editorial on the Research Topic
mHealth tools for patient empowerment and chronic disease management

Modern societies are facing new healthcare challenges with the integration of digital health interventions as a part of their healthcare systems. However, the digital transformation of healthcare requires active patient engagement as a core component of healthcare interventions. In the case of chronic diseases, new digital tools are believed to help maintain and improve patient health and care, by optimizing the course of disease treatment.

Indeed, facilitating access to quality health services and building the capacity to reduce risk are key priorities around the world. Nevertheless, health systems are facing unprecedented financial pressures at a time of growing demand for their services.

Technology can help people use care services less by promoting healthier lives. Prompt advances in wearable sensor technologies and mobile communications could close the gap between home- and clinic-based care delivery models by linking accessibility, availability, and responsive, tailored clinical oversight. Digital health solutions can help democratize access to medical care.

Even though mobile health (mHealth) tools are widely recognized as a promising resource capable of changing healthcare, additional research is needed to enhance knowledge about their limitations and benefits for chronic disease management and patient empowerment.

The major aim of the present Research Topic was to collect new evidence, reviews, clinical experiences, and perspective articles about the current practice for chronic disease management and patient empowerment using digital solutions and mobile technology.

This Research Topic includes 19 articles of different types: 11 original research papers, 3 perspective papers, 3 study protocols, 1 systematic review and 1 methods paper. The collection includes diverse digital solutions, such as conversational agents, medical devices, online healthcare platforms, clinical decision support systems, and mHealth apps, among others. Regarding the chronic conditions addressed by these articles, we may find cardiovascular diseases, diabetes, hypertension, cancer, tuberculosis, rheumatic diseases, Parkinson's, inflammatory bowel disease, and palliative care, among others.

Technology advances are producing innovative tools and resources for patient monitoring and health management, specifically important for chronic conditions. The use of mHealth technologies is raising, and these methods are contributing to assisting both healthcare professionals and patients in education and disease management.

Laranjeira et al. propose a mixed-method study that offers new insights into the expectations and needs of nurses and patient-informal caregivers' dyads in community palliative care on online health resources and caregiving preparedness. With the implementation of an adaptive digital tool, they aim to enhance access to palliative care family support, addressing the lack of accessible and available in-person counseling resources. This Digital Health Intervention may be used for communication, symptom management, decision-making, and education, to improve the informal caregivers' and patients' quality of Life, promoting anticipatory grief and the efficiency of the services.

The ubiquitous usage of mobile phones makes them an adequate platform for delivering interventions to promote awareness and knowledge. In the Yusuf et al. study, the use of a mobile app increased the women's knowledge of breast cancer risk factors, confidence level for breast self-examination and warning signs awareness.

mHealth reminders also become promising approaches to support chronic patients' treatment. Wu et al. evaluated the effect of a reminder app and the smart pillbox on tuberculosis treatment outcomes compared with standard care. They concluded that the reminder app and the smart pillbox interventions were acceptable and improved the treatment outcomes.

Rosa et al. article reviewed some of the mobile apps available to monitor individual chronobiology and lifestyle behaviors. They also described the development of a mHealth solution developed to monitor these variables, the NutriClock system.

Additionally, Yao et al. evaluated the reliability and accuracy of steps tracked by the smartphone-based WeChat app compared with the Actigraph-GT3X accelerometer. Despite the limitation in predicting body composition, they concluded that the app was reliable and could be used to assess physical activity step counts in free-living conditions.

Indeed, there is a raising number of digital resources, including diagnostic decision support systems, to better manage and assess symptoms, provide tailored treatment, and understand where and when to seek medical care. Ventura, Sousa, et al. presents a study protocol to assess the effectiveness of a comprehensive Clinical Decision Support System for remote patient monitoring of cardiovascular disease patients. mHealth tools may contribute to more tailored patient recommendations according to their specific needs.

mHealth tools allow sharing of relevant information and data with physicians and other healthcare professionals, continuous monitoring of patients, and accessing education resources to support informed decisions.

The development of e-health contributed to the growth of online health communities, representing convenient sources of information for patients who have temporal and geographical constraints on visiting physical healthcare institutions. Zhang L. et al. analyzed an online healthcare platform (Spring Rain Doctor), a new form of medical treatment that tried to minimize the unbalanced distribution of medical resources in China. According to the authors, the online healthcare platform has reduced the medical pressure of the hospital and the risk of cross-infection, especially during the COVID-19 pandemic. The total number of platform users is 130 million, and its daily consulting times go beyond 300,000. Additionally, the study by Liu et al. explored how patients' self-disclosure affects the establishment of patients' trust in physicians, analyzing computer-mediated communication in an online health community.

Effective management of chronic conditions requires patients to be motivated to make significant behavior changes to improve wellbeing, quality of life, and health outcomes. Digital solutions may be crucial to achieving these aims, although is still scarce the information about which features increase treatment adherence, which can contribute to behavior change and are more engaging over time.

Kassavou et al. present a post-trial process evaluation of the mechanism by which an e-health intervention was effective at increasing medication adherence in non-adherent patients with Type 2 Diabetes or Hypertension. This mixed methods research found that effectiveness was associated with the primary mechanisms of behavior change and that the intervention supported motivation and ability to adhere.

Also, Ventura, Brovall, et al. considered that digital health solutions became essential complementary solutions in health to improve communication and support at a distance, with evidence of enhancing patient outcomes. Their discussion supports the adoption of mixed-methods studies, to gather the perspectives of end-users and stakeholders, as well as pragmatic evaluation approaches that value effectiveness and process outcomes.

Anthropomorphic conversational agents are other promising digital tools to support the self-management of chronic diseases. Recently, the systematic review of Griffin et al. (2021) showed some evidence that text-based conversational agents (chatbots) are acceptable, usable, and effective in supporting chronic disease self-management. In this Research Topic, Pernencar et al. also undertook a literature review associating the use of chatbot technology with inflammatory bowel disease patients' health care. Chatbot technology for chronic disease self-management increases self-care practice, presenting a huge potential as a part of digital health interventions.

The study of Pimenta et al. describes the development of a theory-based intervention to increase physical activity in older adults with type 2 diabetes, included in a multi-behavior e-health intervention with a chatbot. This study includes several behavior change techniques and may leverage the efforts of others in developing analogous interventions.

Currently, multi-channel appointments have been provided for patients to receive medical care, namely for those with remote distance and severe conditions. Ye and Wu decided to address the long treatment waiting time in the outpatient clinic. This study confirms the effect of Internet use on decreasing patients waiting time and explores the factors that influence patient appointment channel choice, producing several insights into the design of appointment systems in hospitals.

Huang et al. present a novel WeChat Applet to help patients with dental anxiety management, that provides a physical status self-evaluation, online assessment, and teleconsultant. The results of this application show that it is a useful and relevant tool, before and after dental treatment, being effective in improving patients' satisfaction and dentists' convenience and reducing treatment risks, especially regarding the management of high-risk patients during the COVID-19 pandemic.

Chronic disease management is a lifelong process, commonly self-managed by the patient. Artificial Intelligence can help patients improve treatment adherence and continuously monitor their health data (Kent, 2020). Artificial Intelligence also addresses the need for clinicians to make efficient informed decisions by keeping track of several patients at once and directing treatment to those who need it the most (DrKumo, 2022).

Knitza et al. evaluated the usability, usefulness, acceptability, and potential impact of artificial intelligence-based symptom checkers and an online questionnaire-based self-referral tool. Results showed that patients increasingly evaluate their symptoms independently online, nonetheless only few used diagnostic decision support systems or dedicated symptom assessment websites. Decision support systems, such as online questionnaire-based self-referral tools and artificial intelligence-based symptom checkers are easy to use, well accepted among patients with musculoskeletal complaints, and may replace online search engines for patient symptom assessment, increasing helpfulness and saving time.

The study protocol of Bevilacqua et al. aims to evaluate a rehabilitation program for Parkinson's disease patients based on a new system called "SI-ROBOTICS", composed of multiple technological components, as a dance-based game, a social robotic platform with an artificial vision setting, wearable and environmental sensors. The study proposes a new approach to Parkinson's disease rehabilitation, focused on the use of Irish dancing, including a new technology that helps patients to perform dance steps and collect performance and kinematic parameters.

We may also highlight the importance of smart devices and wearables, that provide patient-centered health data in real-time, helping inform self-management decision-making. Although their perceived benefits in improving chronic disease self-management, their influence on healthcare outcomes continues weakly understood.

Bernardes, Ventura, et al. present a perspective on integrating wearable technology and IoT to support the self-management and telemonitoring of Parkinson's disease patients. Adding current treatment solutions with e-health strategies in Parkinson's disease patients' real-world environments is critical to improving their quality of life. Thus, IoT and wearable technology might constitute resources of excellence in self-management and continuous monitoring in people's home environments.

Bernardes, Caldeira et al. present a study protocol to perform an innovative evaluation of nursing students' podiatric profile (using a pedobarographic platform), which will allow for an extensive description of foot/ankle changes and their relationship with walking contexts and prolonged standing.

Finally, Zhang X. et al. used an electronic portable spirometer (GOSPT2000), a validated device for dynamic monitoring of lung function, to investigate the possible influencing factors of the large- and small-airway function variation in healthy non-smoking adults.

Taken together, these 19 studies indicate the future direction of the field. They show that digital health tools, including digital therapeutics, wearables, remote patient monitoring, coaching, and education, among others, can assist with condition-specific factors. Despite the potential for the delivery of cost-effective healthcare, the implementation of e-health interventions is not an easy effort. It is unreasonable to have a universal "digital recipe" for managing chronic diseases (Bashi et al., 2020). From a patient's perspective, self-management strategies for a chronic disease depend on the economic and socio-cultural status of people. From a health system's perspective, different countries have different policy and legislative implications for the adoption of digital health interventions.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Process Evaluation of MAPS: A Highly Tailored Digital Intervention to Support Medication Adherence in Primary Care Setting

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Background: Medication adherence can prevent health risks, but many patients do not adhere to their prescribed treatment. Our recent trial found that a digital intervention was effective at improving medication adherence in non-adherent patients with Hypertension or Type 2 Diabetes; but we do not know how it brought about behavioural changes. This research is a post-trial process evaluation of the mechanism by which the intervention achieved its intended effects.

Methods: A mixed methods design with quantitative and qualitative evidence synthesis was employed. Data was generated by two studies. Study 1 used questionnaires to measure the underlying mechanisms of and the medication adherence behaviour, and digital logfiles to objectively capture intervention effects on the process of behaviour change. Multilevel regression analysis on 57 complete intervention group cases tested the effects of the intervention at modifying the mechanism of behaviour change and in turn at improving medication adherence. Study 2 used in depth interviews with a subsample of 20 intervention patients, and eight practise nurses. Thematic analysis provided evidence about the overarching intervention functions and recommendations to improve intervention reach and impact in primary care.

Results: Study 1 found that intervention effectiveness was significantly associated with positive changes in the underlying mechanisms of behaviour change ($R^2 = 0.26$, $SE = 0.98$, $P = 0.00$); and this effect was heightened twofold when the tailored intervention content and reporting on medication taking ($R^2 = 0.59$, $SE = 0.74$, $P = 0.00$) was interested into the regression model. Study 2 suggested that the intervention supported motivation and ability to adherence, although clinically meaningful effects would require very brief medication adherence risk appraisal and signposting to ongoing digitally delivered behavioural support during clinical consultations.

Conclusion: This post trial process evaluation used objective methods to capture the intervention effect on the mechanisms of behaviour change to explain intervention effectiveness, and subjective accounts to explore the circumstances under which these

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effects were achieved. The results of this process evaluation will inform a large scale randomised controlled trial in primary care.

Keywords: medication adherence, process evaluation, behaviour change, Hypertension, Type 2 Diabetes

INTRODUCTION

Medication adherence can prevent morbidity and mortality associated with Hypertension and Type 2 Diabetes (1, 2). However, many patients do not adhere to their prescribed treatment (3), contributing to increased cost for the National Health Service (4). Currently there are no effective ways to improve adherence (5) and the UK Department of Health recommends that cost-effective and innovative interventions should be developed and evaluated.

We have therefore developed a highly tailored and interactive behavioural intervention, the Medication Adherence for Patients Support (MAPS) to support treatment adherence in primary care. To develop the intervention, we have reviewed theory, evidence, and obtained insights from Patients and Public Involvement and Engagement (6–9).

The MAPS intervention aims to support medication adherence by modifying the theoretical determinants that underpin behaviour change; that is, the non-intentional and intentional non-adherence, the health outcome expectations, the medication adherence self-efficacy and the social norms. One way to effectively modify the underlying mechanisms of behaviour change is to provide highly tailored advice to the individual and further support reports on behavioural performance (8). The intervention utilised behaviour change techniques (10) and strategies (8) aiming at modifying each or combination of the theoretical determinants and thus to bring about change in medication adherence behaviour (6).

The MAPS intervention was evaluated at a pragmatic randomised controlled trial with 135 non-adherent patients with Hypertension or Type 2 Diabetes recruited from eight primary care practises in the UK; and it was found to be effective at improving medication adherence and reducing blood pressure and glucose levels (11). However, we do not know how the intervention brought about changes on medication adherence behaviour (12, 13).

Disentangling the effective and replicable intervention processes that bring about improvements in medication adherence could inform effective and scalable medication adherence programmes in primary care. Though, to date our knowledge about the ways by which medication adherence is improved is based on self-reports, which makes the identification of effective and replicable interventions challenging.

This research is a post-trial process evaluation of the MAPS intervention which utilised the technology to collect objective evidence to inform knowledge about the ways by which the intervention achieved its indented effects. It has also obtained subjective accounts to explore the implementation conditions that enabled intervention reach and impact in primary care setting. The ultimate aim of this research was to inform evidence for effective and replicable medication adherence interventions real-world practise (13).

Abbreviations: MAPS, Medication Adherence for Patients Support; MARS, Medication Adherence Report Scale.

MATERIALS AND METHODS

Description of the MAPS Intervention

The Medication Adherence for Patients Support (MAPS) is a highly tailored and interactive behaviour change intervention: the content of the intervention was tailored to each patient's values of intentional non-adherence, non-intentional non-adherence, health outcome expectations, medication adherence self-efficacy and social norms. The content, intensity and schedule of the intervention messages was pre-specified based on theory, qualitative and quantitative evidence, consultations, and Involvement and Engagement of the Public (6). The digital mode to facilitate the behaviour change intervention was interactive voice and text messaging. The duration of the intervention was three months.

The intervention included three broader categories of messages: (1) advice messages tailored to the theoretical determinants of medication adherence, (2) reminder messages about the prescribed regimen, and (3) query messages that included behaviour change strategies to prompt active engagement with the tailored intervention content by asking patients to report whether or not they have taken their medications as prescribed (for example of messages, see **Supplementary Table 1**). Participants had the option to reply to these queries in real time during the pre-scheduled automated phone calls, or at any time using the inbound function of the interactive voice response or the text messaging service.

The schedule (i.e., sequence of messages) and intensity (i.e., target of one or more theoretical determinants) of the intervention was pre-specified as following: during the first week, each patient was asked to complete questions about the determinants of medication adherence behaviour and was sent highly tailored feedback aiming to address these behavioural determinants. During the first month, the intervention included more reminder messages, which were gradually reduced during the second month and were stopped during the third month of the intervention. Advice messages followed a reverse delivery sequence: they were introduced during the first month and gradually replaced the reminder messages during the second and the third intervention month.

We adopted a flexible approach to intervention delivery: the number of the reminder messages and the timing of all messages were pre-selected by participants, and participants could change these options during the 3-month intervention i.e., they had the option to request less or more messages, or to stop receiving messages.

Recruitment and Setting

The trial was implemented in eight primary care practises in the UK. Recruited primary care practises were located at different areas of deprivation, with the majority of them in deprived or highly deprived areas, ensuring that the trial reached patients from a wide range of deprivation areas. Practise nurses who advised patients about medication adherence, blood pressure checks or other similar consultations, were invited and participated in the trial.

Patients were eligible to participate if they met all four inclusion criteria: (1) were above 18 years old, (2) had a diagnosis of either Hypertension or Type 2 Diabetes mellitus, or both health conditions; (3) had been prescribed at least one antihypertensive medication or glucose lowering medication; and (4) had either poorly controlled blood pressure or glucose levels as logged in their medical records, or had gaps in collecting repeat prescriptions during the six months before study invitation. Patients were excluded if they were taking part in another medication adherence intervention or had a health condition that could impair their participation.

Eligible patients were identified from the practise database by a practise manager and confirmed for eligibility by a practise GP. Patients were then approached opportunistically by practise nurses during usual care consultations or proactively by sending text message or postal invitations. Patients were prompted to contact their practise nurse or the research team, to book their baseline consultation. During baseline consultation patients provided written informed consent and completed baseline data measurements. All methods and procedures have been approved and were carried out in accordance with the guidelines and regulations of the Ethics Committee of East of England, Essex Research Ethics Committee (REC Reference number 17/EE/0203) and Health Research Authority.

At completion of baseline measurements, patients were randomised to either the digital intervention as an adjunct to usual care or to usual care only. The random sequence was generated by a centralised web-based service and was stratified by two important confounders: medication adherence intention as measured by the Medication Adherence Report Scale (14) and burden of pills. MARS threshold of 24 was selected to indicate low (below 24) or high (above or equal to 24) intention to adherence. Burden of pills ratio of 10:6 (10 tablets: six different health conditions) was selected to indicate low (below 10:6) or high (above or equal to 10:6) burden of pills; and ratio was based on our pilot studies (6). The data to calculate the burden of pills was extracted by objective records of patient most recent repeat prescription recorded in practise databases. More information about the trial design and implementation procedures is provided elsewhere (11).

Process Evaluation

A mixed methodology was employed in line with recommendations for the process evaluation of randomised controlled trials (12, 13). In line with this, we synthesised data generated by two supplementary studies: Study 1 was a quantitative evaluation of the mechanisms of behaviour change and therefore of intervention effectiveness; and Study 2 was a qualitative evaluation of the circumstances under which these mechanisms brought about medication adherence in non-adherent patients with Hypertension or Type 2 Diabetes in primary care.

We collected data, using questionnaires, digital log files and in-depth interviews, to triangulate data synthesis and generate findings.

The population for this process evaluation was (1) the intervention group patients only, selected due to the data utilised for the process evaluation i.e., digital log files to objectively capture intervention effects, and (2) both intervention group patients and health care facilitators (i.e., practise nurse), given the importance of this evidence to inform future medication adherence programs in primary care.

Specifically, the process evaluation aimed to respond to the following research questions:

a) Was intervention effectiveness associated with improvements in the theoretical determinants that underpin behaviour change i.e., intentional and non-intentional non-adherence, medication adherence self-efficacy, health outcome expectations and social norms?
b) Did tailoring and reports on behaviour moderated the effects of the theoretical underpinnings at improving medication adherence?
c) What were the overarching intervention functions that supported intervention effectiveness?
d) What were the conditions under which the intervention achieved reach and impact of non-adherent patients in primary care setting?

Study 1 provided evidence to respond to research question a and b; and study 2 provided evidence to respond to research questions c and d.

Data Collection and Coding

Study 1. Quantitative Evaluation

To evaluate the underlying mechanisms of behaviour change we collected data using a baseline and 3-month follow up questionnaire measuring non-intentional non-adherence, intentional non-adherence, health outcome expectancies, medication adherence self-efficacy, social norms and medication adherence behaviour.

Non-intentional non-adherence refers to patients' non-conscious consideration of performing a behaviour; such as forgetting or misunderstanding the prescribed treatment. Intentional non-adherence refers to patients' conscious consideration of performing a behaviour; such as not taking their medications as prescribed because they decide not to take a dose or stop taking their medications (15, 16). Non-intentional non-adherence and intentional non-adherence were measured using the MARS (14): one item measured non-intentional non-adherence ('I forget to take my tablets'), and four items measured intentional non-adherence (4-items, Cronbach's $\alpha = 0.924$ e.g., "I alter the dose of my tablets," "I stop taking my medications for a while").

Health outcome expectations refers to patients' outcome expectations, such as the perceived reduction in risks of developing health complications that follows medication adherence (17). Health outcome expectations was measured

by a single item ("If I were to take my meds as prescribed and without missing a day it would reduce my chances of developing complications from the health condition I've been diagnosed with").

Medication adherence self-efficacy refers to patients' perceptions about their ability to take all the doses of their prescribed medications as prescribed, as well as their optimistic beliefs about their ability to sustain their behaviour regardless the barriers specific to long-term medication adherence (17). Such barrier may include the perceived burden of pills (e.g., perception about the number of pills and complexity of health condition) or the focus on the emotional state (e.g., emotional state as a primary drive of the behavioural performance). Medication adherence self-efficacy was measured by three single items; one item measuring generic medication adherence self-efficacy ("I am confident that I can take all my prescribed tablets without missing a day"), and two single items measuring self-efficacy to long-term adherence (ability to sustain adherent regardless the perceived burden of pills "I am confident that I can take all my medication as prescribed every day and without missing a day, even if I have other medications to take"; and ability to sustain adherent regardless the emotional state "I am confident that I can take all my medications as prescribed every day and without missing a day, even if I am stressed out"). The last two items were selected by the Medication Adherence Self Efficacy Scale questionnaire (18), and the decision on selecting these two items was based on the results of our previous studies that have identified the barriers to medication adherence (6, 7).

Social or subjective norms refer to perceptions about others' views about taking medication or others' adherence to medication (e.g., beliefs about others medication adherence behaviour) (16). Social norms were measured by two items (Cronbach's $\alpha = 0.800$ "most people who are important to me would approve of me taking all my prescribed tablets without missing a day," "if they were prescribed tablets, most people who are important to me would take all their prescribed tablets without missing a day").

Medication adherence was measured by one single item ("how many days in the past week have you taken all your prescribed tablets?").

To disentangle the intervention content that brought about change, we coded the data objectively captured by digital log files during the three months intervention based on the following operational definitions: we coded the variable "tailoring" when there was a confirmation of receipt of the tailored intervention advice. The median score for tailoring was used as a threshold to indicate low (below or equal to threshold) or high (above threshold) tailoring.

We coded the variable "report behaviour" when there was a "yes" or "no" response to intervention query messages to report medication taking. Report behaviour was coded as "high" when all responses confirmed medication taking, "medium" when at least half of the responses confirmed medication taking and "low" when less than half of the responses confirmed medication taking.

Tailoring and report on behaviour were conceptualised and coded as different variables, because tailoring required confirmation of the tailored intervention advice, whereas report on behaviour required confirmation of the behavioural performance (8).

We have also coded "overall intervention usage," that is a combined score of the objectively measured intervention components received i.e., confirmation of receipt of the tailored intervention content, responses to intervention query messages, and interactions regarding the intervention delivery options (e.g., request to receive more or less messages)—to explore potential effects of the overall intervention usage on intervention effectiveness. Data that captured usage of the intervention regarding the study procedure (i.e., messages about completing study visits or procedures) were excluded.

Data captured at digital log files during the three months intervention were extracted and coded. Each patient's digital log files were coded separately. Data summarising tailoring, report on behaviour and overall intervention usage across all participants was then grouped into one coding and included in the analysis.

Study 2. Qualitative Evaluation

The qualitative evaluation explored two aspects of intervention impact; (a) the overarching intervention functions that supported intervention effectiveness; and (b) the conditions under which the intervention reached non-adherent patients with Hypertension or Type 2 Diabetes in primary care.

We conducted in-depth interviews with a subsample of the intervention group patients and all practise nurses or health care assistants who took part in the trial, to obtain multi-perspective views about the individual and context-specific elements of the intervention reach and effectiveness.

The patients semi-structured interview guide was developed by a researcher based on theory and aimed to explore views about the intervention content and prompt recommendations for improvement. Patients were asked their views about specific intervention messages, whether and how messages supported medication adherence and under what circumstances. When patients could not remember or elaborate about a specific intervention message, an example of a received message as recorded by digital log files was provided.

Each of the patient's interviews lasted from 90 to 180 min. Longer interviews with patients were required to establish rapport and overcome potential bias regarding the role of the interviewee and the interviewer. The first 13 interviews were conducted face-to-face at patient's home until main codes were created, the remaining seven interviews were conducted by phone to confirm or further explore the elicited codes.

The semi-structured interviews with practise nurses aimed to explore elements that impacted on intervention reach and obtain recommendation to improve intervention scalability in primary care. Practise nurses were asked about patients' characteristics for whom the intervention was acceptable and potentially effective, and the practise-level conditions that could facilitate intervention reach and scale up (for a copy of the interview guides, see **Supplementary File**, interview schedule). Practise nurse interviews took place at the completion of patients' recruitment, were conducted face-to-face at the GP practises, and each interview lasted for an average of 45 min.

Three members of the research team (AK, CAC and VM) conducted the interviews independently. AK conducted the interviews with practise nurses, AK and VM conducted the face-to-face interviews with patients, and CAC and VM conducted the telephone interviews with the patients. All interviews were audio-recorded and transcribed by an independent transcription service. Transcripts were double checked for accuracy against recordings by the researchers, and all personal identifiable data were removed before analysis. Field notes were collected during the face-to-face interviews to inform data analysis. One of the researcher's had experience in developing and evaluating medication adherence interventions, including process evaluation using quantitative and qualitative methods, and the two others had training on qualitative data collection and analysis. The researchers had no previous knowledge or relationship with the participants.

Questionnaires and interviews were completed by patients at the end of the 3-month intervention; from June 2018 to April 2019. Data were recorded at the digital log files during the 3-month intervention; from March 2018 until March 2019. Quantitative data coding and analysis was conducted during December 2019. Qualitative coding was conducted by two researchers, and analysis were conducted during September 2019. Data triangulation and mixed methods analysis was completed during January 2020. The trial was first registered at ISRCTN on 08/08/2017 and the reference number is 10668149.

Sample Size

Study 1

In total 77 patients were randomised and enrolled into the intervention group, and 57 of them provided complete data and included in the quantitative analysis.

Study 2

The selection of patients who were invited to take part at a post-trial in depth interview was informed by the coding of the digital log files: invited participants were selected based on level of intervention engagement (high engagement: daily use of the intervention for more than 11 days; or low engagement: $\leq$11 days) and basic demographics (e.g., age, gender, deprivation level) to ensure that a variety of views were explored. From those meeting the eligibility criteria, we randomly selected 25 and invited them to take part in the interview using phone calls. Five participants refused to participate, three because of time constraints and two because of lack of interest. In total 20 patients completed the end of intervention interview: 13 face-to-face and seven over the phone.

Eight practise nurses, one from each of the eight primary care practises, who either identified or invited patients during usual care consultations, were invited by phone and took part in the in-depth face to face interview.

Data Analysis

Study 1. Quantitative Evaluation

Principal component analysis suggested that multi-collinearity was not an issue for the variables. Histograms explored continuous variables' distribution, and the Levene test assessed the assumption of equality of variance. Regression analysis explored whether intervention effectiveness was associated with the underlying mechanisms of behaviour change. Multivariable regression analysis tested whether, and to what extent, intervention tailoring and report on behaviour modified the effects of the theoretical underpinnings at improving medication adherence. Data were inserted into the regression model, with medication adherence as a dependent variable and each of the theoretical determinants as an independent variable. Interactive effects were explored between the theoretical determinants with tailoring and report on behaviour. The variables measuring theoretical determinants were adjusted for baseline values. Analysis was conducted using SPSS v26.

Study 2. Qualitative Evaluation

Qualitative data were analysed thematically (19) using NVivo. At the first stage of the qualitative analysis the researchers worked independently: they coded each transcript using an inductive approach and developed one mind map for each of the transcripts. During the second stage of the analysis, the researchers met and discussed each transcript and mind maps and merged themes and sub-themes into one mind map. At the third stage of analysis, the researchers met and merged all mind maps into a broader mind map describing the main themes and subthemes, using a deductive approach. Analysis was completed when data saturation was achieved. Any additional data generated by the inductive approach were treated as recommendations for improvements.

RESULTS

The majority of patients were registered with primary care practises located at highly deprived areas and were above the age of 50 years. The 3-months follow up results on behavioural and clinical outcomes have been reported previously (11). Medication adherence was significantly improved in the intervention group compared to control (improvement of 2 days, $P = 0.04$; 6.85 ± 0.47 vs. 6.36 ± 1.59). Similar direction of effects was observed for improvements at both the systolic blood pressure (reduction of 0.6 mmHg, 95%CI -7.423 to 6.301) and glucose levels (reduction of 4.53 mmol/l, 95% CI -13.099 to 4.710) favouring the intervention group.

Study 1. Quantitative Process Evaluation

At 3 months, improvements in medication adherence were positively and significantly associated with improvements in intentional non-adherence ($b = 0.46$, $P = 0.03$), non-intentional non-adherence ($b = 0.77$, $P = 0.00$) and medication adherence self-efficacy ($b = 0.34$, $P = 0.00$) within the intervention group. There was a trend towards positive associations between medication adherence and improvement on each of the health outcome expectations ($b = 0.23$, $P = 0.08$) and the two specific self-efficacy variables ($b = 0.32$, $P = 0.07$ for burden of pills; $b = 0.14$, $P = 0.24$ for emotional state), but these effects were not statistically significant. There were no effects of the social norms on intervention effectiveness (see **Supplementary Table 2; Supplementary Figures 1–4**).

During the 3 months intervention, objective measures confirmed high intervention tailoring (73.4%, 42/57), which

was significantly associated with improvements in medication adherence ($b = 1.02$, $P = 0.01$). Reports on medication adherence was 26.8% low, 60.7% medium and 12.5% high, and it was positively and significantly associated ($b = 1.32$, $P = 0.00$) with improvements in medication adherence within the intervention group (see **Supplementary Figures 5, 6**). There were no effects of overall intervention usage at explaining intervention effectiveness.

Multilevel regression analysis suggested that intervention effectiveness was explained by positive changes in intentional non-adherence, non-intentional non-adherence and medication adherence self-efficacy ($R^2 = 0.26$, $SE = 0.98$, $P = 0.00$), and this effect was heightened further when tailoring ($R^2 = 0.32$, $SE = 0.95$, $P = 0.00$) and report medication adherence behaviour ($R^2 = 0.59$, $SE = 0.74$, $P = 0.00$) was included in the regression model (see **Table 1**).

Study 2. Qualitative Process Evaluation

The qualitative analysis obtained subjective accounts about the overarching intervention functions and obtained recommendations to improve intervention effectiveness, reach and scale up in primary care.

Three overarching themes were identified: the intervention (a) facilitated motivation to medication adherence; (b) enabled medication adherence behaviour, and (c) prompted social integration. To improve intervention impact and scale up, participants recommended the integration of the behavioural intervention into usual care consultations to facilitate control over the long-term clinical indicators of the health condition.

Intervention Facilitated Sustained Motivation to Adherence

Patients reported that their motivation to take medication was embedded in improving their health condition and thus achieve health benefits, whereas barriers to adherence were mainly influenced by their everyday lifestyle; and that the intervention supported them to sustain adherent by reinforcing their motivation and by prompting them to specify and address the barriers to adherence (see **Table 2**, quotes 1.1).

It was also reported that the intervention facilitated awareness of medication adherence and reduced the perceived complexity of the prescribed regimen i.e., burden of pills. This was particularly useful for those patients who at baseline reported that they took more tablets than those recorded at their medical records (see **Table 2**, quotes 1.2). Furthermore, it was reported that the intervention supported daily adherence to medication and the acceptability of adherence to prescribed treatment in the long term (see **Table 2**, quotes 1.3).

Intervention Facilitated Patients' Ability to Adherence

The intervention messages prompted participants to contextualise and adjust their medication taking behaviour to achieve adherence. It was reported that the intervention raised awareness about the circumstances under which the behaviour is performed and enable them to exercise control over and adhere to their prescribe regime (see **Table 2**, quotes 2.1)

All patients reported that medication adherence is a dynamic process and affective attitudes about medication taking are influenced by side effects and vice versa (see **Table 2**, quotes 2.2). Thus, it was recommended that the advice about medication adherence affective attitudes should be tailored to patients' emotional state, their available resources and facilitate access to additional support when required.

Some patients reported that the intervention facilitated affective attitudes about medication taking when their emotional state might counter behavioural performance (see **Table 2**, quotes 2.3). They suggested that the messages to address medication adherence affective attitudes should be linked to behavioural performance and not to generic emotional state; primarily because their affective attitudes are informed by the behaviour (see **Table 2**, quotes 2.4)

Many patients reported that the tailored intervention content enhanced the acceptability of the advice provided, increased relevance and enabled medication adherence (see **Table 2**, quote 2.5). Patients recommended to integrate feedback on behavioural performance to further enable sustained medication adherence (see **Table 2**, quote 2.6).

Intervention Prompted Integration of Medication Adherence in the Social Context

The intervention messages prompted integration of medication adherent behaviour in the social context (see **Table 2**, quotes 3.1), especially for those patients who reported favourable social norms about medication adherence. Patients with favourable social norms but lack of social support reported that the tailored messages provided them with emotional support and prompted generic social integration (see **Table 2**, quotes 3.2). These patients also reported higher levels of satisfaction with their health care provider and GP practise (see **Table 2**, quote 3.3).

TABLE 1 | Model summary.

Model	R	R square	Adjusted R Square	SE	F change	Sig. F Change
1	0.51[a]	0.26	0.21	0.98	6.00	0.00
2	0.56[b]	0.32	0.26	0.95	6.11	0.00
3	0.77[c]	0.59	0.55	0.74	14.59	0.00

[a] *Predictors: intentional non-adherence, non-intentional non-adherence, medication adherence self-efficacy.*

[b] *Predictors: intentional non-adherence, non-intentional non-adherence, medication adherence self-efficacy, tailoring.*

[c] *Predictors: intentional non-adherence, non-intentional non-adherence, medication adherence self-efficacy, tailoring, report behaviour.*

Variables intentional non-adherence, non-intentional non-adherence and medication adherence self-efficacy are adjusted for baseline values.

TABLE 2 | Qualitative data.

	Quotes per theme
1	**Intervention facilitated motivation to adherence**
1.1.	"(I do not take my tablets) in the morning, if I break the routine, and start doing something else, when I don't follow my routine" patient 10042 "it (the intervention) emphasised … the importance of you not forgetting to take medication and the effect that it could have if you didn't take it. So, I think it was quite useful … they weren't very detailed message so, it was quite short message, about taking your pills …it gave you a bit of a jolt, so you did not become complacent about what it is, and stress I should be taking it" patient 50012 "I felt mainly motivation from it" patient 30006 "That me saying yes, my name is John you know, and then they gave me a good, nice message, and it was always relevant" patient 20031
1.2	"And make sure you take them exactly at the same time all the time cos I used to vary my times in taking the tablets... a few minutes it does not matter either way, but if, you know, you don't get the text you might not take them, you might forget all about them" patient 10003 "I suppose it made sure that I took my tablets, which I normally do anyway, but it made me take them at a more specific time" patient 50012 "Okay, well, for me it (the intervention) was positive, it definitely helped me get into the habit more of my medication because I don't really have a routine, so because of that, I'm here, there, everywhere doing things, cos I don't, cos I don't have a routine" patient 10042 "since the phone calls, I do not know whether it's subconscious and "make sure you take them exactly the same time, all the time" patient 10038
1.3	"Yeah … this is, erm, what the tablets are gonna do for you in a positive manner going forwards, you know, maybe not, not tomorrow or next week, but this time next year" patient 10042 "but if you get a reminder it makes you think perhaps it is important (to take your medications)... so I think, when somebody's prescribed a new medication, send them message for couple of months, two or three months, to establish a pattern" 50013
2	**Intervention facilitated patients' sustained ability to adherence**
2.1.	"Maybe I should have had it at 09:00, maybe that's when I should have asked for the reminder" patient 50013 "it's, you know, it's just sort of being at right place, right time, no interruptions" patient 50012 "it makes you more of your condition and how it should be... it just wanted to be certain people were actually getting the responsibility to it" patient 50012 "Maybe at the midpoint (of the intervention), because people might not know what their triggers are early on … just have a quick review what's working best and then perhaps tailor things slightly more to that person once they've had the experience of the service that comes through … after a months or two months … there is the opportunity to tailor it to that person" 30006 "well basically just made me think about it and think how I could actually work to control it in a particular way … I've forgotten, and you know, I sort of tried to take on board what the whole system was and try to help myself in the process" patient 10043
2.2.	"mind you, medications don't always make you feel better, do they? … you ask people what they thought, and you get a blatant truth about how they thought and felt, and I said, oh … so, you've got to be careful what you ask" patient 50012
2.3.	"I think it is important that people know that if they feel that it's not beneficial or it's making them feel ill that they should go back to their GP and chat to them about it" patient 10042 "it made clear that, if I am feeling good it's because I' m doing that (taking my medications)" patient 20031
2.4.	"I would basically recommend more messages about the behaviour and taking or not taking tablets rather than how you feel about taking or not taking tablets?" patient 50012
2.5.	"It was a random selection of what the message was going to be, you know, it just felt a bit more personal … I could relate to that, just because the messages were different, it was varied, and you felt it … there was somebody there talking, and you know, it was more geared to you and your medication … that is something that will set you on the path to take your medication as prescribed" patient 50012
2.6	"On a personal level, ask people "did you take your medication?" and then send a text message saying "according to you, you took 85% of your medication this month, that' good, but you can improve" … and that'll just help people think "oh blimey, is that all I've done?"...just make people aware of how well they really are doing" patient 20031
3	**Intervention prompted integration of medication adherence in the social context**
3.1.	"I've told my grandchildren and let them listen to the messages … and they were copying it... but everyone knows that (I am taking medications), you know, and will say to me, "have you taken your tablets?", especially if we're out for lunchtime … and my husband at 09:00 he is saying 'go and take your tablets', I say "I'll go in half an hour," and he is like "no, you'd better take them now" … and my daughter said to me the other say "who are you taking to" and I said "Its MAPS calling about my pill reminder" and she is "oh yeah, that's okay" patient 50012 "I liked the message to remind you to ask your husband or a friend to remind you, that was good … I have not really thought about this, because it is a private thing, isn't it" patient 50013
3.2.	"it's (the intervention) speaking to you basically instead of just a sentence coming up on your mobile phone... I think a lot of people, if they live on their own and they are a bit lonely or whatever, it's a voice at the other end of the phone" patient 10038 "I suppose the voice messages had more of an impact because you had to take note of them more and listen and it made you think a bit more than the text messages, because they were just simple" patient 20052
3.3.	"It is like someone is paying notice on how you are, and how are you doing with (taking) your medication in everyday life" patient 20031 "I think they like the idea that it is offered by a practise nurse…they feel this extra support" practise nurse 10025
3.4.	"you have less chance especially in a big family of them (the intervention messages) going to the right person, so, it does help just sort of like do it on their own personal mobile phone... there was no privacy attached to the intervention messages, and taking medication is a private thing" patient 10036
3.5.	"Because people say "oh waste of money, do not take them, they're not gonna do any good. I've taken them for so long, they haven't done me any good" … then I thought I am not gonna take notice of anybody else, I'm going to start doing this (taking my tablets) on a regular basis... it's important that you take these things because you've got to look after your health" patient 10045

(Continued)

TABLE 2 | Continued

	Quotes per theme
4	**Recommendations to improve intervention efficacy, as well as reach and scale up in primary care**
4.1.	"it is challenging to recruit patients who do not even attend their practise appointments, am not sure how you could convince these people, we tried several times but with no response" practise nurse 10030 "[when we followed up the invitation to the study] they did not feel there was a problem and that was, that was the, the answer mainly we got back from them, "no there's no problem, I'm taking the medication and I do not forget" so even though their clinical signs were that their blood pressure was out of control or their blood sugars were raised, they said they took their medication" practise nurse 10025 "with the searches you can see when they last had one (prescription), it is recorded, but there is a small core of participants that will deny that there is a problem whatever you put in front of them" practise nurse 10026 "some of these, they do not want to take the amount of tablets, they want to take less" practise nurse 10032 "If the practise feels there was a problem with adherence, so we should refer patients to additional support to help solve the problem" practise nurse 10031
4.2.	"identify them when we see their blood results, perhaps on their annual review … and ask them if they would like to take up this service… and probably do not ask them if they take their tablets, when we asked them, they always say "yes" practise nurse 10026 "there are some people who need evidence that this service will work for them" practise nurse 10032
4.3.	"in theory there should be enough time for a very brief intervention within the consultation, but sometimes we get extra patients added in so then you've got to, you know, if you get emergency patients coming in or whatever, then you do not even get your 20 min so then it would be very difficult" practise nurse 10027 "Perhaps a small appointment time which is taken up by the whole of the review" practise nurse 10029 "I think they would participate in the intervention, as long as this it is a shorter questionnaire and it [the intervention] is recommended by their practise nurse…a very brief introduction about the clinical signs and response to adherence and then the text message" practise nurse 10026
4.4.	"probably if there was a mechanism for the patient to report back to their health care provider about their health and well-being" practise nurse 10028

However, patients with unfavourable social norms about taking medications reported concerns with receiving support for medication adherence (see **Table 2**, quote 3.4). Nevertheless, some patients reported that the intervention supported medication taking even when social norms or practical social support was not in favour of medication adherence (see **Table 2**, quote 3.5.).

Recommendations to Improve Intervention Reach and Scale Up

Practitioners reported limited ability to address medication non-adherence, highlighted the challenge to engage non-adherent patients on shared decision making about taking and adhering to their prescribed treatment; and they recognised the need to signpost patients to additional behavioural support (see **Table 2**, quote 4.1). To increase scale up, practitioners recommended to integrate brief risk behavioural appraisal into blood pressure checks and diabetes reviews (see **Table 2**, quote 4.2) and recommended effective ways and methods to signpost patients to additional digitally delivered behavioural support (see **Table 2**, quote 4.3), that could be more feasible within the time constrains of primary care consultations and could increase intervention impact and scale up (see **Table 2**, quote 4.4).

Qualitative data supported that the intervention increased motivation to adherence, enable patients to sustain adherent and prompted integration of medication adherence behaviour into social context. To improve intervention reach and scale up, the intervention could provide very brief behavioural risk appraisal during usual care clinical consultations and signpost patients to an ongoing digitally delivered behavioural support.

DISCUSSION

Principal Findings

This post-trial study evaluated the process by which the MAPS intervention improved medication adherence in non-adherent patients with Hypertension or Type 2 Diabetes in primary care. It was found that the intervention improved medication adherence by modifying the underlying theoretical determinants of intentional non-adherence, non-intentional non-adherence and medication adherence self-efficacy (these explained 26% of intervention effectiveness). Intervention tailored advice and reporting on behaviour captured objectively by digital log files significantly amplified these effects by twofold (heightened explanation of intervention effectiveness at 59%).

Strengths and Limitations

The results of this research were based on data obtained by the intervention group of patients taking part in a pragmatic randomised controlled trial implemented in primary care setting. To our knowledge, this is the first process evaluation of a medication adherence digital intervention in the primary care. This study elucidated the mechanism by which the intervention brought about behaviour change in non-adherent patients and provided the evidence-base of effective medication adherence interventions in primary care.

A strength of this research is the measurement of intervention content captured objectively by digital log files, which provided objective data about patients' engagement with the tailored intervention content. The research has also obtained data from multiple perspectives and facilitated data triangulation. Another strength of this research is its mixed methodology approach. This process evaluation synthesised both quantitative and qualitative evidence to provide comprehensive responses to our research questions.

A limitation of this research is the lack of evaluation of the underpinnings of health behaviour change against the control group of the trial. However, between group comparisons were not possible due to the primary aim of this study and the data required to respond to the research questions. The evidence of this research is based on a subsample of patients, and the results should be treated with caution when interpreted to larger population. Although the sampling was stratified and controlled for important confounders, quantitative process evaluation might require data from larger samples to provide

the necessary power to detect the impact of digital interventions on modifying the determinants of medication adherence and on subsequently improving adherence.

This research study did not control for the effect of other potentially important cofounders on the intervention effectiveness, like the effect of the health care provider or patient demographics (e.g., gender, age, ethnicity). Future research could explore the effect of these cofounders on intervention effectiveness, to increase knowledge about the scalability of the intervention to non-adherent patients.

Implications to Improve Intervention Effectiveness and Impact

This research provided evidence about the process by which a behavioural intervention improved medication adherence. It was found that the intervention effectiveness was supported by improvements in non-intentional non-adherence, intentional non-adherence and medication adherence self-efficacy. This finding suggests that intention to adherence and positive appraisals about the capability to medication adherence are important mechanisms of effective interventions. Furthermore, this study found that the intervention tailored advice and reports on behaviour heightened this effect twofold at improving medication adherence. Positive improvements were observed for the perceived reduction in risks of developing health complications that follows medication adherence and beliefs about ability to adherence regardless the perceived burden of pills, suggesting that these could potentially be effective mechanisms of medication adherence.

Future research could usefully investigate the effects of these mechanisms using larger sample size and against the control group to provide rigorous evidence about the mechanisms of medication adherence. A combination of highly tailored and interactive digital intervention with very brief health care provider behavioural advice about medication adherence could act synergistically to strengthen the impact of the intervention in the primary care.

Implications for Policy and Practise

Participants actively engaged with the tailored intervention daily for an average of 11 min, during the intervention (duration of daily messages was ∼1 min). Considering the challenges to engage non-adherent patients with usual care advice (20), and the limited time of the health care professionals to provide ongoing support, this engagement score suggests that this digital intervention is feasible and could provide brief, effective and real-time support to improve medication adherence in non-adherent patients. It also suggests that this digital intervention could be a cost-effective solution for the provision of health care services.

CONCLUSION

To our knowledge this is the first research that has evaluated the mechanisms by which an interactive text and voice message intervention has supported medication adherence within non-adherent patients in the intervention group of a randomised controlled trial in primary care. It was found that tailored intervention content and reports on behavioural performance doubled the effect of intentional non-adherence, non-intentional non-adherence, and adherence self-efficacy in explaining improvements in medication adherence. Patients reported motivation and ability to be important intervention effects in improving medication adherence behaviour. Practise nurses recommended very brief medication adherence risk appraisals followed by signposting to additional digitally delivered behavioural intervention to support non-adherent patients as part of the time constrained usual care consultations. Future research could usefully investigate and evaluate the effects of active and objectively captured intervention content at modifying the mechanisms of behaviour change and at improving medication adherence and clinical outcomes using rigorous designs.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

All methods and procedures have been approved and were carried out in accordance with the guidelines and regulations of the Ethics Committee of East of England, Essex Research Ethics Committee (REC Reference number 17/EE/0203) and Health Research Authority. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AK and SS have developed the intervention and designed this study. CC and VM assisted with patients' invitation to the telephone interviews, qualitative data collection, and data coding, supervised by AK. JB and SE developed the digital platform to facilitate the delivery of the tailored behavioural intervention and to capture data about patients' intervention usage at digital log files. AK conducted the analyses and drafted this publication, with comments and advice by SS. All authors have read and approved this manuscript for publication.

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SUPPLEMENTARY MATERIAL

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Dancing With Parkinson's Disease: The SI-ROBOTICS Study Protocol

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Introduction: Parkinson's disease (PD) is one of the most frequent causes of disability among older people, characterized by motor disorders, rigidity, and balance problems. Recently, dance has started to be considered an effective exercise for people with PD. In particular, Irish dancing, along with tango and different forms of modern dance, may be a valid strategy to motivate people with PD to perform physical activity. The present protocol aims to implement and evaluate a rehabilitation program based on a new system called "SI-ROBOTICS," composed of multiple technological components, such as a social robotic platform embedded with an artificial vision setting, a dance-based game, environmental and wearable sensors, and an advanced AI reasoner module.

Methods and Analysis: For this study, 20 patients with PD will be recruited. Sixteen therapy sessions of 50 min will be conducted (two training sessions per week, for 8 weeks), involving two patients at a time. Evaluation will be primarily focused on the acceptability of the SI-ROBOTICS system. Moreover, the analysis of the impact on the patients' functional status, gait, balance, fear of falling, cardio-respiratory performance, motor symptoms related to PD, and quality of life, will be considered as secondary outcomes. The trial will start in November 2021 and is expected to end by April 2022.

Discussions: The study aims to propose and evaluate a new approach in PD rehabilitation, focused on the use of Irish dancing, together with a new technological system focused on helping the patient perform the dance steps and on collecting kinematic and performance parameters used both by the physiotherapist (for the evaluation and planning of the subsequent sessions) and by the system (to outline the levels of difficulty of the exercise).

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Ethics and Dissemination: The study was approved by the Ethics Committee of the IRCCS INRCA. It was recorded in ClinicalTrials.gov on the number NCT05005208. The study findings will be used for publication in peer-reviewed scientific journals and presentations in scientific meetings.

Keywords: Parkinson's disease, rehabilitation, Irish dance, balance, gait, older people, technology acceptance, social assistive robotics

INTRODUCTION

Parkinson's disease (PD) is one of the most frequent causes of disability among older people. According to the Parkinson's Foundation, more than 10 million people worldwide are living with PD[1]. PD is a chronic-progressive neuro-degenerative disease, characterized by motor disturbances such as bradykinesia (poor and slow movement), tremor at rest, rigidity, posture in flexion and "shuffling gait," and, not least, a lack of balance resulting in a high risk of falling (1–4). Balance disorders do not always respond to the dopaminergic therapy used in PD. Therefore, physiotherapy becomes an important intervention for their management (5, 6). Postural instability and the resulting falls are among the main factors leading to poorer quality of life, morbidity, and increased mortality risk for people with PD (7). These pathological conditions are routinely treated by rehabilitation approaches aimed at improving static/dynamic balance, recovering walking ability, and preventing falls (3, 8).

Recently, dance has started to be considered as effective training for people with PD, especially for those at the initial stage of PD and with mild/moderate disease severity (9, 10). It has been shown that dance in people with PD can have a positive effect on balance and mobility and can help improving quality of life by reducing symptoms of depression (11–14). Recent studies have shown that sometimes dance can improve balance and functional mobility (15, 16).

Irish dancing, along with tango and other forms of modern dance, may be a valid strategy to motivate people with PD to perform physical activity. Recent studies have shown that Irish dancing can improve balance, mobility, and quality of life through the integration of complex learning patterns of motor skills, dynamic balance, musicality, and socialization (17–20). In addition, Irish music, due to its rhythm, has a predictable pattern that can improve gait and walking (18).

A recent review of the literature (21) pointed out the relevance of different types of dance for improving motor and non-motor symptoms in PD. Despite limited evidence, this review highlights an improvement in motor function, freezing, balance, and gait, as compared to physiotherapy, in people with PD who underwent Irish dance intervention.

In a recent study (22), the researchers have examined the feasibility of a randomized controlled study design and the benefits of an Irish dancing-based intervention, with 90 patients with idiopathic PD. The participants were randomized to Irish set dance classes or to a usual care group. The dance group attended a 1.5-h dancing class each week, for 10 weeks and undertook a home dance program for 20 min, 3 times per week. The usual care group has followed usual care and daily activities. The results have shown that, in the case of mild to moderately severe PD, the Irish dance is a feasible and enjoyable strategy to improve patients' quality of life.

Besides highlighting the positive impact of dancing, several studies have also tried to assess the impact of robot dancers to support older people (23), especially with PD (24). In comparison to human–human partner dance, robot dance partners may support the collection of objective health parameters during the performance, allowing the customization on the basis of the older people's needs and preferences. Furthermore, robot dance partners potentially complement human–human dance by giving the opportunity of also training alone (25).

Moreover, a recent study (26) has demonstrated the acceptability and feasibility of a dancing intervention such as a robot as a partner. The results of this study underline that the 16 older dancers perceived the robot as useful, easy to use, and fun, suggesting a positive attitude toward the system and thus the intervention, evaluated through the Technology Acceptance Model (TAM) scale (27), a specific tool to assess and predict user acceptance of information systems and information technology. The authors have highlighted the need of increasing the complexity of dance exercises with the robot, to favor the engagement of the older dancers.

In line with the literature in the field, the main objective of this paper is to present the protocol for the "SI-ROBOTICS" intervention, aimed at assessing the acceptability of an innovative robotics-based system for engaging patients with Parkinson's disease in an Irish set dancing intervention.

METHODS AND ANALYSIS

Trial Design

The study is designed as a technical feasibility pilot to test the SI-ROBOTICS system on a group of 20 older people with PD at an early stage (Hoen and Yahr Scale 1–2), during an Irish set dancing training. Assessment will be performed at the baseline (T0), after 4 weeks (mid-T1), and after 8 weeks of intervention (end-T2).

The primary aim is to evaluate the acceptability of the SI-ROBOTICS system in a group of patients with PD while performing a rehabilitation treatment based on Irish dancing, using the Unified Theory of Acceptance and Use of Technology (UTAUT) scale (28).

The secondary aim is the analysis of the modification of dimensions related to the general functional status, in terms

[1]Available online at: https://www.parkinson.org/Understanding-Parkinsons/Statistics.

of gait, balance, fear of falling, cardio-respiratory performance, motor symptoms related to PD, and quality of life.

Study Setting

This study will be conducted at the Clinical Unit of Physical Rehabilitation of the Istituto Nazionale Ricovero e Cura per Anziani IRCCS INRCA, Ancona, Italy. The last version (second version) of the current protocol is dated May 25, 2021.

Participants

The inclusion criteria will be:

- Aged 65 and over;
- Capacity to consent;
- Hoen and Yahr scale: 1–2 stage;
- Functional Ambulation Category (FAC) ≥ 2;
- Rankin Scale score ≤ 3;
- Stability of drug treatment for at least 1 month;
- Geriatric Depression Scale 4-items ≤ 1;
- Mini Mental State Examination ≥ 24;
- Maintaining an upright posture ≥ 30, evaluated by a trained physiotherapist during the recruitment.

The exclusion criteria will be:

- Failure to meet the inclusion criteria;
- Concomitant participation in other studies;
- Lack of written informed consent;
- History of syncopal episodes, epilepsy, and vertigo not controlled pharmacologically;
- Serious dysfunction of the autonomic system;
- Severe behavioral syndromes not compensated by drugs;
- Concurrent neurological and/or cardiac diseases;
- Recent femur fracture;
- Chronic medium to severe pain affecting standing or walking.

Recruitment

Patients will be selected by the outpatient department at the Clinical Unit of Physical Rehabilitation, of IRCCS INRCA, in the Ancona branch. These patients will be contacted to schedule a visit with the clinical team. Once the compliance with the inclusion and exclusion criteria of the study will be verified and the informed consent will be obtained, the doctor will proceed with the baseline evaluation and with the acquisition of gait assessment parameters through G-walk sensor. The trial will start in November 2021 and is expected to end in April 2022.

Intervention

For this study, 20 patients with PD will be enrolled. Sixteen therapy sessions of 50 min will be conducted (two training sessions per week, for 8 weeks), involving two patients at a time. Cardiac and respiratory activity monitoring will be conducted during dancing treatments in order to detect heart rate and breathing frequency. Participants will have to complete at least 80% of the sessions.

Each session will involve the following activities:

- breathing, relaxation, and postural harmonization exercises (5 min);
- active mobility and stretching exercises (5 min);
- Irish dancing with the SI-ROBOTICS system (35 min);
- relaxation exercises (5 min).

Platform Description

The SI-ROBOTICS system is composed of multiple technological components. Usability and acceptability of the single components have been evaluated singularly before the system integration. These components are:

- **A robotic platform:** a social robot that will motivate the participants during the sessions, equipped with the Inter Real Sense camera, able to collect information on kinematic parameters such as position of pressure center in relation to the support base, steps, and body symmetry.
- **The let's dance game**: a serious game based on the choreography and a personalized avatar which will guide the participants to perform the dance sessions.
- **Wearable wellness system sensorized shirt:** to collect data on the patient's main clinical parameters (e.g., heart rate, breathing frequency, etc.) during the performance. These data will allow to collect the patient's performance data during the execution of tasks.

In addition, the system is constituted by:

- **The AI reasoner module**: the backend intelligent part of the SI-ROBOTICS system that will allow the adaptation of the dance sessions, based on the users' performance and the data collected through the sensors. In this way, it will be possible to dynamically customize the session according to the user's needs and abilities.
- **The artificial vision setting**: a commercial camera called Inter Real Sense, installed in the experimental setting for the extraction of kinematic parameters. To extract features of interest from the signals, proprietary skeleton tracking software of the Real Sense camera will be used, together with specially developed algorithms for feature extraction.

Figures 1A,B shows the experimental setting in a protected environment (gymnasium) and the positioning of the technologies, the user and the physiotherapist, during the training sessions. In particular, the two participants will be placed in front of the screen and the central camera at a distance of 3.40 m. The robot and the physiotherapist will be positioned laterally, at a distance of 3 m. The robot will move without entering the blue area drawn in **Figure 1B**, using the navigation algorithm based on literature (29, 30).

The technical components are described in details in the following paragraphs.

Robotic Platform

From a technical point of view, the SI-ROBOTICS robot is composed of the MoVeR1 robotic platform (Co-Robotics, Italy) as shown in **Figure 2**, a two-axle autonomous vehicle with two front driving wheels and two rear omni-drive wheels, and an external cover, whose customized design was realized in collaboration with the Department of Design of the University of Genova.

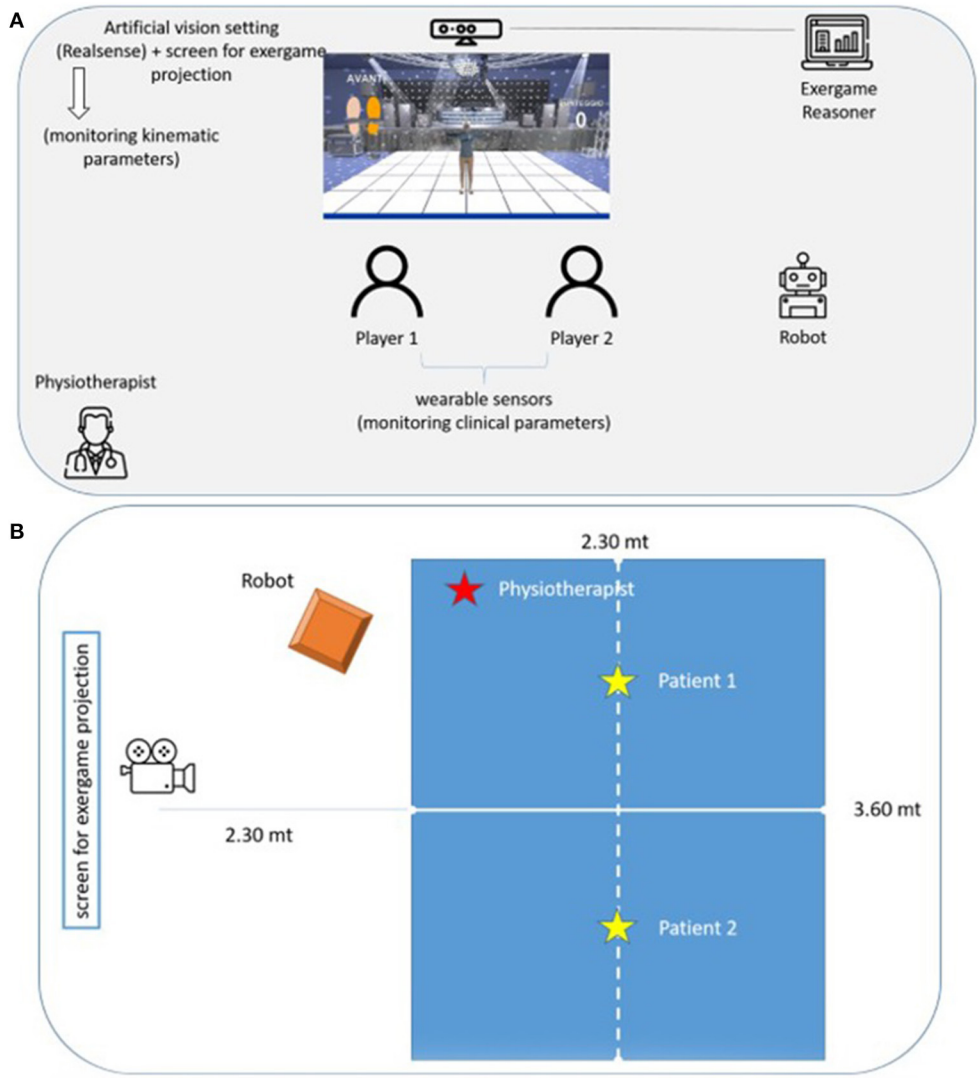

FIGURE 1 | SI-ROBOTIC system **(A)**. Expermental setting **(B)**.

The platform has been equipped with the following commercial sensors to be compliant with the scenario requirement:

- a microphone and a speaker to interact with the participants;
- a tablet, providing a web interface to support the interaction during the service;
- an Intel RealSense D435i RGB-D camera (Intel, USA), which helps the patient–robot interaction, measuring movements, and which performs the remote plethysmography service, by real-time measurement of heart rate and breath rate (31, 32);
- a SICK TIM781 laser 2D, able to detect obstacles and people in the environment.

The robot software is based on the Robot Operating System (ROS) (33), which performs middleware function, i.e., connection layer of all software components strictly related to the robot operation. Among the relevant modules built on ROS, the autonomous navigation module is devoted to performing motor control, avoiding obstacles, planning the best paths, and so on. Furthermore, for the user interaction part, basic modules deal with synthesizing text into dialogs. Other two modules have been developed to link the robot tasks to the application scenarios defined in the project: (1) the social navigation module (34), which is used to make the robot autonomously approach the users, following methodologies in line with social behaviors and (2) the dialogue module, providing motivational statements based on the context and data collected during the dance session, which will be sent to the underlying speech synthesis module for vocal interaction.

Let's Dance Game

Let's dance is a game based on Irish dancing sessions. It has been designed to be intuitive and easy to use for both the patient and

FIGURE 2 | SI-ROBOTICS platform.

the physical therapist. After selecting a difficulty level, players are presented as dancers on the screen, along with footprints that suggest the movement to be done.

Each task can vary from simple aerobic exercises (side steps, arm raising, hand-clapping, etc.) to choreographies.

Preliminarily to the use of the game, warm-up exercises will be proposed, in order to minimize physical problems related to the execution of dance steps. After the warm-up, the therapist will log in, will select the involved patients, and will choose the first song and level to be performed. At the end of the dance session, cool-down exercises will be carried out in order to restore the resting condition.

The complexity of the step sequence may increase, ranging from simple steps interspersed with pauses, to sequences of steps, up to complete choreographies, based on the dance movements in the Irish style and Irish music.

An example of steps that will be used: rest, step forward right or left foot, step backward right or left foot, side-step right or left, fake step forward right or left foot, fake step backward right or left foot, full lift right or left arm, partial lift right or left arm.

Wearable Wellness System Sensorized Shirt

During the rehabilitation session, patients will wear the Wearable Wellness System (WWS) sensorized shirt, produced by Smartex (http://www.smartex.it/it/prodotti/204-wws). WWS offers a high level of comfort that makes it particularly suitable for monitoring physiological parameters even for long periods. The sensorized garment is produced using natural and synthetic yarns and it can be used as underwear.

The shirt is a fully integrated wearable system for the continuous monitoring of physiological parameters, composed of a sensorized undershirt and an electronic board allowing the continuous monitoring of some clinical parameters relevant to the evaluation of the user's stress and physical state. The shirt is composed of:

- a sensorized garment (t-shirt, in different sizes and profiled for female and male silhouette);
- an electronic device designed for data acquisition, pre-processing, storage, and transmission;
- a customized software for the configuration of the device and the processing, management, transmission of the acquired data.

The system is capable of simultaneously acquiring the following signals:

- ECG signal and
- respiratory signal.

The ECG and respiratory signals are obtained through the use of textile-based fiber sensors integrated directly into the structure of the garment.

The processor on board the electronic device elaborates the acquired signals, through sophisticated signal processing algorithms for artifacts/noise reduction and for the real-time extraction of heart and breathing rate values in a reliable way.

The system has been tested to evaluate its duration in number of washes and times of use. The first signs of aging appear after 50 cycles of delicate washing.

AI Reasoner

Its role is to realize the reasoning capabilities necessary to contextualize and adapt the behavior of the SI-ROBOTICS system according to the clinical objectives of the session and the "dynamic performance" of the users. During the session, the artificial vision system and the installed physiological sensors will produce a flow of data used by the reasoner to monitor the progress of the session and the status of the users.

The step sequences generated by the reasoner will be sent to the game for the dance session execution. During the exercise, the reasoner's role will be to monitor performance and to dynamically adapt the exercise when necessary.

Generally, there are two types of scenarios that we will consider during the course of the session:

- Complete session: in this scenario, the reasoner will not face any special situations and/or conditions during the exercise.
- Interruption or dynamic adaptation of the session: in this scenario, the reasoner encounters abnormal situations that require direct intervention of the system and dynamic adaptation of the session.

Moreover, the reasoner will suggest to the therapist the change from one level of difficulty to another during the treatment, on the basis of variations calculated on patient-specific baseline values taken at the beginning of the intervention.

Artificial Vision Setting

As already said, another Intel RealSense depth camera will be installed in the experimental setup and will be used for the extraction of kinematic parameters, thanks to the Skeleton Tracking SDK developed by Cubemos (München, Germany). Indeed, for each detected skeleton, the spatial coordinates (x, y, and z) and the detection confidence of 18 joints will be estimated. For each step involved in the Irish dance subsession, the following clinical key performance indicators (KPIs), agreed with the physiotherapists, will be extracted in real-time:

- step symmetry;
- symmetry between left and right foot (computed for lower limbs);
- symmetry between left and right arm, with respect to the request, i.e., 90° or 180° lift exercise (computed for upper limbs);
- inclination of the trunk: the flexion of the trunk will be measured during the dance. A warning will be triggered if the person tilts the trunk forward exceeding the tolerance.
- the center of gravity: the stability of the subject will be evaluated by calculating the position of the center of gravity. The system will give a warning when the projection of the center of mass exits the support base defined by the length and position of the feet.

A Middleware to Facilitate Module Interaction

The interoperable platform is intended as a distributed middleware, i.e., a set of protocols, interfaces, and services for the development of applications capable of processing large amounts and streams of data from heterogeneous sources.

For the rehabilitation program, the platform will monitor the values and allow the exchange, and processing of data through artificial intelligence algorithms, thus obtaining information useful to the physical therapist in the evaluation of the patient's performance.

This is possible through the main components internal to the middleware:

- Event bus interoperability framework: it allows communication and data exchange between the components through the use of *connectors* and *topics* according to the *publish–subscribe* mechanism (a publisher publishes an event to the Event Bus; on the other hand, the subscriber receives this event).
- Stream and batch processing for the data analysis in real-time or batch.
- Persistence layer: it allows the persistence of circulating information.

Outcomes

All outcomes will be measured following a standardized operating procedure. **Table 1** shows the primary and secondary outcomes.

A summary of all data collected and when these are collected is provided in **Table 2**.

The scales which will be used during the evaluations are described below.

TABLE 1 | Outcomes and clinical assessments.

Outcome(s)	Clinical assessment
Primary: acceptability of the SI-ROBOTICS system	UTAUT
Secondary: gait improvement (increase in walking speed)	Gait speed during 6 MWT though (G-Walk sensor)
Secondary: balance	POMA
Secondary: fear of falling	FES-I Short form
Secondary: general functional status	SPPB and TUG
Secondary: user satisfaction	GAS
Secondary: cardiac and respiratory performance	HR and RR using wearable sensors
Secondary: quality of life	SF-12

UTAUT, Unified Theory of Acceptance and Use of Technology; 6 MWT,6 Minute Walking Test; POMA, Performance-Oriented Mobility Assessment; FES-I, Short Falls Efficacy Scale – International; SPPB, Short Physical Performance Battery; TUG, Time Up and Go; GAS, Goal Attainment scale; HR, Heart Rate; RR, Respiratory Rate; SF-12, Short Form (12).

TABLE 2 | Schedule of assessment and outcome measures.

	R	T0	T1	T2
Mini Mental State Examination (MMSE)	✓			
Functional Ambulation Category (FAC)	✓			
Rankin Scale	✓			
Hoen and Yahr Scale	✓			
Geriatric Depression Scale—5 items (GDS)	✓			
Socio-demographics check list		✓		
Barthel Index		✓		
Short Form Health Survey (SF-12)		✓		✓
Assistive Device Predisposition Assessment—Scale E (ATDPA)		✓		
Unified Theory of Acceptance and Use of Technology (UTAUT)				✓
Performance-Oriented Mobility Assessment (POMA)		✓	✓	✓
Short Falls Efficacy Scale—International (FES—I)		✓	✓	✓
Short Physical Performance Battery (SPPB)		✓	✓	✓
Unified Parkinson's Disease Rating Scale—III (UPDRS—III)		✓	✓	✓
Timed Up and GO (TUG)		✓	✓	✓
6 Minute walking test (6 MWT)		✓	✓	✓
Goal Attainment scale (GAS)		✓		✓
Ad hoc scale on satisfaction with the SI-ROBOTICS intervention				✓

R, Recruitment; T0, Start of treatment; T1, Mid-treatment (4 weeks); T2, end of treatment (8 weeks). ✓indicates when the test has been performed.

Mini-Mental State Examination

Mini-Mental State Examination was designed as a clinical method for grading cognitive impairment. The score ranges from 0 to 30: scores $\geq$ 24 indicate normality between 18 and 23 indicate mild cognitive impairment, between 11 and 17 average cognitive deficits, scores $\leq$ 10 severe cognitive impairments.

The reported score is corrected according to age and education (35).

Functional Ambulation Categories

The scale is used to classify the severity level of gait disturbances in neurological disorders. It provides a hierarchical classification from level 0 (impossible walking) to level 5 (no limitation) (36).

Rankin Scale

It is a simple scale for the evaluation of the outcomes following a stroke. Reliability is well-defined. The individual categories are essentially based on patient mobility. There are 6 grades of classification from 0 to 5, where 0 means independence and 5 means severe disability (37).

Hoehn and Yahr Scale

This scale is used in the medical field to describe the symptoms of PD progression. It was originally published in 1967 in the Neurology Journal by Melvin Yahr and Margaret Hoehn, and included stages 1–5. Since then, a modified scale has been proposed, with the addition of stages 1.5 and 2.5 describing the intermediate course of the disease (38).

Geriatric Depression Scale 5-Items Version

This questionnaire assesses the current condition of the patient's mood. For the screening required by our study, only the first five items of the scale can be used. The answers highlighted indicate the statements expected by a non-depressed subject (39).

Barthel Index

Barthel index is an ordinal scale used to measure a subject's performance in everyday life activities. The index analyzes ten variables that describe the activities of daily life and mobility. A high overall score is associated with a greater probability of being able to live at home independently after discharge from the hospital (40).

SF-12 Health Survey

The SF-12 is composed of 12 items that produce two measurements related to two different aspects of health: physical health and mental health. The subject is asked to answer on how he feels and how he is able to carry out the usual activities, evaluating the current day and the four previous weeks (41).

Assistive Device Predisposition Assessment

The purpose of the tool is to assess the user expectations about technological devices (42).

Unified Theory of Acceptance and Use of Technology

The UTAUT (28) scale is made up of four constructs (performance expectancy, PE; effort expectancy, EE; social influence, SI; facilitating conditions, FC) that determine the level of acceptance of a technology by users, in terms of both attitudes toward the system (behavioral intention, BI) and its use (use behavior, USE). In addition, UTAUT incorporates four moderators (gender, age, experience, and voluntariness) that regulate the existing relationships between independent quantities (constructs) (PE, EE, SI, and FC) and dependent quantities (constructs) (BI, USE).

Tinetti's Scale or Performance-Oriented Mobility Assessment

Tinetti's scale is a tool used to evaluate balance and gait performance. The test is clinically used to determine the mobility status of a subject or to assess changes in balance and gait time. The total POMA (POMA-T) consists of two sub-scales: the balance evaluation scale ("balance scale" or POMA-B) and the gait evaluation scale ("gait scale" or POMA-G) (43).

Short Falls Efficacy Scale – International

The scale measures the "fear of falling." The cut-offs for the fear of falling are divided as follows: a score between 7 and 8 indicates a low concern, between 9 and 12 a moderate concern, and between 14 and 28 a high concern (44).

Short Physical Performance Battery

The SPPB scale is a short battery of tests designed to assess the function of the lower limbs. This scale consists of three different sections: balance assessment, evaluation of walking on four linear meters, evaluation of the ability to perform, for five consecutive times, the sit to stand from a chair, without using the upper limbs. The total scale score, therefore, has a range from 0 to 12 (45).

Unified Parkinson's Disease Rating Scale – III

The UPDRS is the most widely used rating scale in assessing the prognosis of Parkinson's disease. The total number of items investigated in this clinical assessment is 65, which can be scored from 0 to 4. A score of 0 is given in a situation of normality with respect to the problem being investigated, while if there is a minimal impairment, 1 point is given, if it is mild it is indicated by 2 points, while if it is moderate it is marked with a 3, in a more serious situation a score of 4 is given (46).

Timed Up and GO

TUG is a simple test to measure a person's level of mobility and requires static and dynamic balancing skills. It measures the time and takes a person to get up from a chair, walk three meters, turn around, return to the chair and sit down again (47).

Six Minute Walking Test

6MWT is a test that allows measurement of a patient's residual functional capacity. The test is performed by asking the patient to walk for 6 min along a corridor with a rigid walking surface. The 6MWT is based on a so-called self-pace mode, i.e., the patient chooses the intensity of effort (48).

Goal Attainment Scale

GAS is a measure referring to an individualized criterion for assessing the achievement of objectives. Five possible levels are defined for each objective: −2 result much lower than expected; −1 result lower than expected; 0 achievement; +1 result higher than expected; +2 result much higher than expected. Behavioral objectives are usually measured dichotomously: as YES or NO, "achieved" or "not achieved" (49).

Ad hoc scale on satisfaction with the SI-ROBOTICS intervention: The scale consists of 47 items, the domains of which are:

- Social Presence: its sub-dimensions are overall perceived social presence, psycho-behavioral interaction, and trust. The overall perceived social presence consists of six items. Subjects are asked to rate their opinion on a five-point scale. The psycho-behavioral interaction scale consists of five items. The trust scale consists of four items.
- HRI: its sub-dimensions are Language, Communication, and Perceived safety during movement. The language scale is composed of two items, built *ad-hoc* to verify the speech capability of the robotic platform. Communication is composed of three *ad-hoc* developed questions. Finally, the perceived safety scale is built on four items. Two of them are built *ad-hoc* for the project, while the other two are an adapted version of the standardized Godspeed tool on perceived safety, where users are asked to rate their emotional state in relation to the speed of the robot.
- Usability: its sub-dimensions are perceived as easy to use (four items), perceived usefulness (six items), and satisfaction with use (three items). All questions were constructed *ad-hoc* for the SI-ROBOTICS system.
- Acceptability: its sub-dimensions are anxiety (three items), attitude (three items), perceived adaptability (four items), and intention to use (four items). All questions were constructed *ad-hoc* for the SI-ROBOTICS system.

Instrumental Gait Analysis

Gait analysis will be performed through the G-Walk (BTS Bioengineering) during the 6MWT. G-Sensor is a wearable system for gait and movement assessment. It allows having a kinematic evaluation of the trunk and of the spatio-temporal parameters recorded during the different tests and integrated protocols.

Risk Management and Mitigation

The risk of falling is major during any rehabilitation program. The SI-ROBOTICS platform is not only designed to partner dance with patients with PD, but also to motivate them during the training and to capture information on kinematics at a secure distance. Moreover, the robotic platform is equipped with obstacles avoidance sensors at the basis to counteract the risk of hurting the participants during the performance. However, a dedicated physiotherapist will be present and will supervise the entire session, in order to intervene promptly in case of fall risk or any other emergency.

In case a fall occurs, the physiotherapist will follow this procedure: they will ask the patient to stay still before checking for pain, loss of sensation (feeling), and loss of movement in arms and/or legs which might indicate a fracture. If there is no evident injury and no signs of a change in health, in line with the person's wishes they allow them to get up independently if possible, or assist the patient in doing so. However, any adverse event related to the training will be covered by the Institution's insurance.

Data Management

The project committed to the maintenance of participants' anonymity and confidentiality throughout all procedures, such as screening, recruitment, testing, evaluation, and dissemination procedures. Data collection, usage, and storage procedures complied with national laws and the EU's General Data Protection Regulation (GDPR) such as the commitment of participants' the right to access, right to be informed, right to withdraw, and right to data erasure. Data collection will be compliant with the principle of data minimization, i.e., the collection of personal information from study participants will be limited to what is directly relevant and necessary to accomplish the specific goals of the testing and evaluation work packages. Data entry will be carried out using specific software, providing blocks, and data entry checks, in order to reduce the number of entry errors. All screening data were will be discarded upon the project completion. During the testing procedures, all visual, auditory, and sensory data that the robot collects and processes in order to function as planned will be discarded after the procedures have been completed. The exception to this is the collection of the number of interactions that the robot logs with each participant. However, these interactions will be anonymous. All research data shall be made openly available for secondary analysis 3 years after the project completion.

Data Analysis

The first step of the data analysis will deal with the description of the sample. Continuous variables will be reported as either mean and standard deviation or median and interquartile range on the basis of their distribution (assessed using the Kolmogorov–Smirnov test). Categorical variables will be expressed as an absolute number and percentage. The Mann–Whitney *U*-tests (for non-normal distribution), or the chi-square tests (normal or non-normal) will be used to compare the independent and dependent variables between the pre- and post-conditions, in addition to simple descriptive statistics (means, medians, and SDs as appropriate).

In order to verify the achievement of the primary endpoint (i.e., acceptability of the SI-ROBOTICS system), subscales of the UTAUT will be calculated. Means and standard deviation or medians and IQR of the scores will be reported according to their distribution. Correlation coefficients (Pearson for normally distributed variables, Spearman for non-normally distributed variables) of the UTAUT sub-scales with the other rating scales at each stage of the study and with the main characteristics of the subjects will be calculated to check for potential determinants of higher acceptability.

DISCUSSION

In this study, we have described an intervention protocol to evaluate the acceptability of the SI-ROBOTICS system in a group of patients with PD, while performing a rehabilitation treatment based on Irish dancing.

While the focus of common rehabilitative approaches for patients with PD relies on the improvement of static and dynamic balance, walking, and falls (50–52). It was recently found that performance improvements after technology-delivered balance training correlate with evident neurobiological changes in the cerebral cortex. In particular, combining the high personalization and flexibility of the technological system (53) with smart objects

or robots to encourage the participants during the training with Irish dancing (54–58), will strongly motivate the patients with PD in participating in the rehabilitation program, by promoting satisfactory pattern (59) and distracting by fatigue (60).

Moreover, the SI-ROBOTICS intervention has the potential to reduce several barriers to exercise, such as lack of self-confidence, lack of skills, lack of support, costs, and lack of physical activity options (61), while enhancing motivators based on the users' profile. It will also provide evidence to private and public health facilities of an innovative therapeutic treatment based on dance, making the physical therapy more similar to a leisure activity, while improving compliance to an effective treatment, and thus counteracting the exacerbation of motor and non-motor symptoms.

However, there are also limitations in the applicability of the intervention. First of all, at present, participation is limited to patients with PD at an initial stage of the disease. In the future, it is planned to arrange a larger study to better understand the opportunity of involving more participants at different stages of the disease. Moreover, participants need to be controlled in regards to adherence to medical treatments, to avoid the risk of bias during the performance.

ETHICS AND DISSEMINATION

Ethics and Confidentiality

This study was approved by the Ethic Committee of the Istituto Nazionale Ricovero e Cura per Anziani, (IRCCS INRCA) on the June 17, 2021. It was recorded in ClinicalTrials.gov on August 13, 2021 with the number NCT05005208. Any protocol modifications will be notified to the above-mentioned Ethics Committee. The same committee is in charge of data monitoring and periodically assesses the progress of the protocol and compliance with what was declared. The principles of the Declaration of Helsinki and Good Clinical Practice guidelines will be adhered to. Participants in this study provided written informed consent.

Personal data collected during the trial will be handled and stored in accordance with the General Data Protection Regulation (GDPR) 2018. The use of the study data will be controlled by the principal investigator. All data and documentation related to the trial will be stored in accordance with applicable regulatory requirements and access to data will be restricted to authorized trial personnel.

Dissemination of Research Findings

The study findings will be used for publication in peer-reviewed scientific journals and presentations in scientific meetings. Summaries of the results will also be made available to investigators for dissemination within their clinics.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by IRCCS INRCA Ethical Committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

EM and RB led the design and writing of the pilot RCT protocol. GRR, AB, and LRossi helped with the development of the participant identification plan and provided advice on other key study issues. MB helped with the design of the intervention. EM, RB, FF, and GC lead the collection, management, and statistical analysis of the data. GM, AL, NM, and LRosse contributed to the middleware section description and development. MM and GRi contributed to the analysis of the physiological parameters section description. LF, CL, FC, and FGC contributed to the robotic platform section. AL, GRe, ACa, and AM contributed to wearable sensors section description and development. FF, GC, AU, AO, and ACe contributed to the reasoner section description and development. PD and AP contributed to the Let's dance game section description and development. All authors contributed important intellectual content to the written protocol and approved the final version for publication.

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Patients' Self-Disclosure Positively Influences the Establishment of Patients' Trust in Physicians: An Empirical Study of Computer-Mediated Communication in an Online Health Community

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With the development of telemedicine and e-health, usage of online health communities has grown, with such communities now representing convenient sources of information for patients who have geographical and temporal constraints regarding visiting physical health-care institutions. Many previous studies have examined patient–provider communication and health-care service delivery in online health communities; however, there is a dearth of research exploring the relationship between patients' level of self-disclosure and the establishment of patients' trust in physicians. Consequently, this study aims to explore how patients' self-disclosure affects the establishment of patients' trust in physicians. "Good Doctor," which is a China-based online health community, was used as a data source, and a computer program was developed to download data for patient–physician communication on this community. Then, data for communications between 1,537 physicians and 63,141 patients were obtained. Ultimately, an empirical model was built to test our hypotheses. The results showed that patients' self-disclosure positively influences their establishment of trust in physicians. Further, physicians' provision of social support to patients showed a complete mediating effect on the relationship between patients' self-disclosure and patients' establishment of trust in physicians. Finally, evidence of "hope-for-help" motivation in patients' messages weakened the effect of patients' self-disclosure when physicians' social support was text-based, but strengthened it when physicians' social support was voice-based.

Keywords: e-health, self-disclosure, social support, physician-patient trust, media richness, computer-mediated communication

INTRODUCTION

With the continuing development of health information technology (1) and telemedicine, online health communities (OHCs), such as Good Doctor (haodf.com) and Chunyu Doctor (chunyuyisheng.com), are becoming increasingly popular online platforms through which patients and physicians can communicate and exchange information (2–6). OHCs provide patients with an online health consultation service, which allows them to communicate with physicians in order to obtain medical information and services; meanwhile, OHCs can provide physicians with economic and social returns (e.g., such as reputation, if the physicians service the patients on OHCs, the physicians can obtain external reputation which is distinct from offline service, such as the electronic votes, gifts, thanks letters from patients) (7). OHCs are extremely convenient for patients who have geographical and temporal constraints regarding physically contacting health-care professionals (8). Overall, the widespread use of OHC facilitates physician–patient communication and improves the accessibility of health-care services.

When compared with offline, face-to-face communication, OHCs represent extremely convenient resources through which patients can investigate diseases and symptoms. However, as OHCs are internet-based, all contact is virtual; thus, OHCs do not afford tangible diagnoses, such as inspections involving physical appraisals (e.g., palpation) or examinations of symptoms that can only be heard or smelled. Therefore, on OHCs, patients' level of self-disclosure is essential for helping the physicians make appropriate medical decisions. However, dialogue on OHCs occurs through computer-mediated communication (CMC), and combining CMC with non-tangible (i.e., non-face-to-face) diagnoses may lead to patients having less trust in physicians when compared to face-to-face communication and offline diagnoses. Thereby, on OHCs, how to improve the patient-physician trust based on the patients' self-disclosure is important to the patients and the physicians.

Self-disclosure refers to information one person communicates to another and, in the social-psychology context, is considered a kind of social behaviour (9). Previous studies have found that, when compared with face-to-face communication, users of CMC tend to disclose more personal information, mainly as a result of the anonymity such services afford (10–12). Thus, along with being distinct from face-to-face communication and representing a novel and unique method of performing self-disclosure, CMC can, in certain contexts, increase the degree self-disclosure, which could contribute to building trust (13). Therefore, it is essential to explore the relationship between self-disclosure and trust in patient–physician CMC in the OHC context. As to patient–physician trust, Gabay (14) found that perceived participative communication (PPC) can improve patient-physician trust, and the patients' perceived control over health positively moderates the relationship between PPC and patient-provider trust. Meanwhile, the physicians' good listening abilities and impartial concern for patients' well being are important factors that can increase the patients' trust in physician (15). Furthermore, Gabay (16) also discussed the communication barriers to trust (e.g., underrating patient's autonomy and lack of attentive listening) and proposed a way of patient-centred communication to improve patient's self-worth and trust. These studies provide well enlightenment for us to understand patient-physician trust. In real life, when a patient consults a physician through an OHC, the patient's trust in the physician develops gradually during the subsequent slow communication process (17). Notably, a previous study has shown that longer information exchange through CMC is more likely to foster trust (18). Therefore, after multiple rounds of CMC-mediated interaction, the physician and patient should develop an understanding of each other and a trusting relationship. From the patient perspective, trust in the physician is influenced by how much information they disclose to the physician (19, 20). Therefore, high patient self-disclosure is important for the establishment of physician–patient trust. Moreover, social support, which refers to interpersonal relations and, in this context, usually concerns emotional and informational support, is another important element in the OHC context, and can affect cooperation and relationships between physicians and patients. Receiving social support from physicians not only benefits patients' mental health (21), but can also, the field of e-health, play a significant role in patients' self-disclosure and trust (22).

Multiple studies across several fields have directly explored self-disclosure, social support, and trust (23–25); however, there is a dearth of research exploring the mechanisms that influence self-disclosure, social support, and trust. Moreover, little research has explored the mediating role of social support from physicians in the relationship between patients' self-disclosure and their building of trust in physicians. In the present research, we explore the effect of patients' self-disclosure on their trust in physicians, as well as the mediating role of social support from physicians in this relationship. Additionally, showing hope of receiving help when asking questions of physicians can not only indicate to physicians the type of information the patients desire, but may also help patients have good CMC experiences (26). For example, questions such as *Do I need an operation?* and *How should I take the medicine?*, which indicate a hope for help, may help physicians accurately and quickly understand the patients' requests, and also help the physicians provide better social support to the patients. However, existing research on the role of patients' "hope-for-help" motivation in patient–provider communication is sparse. Therefore, this study also investigates the moderating role of patients' hope-for-help motivation on the relationship between patients' self-disclosure and physicians' social support in patient–provider communication.

To explore how to build, and the factors that affect, patients' trust in physicians during online patient–provider communication, this research explores the following three questions:

Abbreviations: ClinicT, Clinical title; CMC, Computer-mediated communication; HFH, Hope for help messages; OHC, Online health community; OnlineT, Time online; PT, Patients' trust in physicians; PTL, Length of patient's textual messages; PTN, Patient's number of textual messages; TL, Text-message length; VisitNum, Number of people who have visited a physician's page; VL, Voice-message length.

RQ1: *How does patients' self-disclosure affect the establishment of patients' trust in physicians?*
RQ2: *What is the role of social support from physicians in the relationship between patients' self-disclosure and the establishment of patients' trust in physicians?*
RQ3: *What is the role of patients' hope-for-help motivation in the relationship between patients' self-disclosure and physicians' provision of social support?*

To answer the above questions, this study constructed a moderated mediation model to verify the relationship between patients' self-disclosure and the establishment of patients' trust in physicians. To the best of our knowledge, this is the first study to explore patients' self-disclosure and trust during CMC on OHCs. The research findings may provide some insights into physician–patient trust and patient–provider communication in telemedicine and e-health.

THEORETICAL BACKGROUND AND HYPOTHESES

Physician–Patient Computer-Mediated Communication in Online Health Communities

CMC originated from the "computer supported cooperation" in the 1980s. With the progress of electronic communication technology and the increase of the human being's cooperation, to communicate conveniently, more and more people begin to use the emerging communication tools to communicate and carry out cooperation based on computers. Later, this communication is called computer-mediated communication, which is abbreviated as CMC. At present, CMC is widely regarded as a new communication mode for people to search, transmit, process and communicate with each other under the help of the Internet. There are three basic communication elements in CMC: the disseminator, the media, the receiver of information. Consequently, CMC is essentially a way of information transmission to some extent. Now, CMC has been applied to many fields, such as electronic commerce, online healthcare, distance learning, online communication, and online cooperation. In online healthcare, with the development of telemedicine and e-health, CMC through OHCs has become an important medium of patient–provider communication. CMC can negate geographical and temporal constraints, representing a convenient method by which physicians and patients can communicate.

Previous studies have explored physician–patient CMC from multiple perspectives, such as interaction frequency (3), interactional unfairness (27), communication competences (28), and interaction engagement (29). However, few studies have investigated the relationship between patients' self-disclosure and the establishment of patients' trust in physicians in the context of OHCs. Further, little research has sought to answer the following questions: what role does social support from physicians play in the relationship between patients' self-disclosure and the establishment of patients' trust in physicians? Does it act as a mediating variable affecting the relationship between physicians and patients? Additionally, few studies have explored the moderating effect of patients' hope-for-help motivation on the relationship between patients' self-disclosure and physicians' provision of social support.

Patient Disclosure and the Establishment of Trust in Physicians

Self-disclosure is defined as the communication and presentation of personal information to another person (30–32), and plays an important role in the establishment of trust in others. Specifically, when individuals disclose personal information to one another, they improve understanding of each other and create trust (33). Social penetration theory (34) suggests that self-disclosure is a basic form of social exchange; as relationships develop, this exchange deepens and becomes more extensive. Meanwhile, Knapp's staircase model of relationships (35) also emphasised that self-disclosure can promote the intimacy of relationships and the formation of trust. The relationship between self-disclosure and trust is applicable to the physician–patient relationship. When a patient consults a physician, more self-disclosure on the part of the patient can promote interaction with the physician (36) and significantly improve the patient's experience, which leads to higher patient satisfaction (37). Additionally, when patients disclose more information to physicians, the physician–patient dialogue and contact increase, and the patients become more willing to trust the physicians (19, 20) and consult further with the physicians regarding their disease. Based on these findings, hypothesis H1 was proposed for the present study:

H1: Patients' self-disclosure positively influences the establishment of patients' trust in physicians.

Mediating Effect of Physicians' Social Support

Generally speaking, social support can be divided into information support (38) and emotional support (39, 40). Information support involves providing actionable and objective information to a recipient. Meanwhile, emotional support, as a form of social support, involves empathising and providing emotional validation and encouragement (41). Regarding the relationship between self-disclosure and social support, Lee et al. (42) showed that individuals who disclose more information are more likely to receive social support. Meanwhile, Kim and Lee (43) suggested that honest self-disclosure positively affects the likelihood of receiving social support. Similarly, in the context of e-health, studies have found that the greater patients' self-disclosure through CMC, the more likely they are to receive physician feedback and social support (44). When patients communicate with physicians, disclosing more information indicates that they want the physicians to understand more about their symptoms and feelings. Furthermore, through high self-disclosure patients can obtain more information support (e.g., in regard to medication instructions and treatment plans) and emotional support (caring comments and tips) from physicians. Physicians can employ textual media to provide text-based social support to patients. However, they can also

use richer media; for example, using voice media to provide voice-based social support to patients. Compared with text-based social support, voice-based social support can, through its greater richness, transmit more information (45, 46). Based on the above findings, we formulated hypotheses H2 and H3:

H2: Patients' self-disclosure positively influences physicians' text-based social support.
H3: Patients' self-disclosure positively influences physicians' voice-based social support.

More social support can increase patients' satisfaction with physicians' services (8), which can make them more willing to carry out further consultations with the physicians regarding their disease. Furthermore, higher level of social support also can often give rise to satisfactory social interaction and increase good psychological perception in physicians (47). Meanwhile, satisfactory social interaction can make patients perceive physicians as holding good intent towards themselves, and impel patients to consider that the information provided by physicians is more trustworthy (48). Besides, the social support can also increase people's health and well-being based on the social relationships, and it can transmit information, emotion, esteem among individuals (49). This can help patients improve the trust and reap more positive health outcomes (50, 51). Based on the above analysis, it can be seen that, not only does patients' self-disclosure have a direct effect on the establishment of trust in physicians, but it also has an indirect effect, through social support. Therefore, hypotheses H4 and H5 were formulated:

H4: Text-based social support from physicians mediates the relationship between patients' self-disclosure and the establishment of patients' trust in physicians.
H5: Voice-based social support from physicians mediates the relationship between patients' self-disclosure and the establishment of patients' trust in physicians.

Moderating Effects of Patients' Motivation

Motivation represents an individual's psychological needs. Previous studies have shown that individuals' psychological needs have an important influence on the reception of social support during online disclosure (42, 52). Li et al. (53) suggested that individual psychological needs can impact the relationship between self-disclosure and social support. In other words, people with strong needs are more likely to disclose more information in order to receive more social support (53). On OHCs, when patients show hope-for-help motivation, this indicates that they are seeking social support. When patients express such motivation (e.g., through questions such as *Is my illness serious? Do I need surgery? How is it treated?*), physicians will find it easier to understand the patients' information demands. In such occasions, physicians will send more information to patients (26). According to the media-richness theory (45, 46), rich media can transmit more information than lean media, and rich media can also deliver multiple additional cues, such as voice tones, intonation, and emotions. During the online consultation process, if the patients present greater hope-for-help motivation, physicians will find it easier to understand the patients' information requests, and will consequently provide more social support. To enhance the effectiveness of their communication, physicians, upon noting hope-for-help motivation, may be more likely to use richer media (e.g., voice) to provide social support than leaner media (e.g., text). Besides, the rich media have faster and real-time feedback ability compared with the lean media. When the patients present hope-for-help motivation, sometimes there are urgent information in the motivation provided by the patients (e.g., through questions such as *Can I go to your hospital? What else needs to be checked? Do I need an operation as soon as possible? I am very anxious and fear for delaying my illness. I hope you can give me a suggestion*). At this time, to feed back information quickly, the physicians may choose a rich media (e.g., voice) to provide social support, other than a lean media (e.g., text). Therefore, hypotheses H6a and H6b were formulated.

H6a: Patient motivation weakens the effect of patients' self-disclosure on physicians' provision of text-based social support.
H6b: Patient motivation strengthens the effect of patients' self-disclosure on physicians' provision of voice-based social support.

The research model for the present study is shown in **Figure 1**.

MATERIALS AND METHODS

Research Context

With the development of telemedicine and e-health, OHCs have become popular online medical consultation platforms. Good Doctor (haodf.com) is a China-based OHC that allows people to seek medical services for a fee. Good Doctor, which was created in 2006, is currently the largest e-health platform; at present, it features over 300 departments, covering over 3,000 diseases. The present research data are sourced from Good Doctor. We chose Good Doctor as the data source for two reasons. First, Good Doctor contains a great deal of data on many diseases, such as chronic diseases, serious diseases, and diseases that patients can be reluctant to disclose in public (high-privacy diseases). Second, Good Doctor contains data regarding physicians' attributes and patient–provider communication; such data greatly facilitated our research.

Data Collection

We collected from Good Doctor patient–provider communication data and data on physicians' attributes for November 2020. We used crawler software to download the data from the Good Doctor website. Thirty diseases were represented in our data, 10 high-privacy diseases and 20 common diseases. After downloading the data, we processed the data through the following steps: (1) deleted data that could not be recognised by a computer, (2) removed "space" characters, and (3) deleted data unrelated to our research (e.g., physicians' notes, tips). After applying these steps, the final dataset featured communication data from 1,537 physicians and 63,141 patients. The patient data contained 196,291 textual items, while the physician data contained 167,702 textual items and 41,538 voice items. The physicians' attribute data contained included physicians'

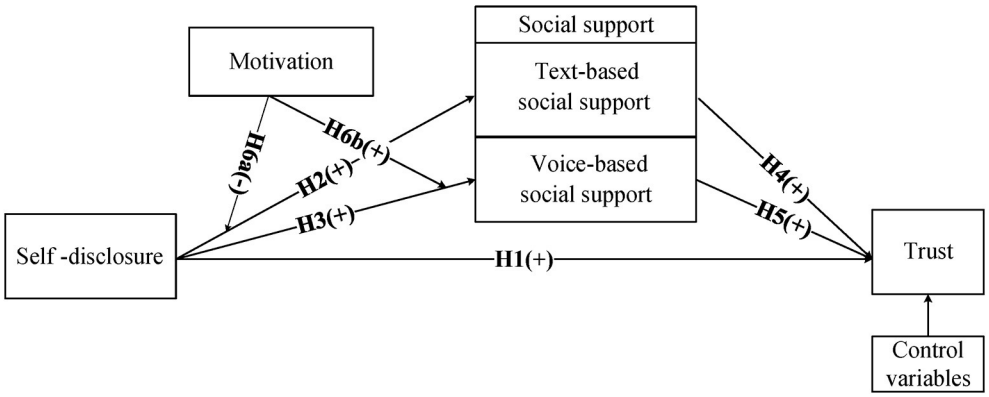

FIGURE 1 | Research model.

Case information

Disease:
The blood sugar is increased from 6.7 to 8.1, and the blood pressure is 140/90.
Hope for help:
How can I reduce my blood sugar? What kind of medicine should I take?
Duration of illness:
Less than six months.

Physician:
Voice: 2".
Patient:
Text: Where can I find the glycosylated haemoglobin on the physical examination form? If it is not present, I'll get it checked. I'm 162 cm, 75 kg, and 57 years old.
Physician:
Text: You need to check the glycosylated haemoglobin and the blood lipids.
Patient:
Text: Ok; are there any other items I should check? I'll contact you when I get the results.
Physician:
Text: No, there are not.
Patient:
Uploaded electronic health record.

FIGURE 2 | Example of a physician–patient communication record.

clinical titles, educational titles, number of patients served, and total number of consultations. Thus, our final dataset featured physicians' attribute data and communication data. An example of doctor–patient communication on Good Doctor is shown in **Figure 2**.

Operationalisation of Variables

The dependent variable was the establishment of patients' trust in the physicians. In e-business, sales of a product/service is an intuitive expression of consumers' trust in a business (54); similarly, in e-health, If the patients trust the physicians, the patients are likely to choose the physicians to consult the disease (20, 55, 56). For example, Gong (55) found that physicians' good service quality and reputation can enable patients to establish a trust relationship with them, and select these physicians in OHCs. Yoo et al. (56) considered that the trust propensity, platform reputation, and perceived physician credibility are important factors that can trigger patients' trust in physicians, and urge these patients to choose the physicians.Therefore, to some extent, the increment of patients who served by physicians can directly reflect the trust of patients to physicians. In our research, we used the increment of patients in the next month as a proxy variable to indicate the establishment of patients' trust in physicians. In this research, for each physician the increment in patients was obtained by subtracting the physician's number of patients in November 2020 from the number of patients in December 2020.

The independent variable was patients' self-disclosure; specifically, if the patients are willing to disclose more information, they will use more words to state their conditions. Contrarily, if they don't want to disclose information, they will employ less words or speak nothing to express their opinions and attitudes (57, 58). Therefore, the amount of disclosure is significantly correlated with the disclosure degree (58, 59). To effectively represent the amount and degree of patient disclosure, for each patient we used the average length (in characters) of their textual messages (PTL) to indicate the patient's level of self-disclosure. Physicians' social support was regarded as a mediating variable. Similarly, we used the average length (in characters) of the textual information (TL) and the duration (in seconds) of the voice information (VL) to quantify text-based and voice-based social support (57), respectively. Meanwhile, this study regards patients' hope-for-help motivation as a moderator variable, and this was quantified using the average length (in characters) of patients' hope for help messages. In addition, the number of textual messages patients send to physicians (PTN) may influence physician's provision of social support; concurrently, physicians who have a high clinical title (ClinicT), good reputation, and rich experience in medical diagnosis and treatment may provide more support to patients. Therefore, we controlled the influence

TABLE 1 | Variable description.

Variable	Description
Dependent variable	
Patients' trust in physicians (PT)	The increment in the number of patients consulting the physician over a 1-month period.
Independent variable	
Length of patient's textual messages (PTL)	The average length, in characters, of the textual information the patient sent to the physician.
Mediating variables	
Text-message length (TL)	The average length, in characters, of the textual information the physician sent to the patient.
Voice-message length (VL)	The average length, in seconds, of the voice information the physician sent to the patient.
Control variables	
Patient's number of textual messages (PTN)	The average number of textual messages that the patient sent to the physician.
Clinical title (ClinicT)	Clinical titles are awarded based on uniform national standards. For this study, titles were stratified into four stages (3 = medical director, 2 = associate medical director, 1 = chief physician, 0 = physician).
Time online (OnlineT)	The length of time the physician has been providing online consultations, from the first consultation to the time of data collection.
Number of visits (VisitNum)	The number of people who have visited a physician's page.
Votes	The number of votes physicians received from patients, it is a kind of reputation which is the same as the gifts and thanks letter.
Price	The price of an online written consultation with the physician.
Moderator variable	
Hope for help (HFH)	The average length, in characters, of hope-for-help messages sent by the patient.

of PTN, physicians' ClinicT, the time physicians spent online (OnlineT), the number of people who visited physicians' pages (VisitNum), the number of votes physicians received from patients (Votes, it is a kind of reputation which is the same as the gifts and thanks letter), and the price of consultation. The specific variable definitions are shown in **Table 1**.

The calculation formulas for *TL*, *VL*, *PTL*, and *PTN* described in **Table 1** are presented below in formulae 1–4, respectively.

$$TL = \frac{\sum_{i=1}^{m}\left(\sum_{j=1}^{n_1}\text{words\_number}\right)}{m} \quad (1)$$

$$VL = \frac{\sum_{i=1}^{m}\left(\sum_{j=1}^{n_2}\text{voice\_time}\right)}{m} \quad (2)$$

$$PTL = \frac{\sum_{i=1}^{m}\left(\sum_{j=1}^{n_3}\text{words\_number}\right)}{m} \quad (3)$$

$$PTN = \frac{\sum_{i=1}^{m} n_3}{m} \quad (4)$$

In the above formulae, *TL* represents the average length (in characters) of the textual information physicians sent to patients, and *VL* represents the average length (in seconds) of the voice information physicians sent to patients. *PTL* represents the average length (in characters) of the textual information patients sent to physicians, and *PTN* represents the average number of textual messages patients sent to physicians. m indicates the number of patients the physician served during November 2020, $n_1$and $n_2$represent the number of text dialogues and voice dialogues, respectively, a physician had with a patient. n_3 represents the number of text dialogues each patient had with each physician.

Model Construction and Measurement

To test the above hypotheses, we applied a moderated mediation model approach, creating four models. To reduce the fluctuation of the data, we created a natural logarithm transformation for all variables; for convenience, the original variable name was used to express the processed variables. We used Model 1 to test the effect of patients' self-disclosure on the establishment of patients' trust in physicians.

Model 1

$$PT_i = \alpha_1 + \beta_1 PTL_i + \rho_1 Control_i + \varepsilon_i \quad (5)$$

Model 2 tests the effect of patients' self-disclosure on text-based and voice-based social support from physicians.

Model 2

$$TL_i = \alpha_2 + \beta_2 PTL_i + \lambda_2 HFH_i + \rho_2 Control_i + \varepsilon_i \quad (6)$$

$$VL_i = \alpha_3 + \beta_3 PTL_i + \lambda_3 HFH_i + \rho_3 Control_i + \varepsilon_i \quad (7)$$

Model 3 tests the mediating effect of physicians' provision of social support on the relationship between patients' self-disclosure and the establishment of patients' trust in physicians.

Model 3

$$PT_i = \alpha_4 + \beta_4 PTL_i + \gamma_4 TL_i + \delta_4 VL_i + \rho_4 Control_i + \varepsilon_i \quad (8)$$

Model 4 tests the moderating effect of patient motivation on the relationship between patients' self-disclosure and social support from physicians.

Model 4

$$TL_i = \alpha_5 + \beta_5 PTL_i + \lambda_5 HFH_i + \theta_5 HFH_i^* PTL_i + \rho_5 Control_i + \varepsilon_i \quad (9)$$

$$VL_i = \alpha_6 + \beta_6 PTL_i + \lambda_6 HFH_i + \theta_6 HFH_i^* PTL_i + \rho_6 Control_i + \varepsilon_i \quad (10)$$

In the above models, the specific meaning of parameters is shown in **Table 2**.

RESULTS

The descriptive statistics of the variables are shown in **Table 3**, and the variable correlations are shown in **Table 4**. The mean variance inflation factor (VIF) was 2.71, and in all models the VIFs were <5. Therefore, there were no multicollinearity

TABLE 2 | Specific meaning of parameters in models.

Parameters	Specific meaning
PT_i	The patients' trust in physician *i*.
PTL_i	The length of the textual information that patient *i* sent to the physician.
TL_i	The length of the textual information that physician *i* sent to the patient.
VL_i	The length of the voice information that physician *i* sent to the patient.
HFH_i	The text length of hope-for-help messages sent by patient *i*.
ε_i	Error term.
$\alpha_1, \alpha_2, \alpha_3, \alpha_4, \alpha_5, \alpha_6$	Constant terms.
$\rho_1, \rho_2, \rho_3, \rho_4, \rho_5, \rho_6$	Coefficients of control variables.

TABLE 3 | Descriptive statistics for the variables ($N = 1{,}537$).

Variable	Mean	Standard deviation	Min	Max
PT	71.15	149.6	0	4,716
PTL	78.51	75.27	0	1,538
TL	77.00	109.7	0	1,522
VL	11.57	28.31	0	411.7
PTN	2.624	2.801	0	75
ClinicT	2.407	0.737	0	3
OnlineT	6.943	3.336	0	12
VisitNum	3,120,000	7.153e + 06	2,616	148,000,000
Votes	318.4	341.6	2	3,142
Price	137.6	159.4	9	2,700
HFH	9.324	7.552	0	50

The above variables are original values instead of the natural logarithmic transformations. ClinicT: clinical title, HFH: hope for help messages, OnlineT: time online, PT: patients' trust in physicians, PTL: length of patient's textual messages, PTN: patient's number of textual messages, TL: text-message length, VisitNum: number of people who have visited a physician's page, VL: voice-message length.

problems in our study. In this study, we use a moderation-mediation model to verify above hypotheses in our research. The moderation-mediation model can be divided into two parts: mediation model and moderation model. The mediation model contains model 1, model 2 and model 3. First of all, model 1 verifies the main effect between independent variable (PTL) and dependent variable (PT). If the coefficient β_1 is significant, the main effect is effective. Secondly, the coefficient β_2 and β_3 must be significant in model 2. Finally, in model 3, the coefficient (γ_4, δ_4) of mediating variable (TL,VL) must be significant and the coefficient (β_4) of independent variable (PTL) must be not significant. When above conditions are met, the mediating effect is effective. The model 4 is a moderation model and it can verify the moderation effect. In model 4, if the coefficient ($\beta_5, \gamma_5, \theta_5$ or $\beta_6, \gamma_6, \theta_6$) of independent variable (PTL), moderator variable (HFH) and the interactive item (HFH*PTL) is significant, the moderating effect is effective. **Table 5** presents the estimation results. Column (1) shows the estimation result for the control variables only. H1 predicted that patients' self-disclosure positively influences the establishment of patients' trust in physicians. Based on the regression result shown in column (2), β_1 ($\beta_1 = 0.132$, $t = 3.19$, $\rho < 0.01$) was positive and significant; thus, H1 was supported, and the main effect was verified.

H2 and H3 predicted that patients' self-disclosure positively influences physicians' provision of text-based and voice-based, respectively, social support. Columns (3,4) indicate that β_2 ($\beta_2 = 0.439$, $t = 8.52$, $\rho < 0.01$) and β_3 ($\beta_3 = 0.347$, $t = 7.58$, $\rho < 0.01$) are positive and significant; thus, H2 and H3 are supported. This indicates that, during the process of patient–provider communication, an increasing amount of information is disclosed by patients, and physicians consequently obtain better understanding of patients' medical conditions and provide more effective treatment and social support to patients.

Column (5) tests the mediating effect of physicians' text-based and voice-based social support. In column (5), β_4 ($\beta_4 = 0.050$,

TABLE 4 | Variable correlations.

Variable	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)
1. PT	1										
2. PTL	0.273***	1									
3. TL	0.227***	0.741***	1								
4. VL	0.236***	0.324***	0.065**	1							
5. PTN	0.221***	0.883***	0.725***	0.272***	1						
6. ClinicT	0.100***	−0.034	−0.073***	−0.010	−0.086***	1					
7. OnlineT	0.065**	−0.003	−0.077***	0.017	−0.058**	0.369***	1				
8. VisitNum	0.401***	0.162***	0.096***	0.157***	0.109***	0.285***	0.634***	1			
9. Votes	0.544***	0.152***	0.072***	0.159***	0.074***	0.189***	0.404***	0.718***	1		
10. Price	0.217***	0.110***	0.060**	0.137***	0.056**	0.240***	0.222***	0.349***	0.394***	1	
11. HFH	0.073***	0.556***	0.572***	0.222***	0.545***	0.008	0.017	0.143***	0.096***	0.101***	1

$^*p < 0.1$, $^{**}p < 0.05$, $^{***}p < 0.01$. The above variable values are natural logarithmic transformations.

ClinicT, clinical title; HFH, hope for help messages; OnlineT, time online; PT, patients' trust in physicians; PTL, length of patient's textual messages; PTN, patient's number of textual messages; TL, text-message length; VisitNum, number of people who have visited a physician's page; VL, voice-message length.

TABLE 5 | Estimated results.

Column	(1)	(2)	(3)	(4)	(5)	(6)	(7)
Dependent Variable	PT	PT	TL	VL	PT	TL	VL
PTL		**0.132*** **	**0.439*** **	**0.347*** **	**0.050**	0.327***	0.420***
		(3.19)	**(8.52)**	**(7.58)**	**(1.11)**	(4.47)	(7.43)
TL					**0.095*** **		
					(3.21)		
VL					**0.092*** **		
					(5.07)		
PTN	0.319***	0.045	0.629***	−0.160	−0.017	0.819***	−0.283*
	(7.12)	(0.47)	(6.25)	(−1.21)	(−0.17)	(6.69)	(−1.96)
ClinicT	0.306***	0.292***	−0.108	−0.188	0.316***	−0.118	−0.182
	(2.87)	(2.75)	(−1.08)	(−1.24)	(2.99)	(−1.19)	(−1.20)
OnlineT	−0.576***	−0.579***	−0.215***	−0.212**	−0.538***	−0.215***	−0.212**
	(−8.87)	(−8.93)	(−3.17)	(−2.27)	(−8.50)	(−3.14)	(−2.27)
VisitNum	0.133***	0.134***	0.047*	0.107**	0.117***	0.0568**	0.101**
	(4.51)	(4.58)	(1.75)	(2.52)	(4.03)	(2.09)	(2.38)
Votes	0.593***	0.580***	−0.038	0.063	0.579***	−0.047	0.069
	(15.24)	(14.93)	(−1.07)	(1.13)	(14.96)	(−1.33)	(1.24)
Price	−0.012	−0.018	−0.007	0.123***	−0.030	0.008	0.113**
	(−0.40)	(−0.58)	(−0.23)	(2.72)	(−1.00)	(0.28)	(2.51)
HFH			0.328***	0.089**		0.283***	0.118**
			(8.25)	(2.25)		(7.71)	(2.54)
HFH*PTL						**−0.080*** **	**0.052*** **
						(−3.27)	**(2.65)**
Constant	−0.880***	−0.976***	0.696***	−1.903***	−0.861***	0.918***	−2.047***
	(−3.37)	(−3.76)	(2.69)	(−5.14)	(−3.33)	(3.29)	(−5.37)
Observations	1,537	1,537	1,537	1,537	1,537	1,537	1,537
R-squared	0.366	0.371	0.606	0.130	0.384	0.613	0.132
F	131.49	118.02	286.41	58.15	101.53	337.65	68.89
Prob > F	0	0	0	0	0	0	0

*t-statistics are in parentheses; *p < 0.1, **p < 0.05, ***p < 0.01.*

ClinicT, clinical title; HFH, hope for help messages; OnlineT, time online; PT, patients' trust in physicians; PTL, length of patient's textual messages; PTN, patient's number of textual messages; TL, text-message length; VisitNum, number of people who have visited a physician's page; VL, voice-message length.

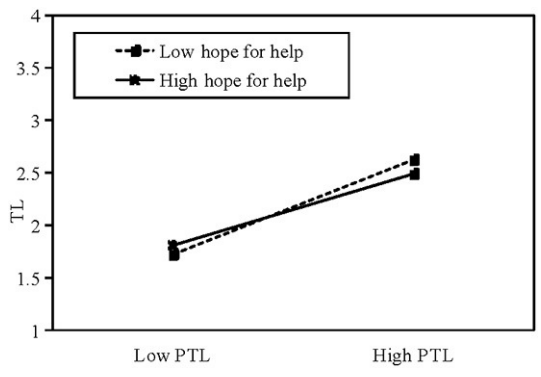

FIGURE 3 | The mediating effect of hope-for-help motivation on TL. PTL: length of patient's textual messages.

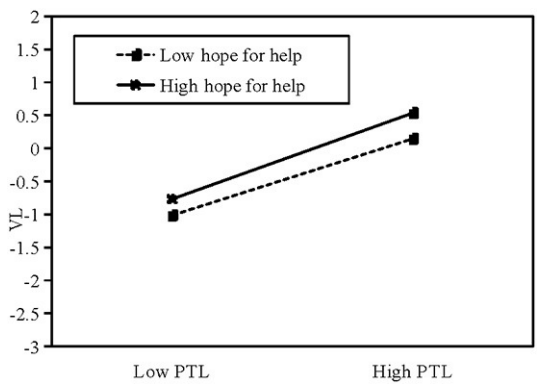

FIGURE 4 | The mediating effect of hope-for-help motivation on VL. PTL: length of patient's textual messages.

t =1.11, $\rho > 0.1$) is not significant, whereas γ_4 ($\gamma_4 = 0.095$, $t = 3.21$, $\rho < 0.01$) and δ_4 ($\delta_4 = 0.092$, $t = 5.07$, $\rho < 0.01$) are positive and significant; this indicates that H4 and H5 were supported. These findings suggest that, in OHCs, if patients obtain more information and support from physicians, they can develop a more favourable perception of their medical

experience and become more willing to build a trust relationship with the physicians. Thus, social support from physicians plays a complete mediating role in the relationship between patients' self-disclosure and the establishment of patients' trust in physicians.

Columns (6,7) test the moderating effect of patients' hope-for-help motivation on the relationship between patients' self-disclosure and physicians' social support. In columns (6,7), θ_5 ($\theta_5 = -0.080$, $t = -3.27$, $\rho < 0.01$) is negative and significant, whereas θ_6 ($\theta_6 = 0.052$, $t = 2.65$, $\rho < 0.01$) is positive and significant; thus, H6a and H6b are supported. The specific moderating effect of hope-for-help motivation is shown in **Figures 3**, **4**. This shows that patients' hope-for-help motivation weakens the effect of patients' self-disclosure on physicians' provision of text-based support, and strengthens the effect of patients' self-disclosure on physicians' provision of voice-based support.

Robustness Cheque

To test the robustness of our results, we used data from December 2020 (communication data) and January 2021 (number of patients who consulted each physician) to verify our results. **Table 6** shows that most of our results are robust and credible.

DISCUSSION

Based on the Good Doctor medical platform, which is a big online health community in China, this study used a moderation-mediation model to explore the relationship among patients' self-disclosure, physicians' social support and the patients' establishment of trust in physicians. Additionally, it also tested the moderating effect of patients' motivation for "hope for help" on the physicians' social support. The results show that the patients' self-disclosure positively affect the patients'

TABLE 6 | Robustness cheque.

Column	(1)	(2)	(3)	(4)	(5)	(6)	(7)
DependentVariable	PT	PT	TL	VL	PT	TL	VL
PTL		**0.095****	**0.398*****	**0.381*****	**0.045**	0.189***	0.414***
		(2.43)	**(7.84)**	**(6.44)**	**(1.06)**	(2.74)	(5.78)
TL					**0.061****		
					(2.31)		
VL					**0.060*****		
					(4.00)		
PTN	0.332***	0.137	0.650***	−0.286*	0.105	1.036***	−0.345**
	(7.57)	(1.57)	(6.37)	(−1.80)	(1.19)	(8.38)	(−1.98)
ClinicT	0.107	0.089	−0.253**	−0.238	0.115	−0.201**	−0.246
	(1.05)	(0.87)	(−2.39)	(−1.29)	(1.12)	(−1.98)	(−1.33)
OnlineT	−0.480***	−0.480***	−0.159**	−0.156	−0.462***	−0.160***	−0.155
	(−8.47)	(−8.46)	(−2.53)	(−1.46)	(−8.11)	(−2.65)	(−1.46)
VisitNum	0.105***	0.105***	0.051*	0.126**	0.093***	0.070**	0.123**
	(3.75)	(3.77)	(1.73)	(2.55)	(3.33)	(2.38)	(2.50)
Votes	0.539***	0.530***	−0.003	0.132**	0.523***	−0.043	0.138**
	(14.85)	(14.49)	(−0.08)	(2.10)	(14.48)	(−1.14)	(2.21)
Price	0.033	0.028	−0.040	0.056	0.027	0.010	0.047
	(1.20)	(1.01)	(−1.26)	(1.10)	(0.99)	(0.30)	(0.93)
HFH			0.247***	0.060		0.152***	0.075
			(6.04)	(1.18)		(3.99)	(1.31)
HFH*PTL						**−0.169*****	0.026
						(−6.97)	(0.94)
Constant	−0.324	−0.380	0.879***	−1.875***	−0.315	1.222***	−1.928***
	(−1.24)	(−1.45)	(3.14)	(−4.08)	(−1.20)	(4.28)	(−4.11)
Observations	1,428	1,428	1,428	1,428	1,428	1,428	1,428
R-squared	0.358	0.361	0.543	0.105	0.369	0.571	0.106
F	122.96	107.18	213.04	29.90	90.49	385.79	28.02
Prob > F	0	0	0	0	0	0	0

*t-statistics in parentheses; *p < 0.1, **p < 0.05, ***p < 0.01.*

ClinicT, clinical title; HFH, hope for help messages; OnlineT, time online; PT, patients' trust in physicians; PTL, length of patient's textual messages; PTN, patient's number of textual messages; TL, text-message length; VisitNum, number of people who have visited a physician's page; VL, voice-message length.

establishment of trust in physicians. The physicians' social support plays a complete mediating effect between the patients' self-disclosure positively and the patients' establishment of trust in physicians. Moreover, the patients' motivation for "hope for help" weakens the effect of patients' self-disclosure on physicians' provision of text-based social support and strengthens the effect of patients' self-disclosure on physicians' provision of voice-based social support. This research has some theoretical and practical contributions. First of all, this study is helpful to understand the patient-physician communication and patient-physician trust. It first establishes the contact between the patients' self-disclosure and the patients' establishment of trust in physicians from the patients. Secondly, this study extends the healthcare theory in OHCs and make the service and trust mechanism clear during the process of CMC. Thirdly, it provides the beneficial and essential practical implications for patients, physicians and the online health platforms. Overall, our research investigated the relationship between patients' self-disclosure, the physicians' social support and the establishment of patients' trust in physicians. It expands the health-care service delivery theory in e-health and has strong practical significance for patients, physicians, online medical platform, and the digital public health of human beings.

Implications

This study provides insights for practise. First, our research provides a new approach for investigating the deep influencing mechanisms for the relationship between patients' self-disclosure and the establishment of patients' trust in physicians. Our research reveals a credible path by which patients can build trust in physicians during CMC. We found that patients' self-disclosure is helpful for building a harmonious and credible trust relationship between physicians and patients. Thus, when patients consult physicians, they should disclose as much information as possible.

Second, social support from physicians is significant for patients. Trust between physicians and patients is an essential element of physician–patient communication. If patients disclose more information to physicians, the physicians will provide more social support to the patients, and the patients will consequently become more willing to trust the physicians. The physicians should pay attention to the patients' self-disclosure, if there are more self-disclosure from patients, it means that the patients want to explain their symptoms and conditions clearly, the physicians should feed back the information as more as possible through text and voice media. At this time, the patients will consider that the physicians' service is worthy and they will trust physicians more. Meanwhile, if patients seek to obtain more social support from physicians, the patients could show more "hope-for-help" motivation to the physicians. Moreover, as a result of its richness as a medium, physicians should use voice media as much as possible when communicating with patients, as such media is helpful for providing increased social support and building a strong physician–patient relationship.

Third, CMC platforms could provide some modular options that help patients indicate their information needs. Such options could relate to medication, operations, diseases, and appointments. With such functionality, patients could disclose information more accurately and conveniently, and physicians could more easily understand patients' desires and, consequently, provide more social support.

Limitations

There are some limitations to our study. First, the data in our research are sourced only from the Good Doctor website, which is a large online e-health community in China; future studies should use data from multiple online platforms to verify our hypotheses. Second, our research data are cross-sectional; future research should use panel data to obtain more robust results. Third, this paper focussed solely on information quantities to determine patients' levels of self-disclosure and physicians' levels of social support; future research should more closely consider the influence of communication content.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary materials, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

All authors made substantial contributions to the research and agree with the content of the final manuscript.

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Patient's Perception of Digital Symptom Assessment Technologies in Rheumatology: Results From a Multicentre Study

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Introduction: An increasing number of digital tools, including dedicated diagnostic decision support systems (DDSS) exist to better assess new symptoms and understand when and where to seek medical care. The aim of this study was to evaluate patient's previous online assessment experiences and to compare the acceptability, usability, usefulness and potential impact of artificial intelligence (AI)-based symptom checker (Ada) and an online questionnaire-based self-referral tool (Rheport).

Materials and Methods: Patients newly presenting to three German secondary rheumatology outpatient clinics were randomly assigned in a 1:1 ratio to complete consecutively Ada or Rheport in a prospective non-blinded multicentre controlled crossover randomized trial. DDSS completion time was recorded by local study personnel and perceptions on DDSS and previous online assessment were collected through a self-completed study questionnaire, including usability measured with the validated System Usability Scale (SUS).

Results: 600 patients (median age 52 years, 418 women) were included. 277/600 (46.2%) of patients used an online search engine prior to the appointment. The median time patients spent assessing symptoms was 180, 7, and 8 min, respectively using online using search engines, Ada and Rheport. 111/275 (40.4%), 266/600 (44.3%) and 395/600 (65.8%) of patients rated the respective symptom assessment as very helpful or helpful, using online search engines, Ada and Rheport, respectively. Usability of both diagnostic decision support systems (DDSS) was "good" with a significantly higher mean SUS score (SD) of Rheport 77.1/100 (16.0) compared to Ada 74.4/100 (16.8),

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($p < 0.0001$). In male patients, usability of Rheport was rated higher than Ada ($p = 0.02$) and the usability rating of older (52 years ≥) patients of both DDSS was lower than in younger participants ($p = 0.005$). Both effects were independent of each other. 440/600 (73.3%) and 475/600 (79.2%) of the patients would recommend Ada and Rheport to friends and other patients, respectively.

Conclusion: In summary, patients increasingly assess their symptoms independently online, however only a minority used dedicated symptom assessment websites or DDSS. DDSS, such as Ada an Rheport are easy to use, well accepted among patients with musculoskeletal complaints and could replace online search engines for patient symptom assessment, potentially saving time and increasing helpfulness.

Keywords: telemedicine, symptom assessment [MeSH], artificial intelligence, eHealth, diagnostic decision support system (DDSS), rheumatology, mobile app

INTRODUCTION

Being confronted with new symptoms, we increasingly turn to the internet first to seek further information (1–3). Besides traditional search engines, an increasing number of dedicated symptom assessment websites and apps exist, that point out diagnostic suggestions and or action advice (4). These patient-facing diagnostic decision support systems (DDSS), often also being referred to as "symptom checkers" (5) are increasingly being used by the general population (1) and rheumatic patients in particular (2, 3, 6, 7). The instant availability of help offered by these digital tools are very appealing to the general public and the low costs make these tools very appealing to politicians and health care systems (1).

DDSS are currently based on very different approaches covering a varying number of disciplines and diagnoses (4, 8). Rheport for example is an online self-referral tool, designed to optimize rheumatology referrals, being based on a fixed questionnaire (9, 10), whereas Ada is an artificial intelligence (AI) and chatbot-based symptom checker covering multiple diagnoses (8, 10). Furthermore, Ada's questions are dynamically chosen and the total number of questions varies depending on the previous answers given.

Due to these different approaches, acceptability and usability might significanty differ between DDSS approaches and not everyone might be able to efficiently use these new tools or appreciate them.

Currently, DDSS evaluation studies largely focus on the evaluation of the diagnostic accuracy (4, 10, 11) and only few studies analyzed the usability and acceptability by their end-users, i.e., actual patients. A recent study conducted by the symptom checker company Ada Health suggests that the majority of patients (511/522, 97.8%) rated the symptom checker Ada as very easy or quite easy to use and would recommend it to a friend or relative (444/520, 85.3%) (12). Importantly, the authors discovered a trend for younger respondents to rate Ada as more helpful. Meyer et al. (13) recently showed that compared with patients who had not previously experienced diagnostic errors (missed or delayed diagnoses: 123/304, 40.5%), patients who had previously experienced diagnostic errors (181/304, 59.5%) were more likely to use a symptom checker (Isabel) to determine where they should seek care (15/123, 12.2 vs. 48/181, 26.5%; $P = 0.002$).

The current literature seems limited to isolated assessments and to our knowledge no study has been carried out yet, directly comparing digital symptom assessment systems to each other and the current "gold standard", conventional online search engines. To generate real-world-based evidence and allow direct comparison, we initiated a crossover randomized controlled multicentre trial, conducted at three rheumatology centers in Germany, where patients completed two DDSS, with different questioning approaches (Ada and Rheport), consecutively before their regular appointment (10). Furthermore, patients completed a questionnaire to assess previous online symptom assessment and DDSS perception. The results of a first interim analysis (10), focusing on diagnostic accuracy and including 164 patients from the first recruiting center suggested that the majority of patients would recommend both tools to other patients and friends, with a slight preference for Rheport (67.1 vs. 64.0%).

The aim of this analysis was to evaluate patient's previous online assessment experiences, to compare the acceptability, usability, usefulness and potential impact of artificial intelligence (AI)-based symptom checker (Ada) and an online questionnaire-based self-referral tool (Rheport) using the final dataset from all three rheumatology centers.

MATERIALS AND METHODS

Study Design and Participants

A crossover randomized controlled multicentre trial, conducted at three rheumatology centers in Germany (University hospital Erlangen, general hospital Bamberg, private practice Planegg), where adult patients newly presenting to the respective outpatient clinic with musculoskeletal symptoms and unknown diagnosis were included. All patients provided written informed consent and completed both DDSS consecutively at the respective rheumatology center on tablets (Erlangen: Apple iPads, others: Samsung Galaxy tablets) before their regular appointment, with assistance provided if necessary. The DDSS order of completion was randomized by using a computer-generated block randomization whereas each block contains $n = 100$

patients, to exclude a bias caused by previous completion of Ada/Rheport. DDSS completion time was recorded by local study personnel and perceptions on the DDSS and previous online assessment were collected through a self-completed study questionnaire following DDSS completion. Usability as a main outcome was measured using the ten-item System Usability Scale questionnaire (SUS) (14). SUS has been translated and validated in multiple languages and is one of the most established usability questionnaires (15). The SUS score ranges between 0 (worst) and 100 (best), where a score >68 should be considered above average and a score >80 as high (14). Furthermore, SUS values were translated to categories such as "excellent" using the adjective SUS rating scale as previously described by Bangor et al. (16). The questionnaire additionally captured: Time spent using online search engines (minutes), perceived helpfulness of online search and DDSS usage, using a 5-Point Likert-scale (1 = not helpful at all, 5 = very helpful); if patients would recommend the DDSS to friends and other patients (yes/no); and what potential impact DDSS would have made on their decision to see a physician and to worry. The study was approved by the ethics committee of the medical faculty of the university of Erlangen-Nürnberg, Germany (106_19 Bc) and was conducted in compliance with the Declaration of Helsinki. This trial was propspectively registered in the German Clinical Trials Register (DRKS00017642). The primary outcome of the trial, DDSS diagnostic accuracy, will be investigated separately and this study reports all secondary outcome findings, namely patient-perceived usability, acceptance and usefulness. A sample size calculation has been carried out only regarding the primary outcome. An interim analysis, including the first 164 patients from the first recruiting center (University hospital Erlangen) has been previously published (10).

Description of Diagnostic Decision Support Systems (Ada and Rheport)

Ada (www.ada.com) is an artificial intelligence and app based chatbot. The app covers a broad range of different symptoms and diseases, not being limited to rheumatology (8). More than 15 million symptom assessments have been completed with Ada in 130 countries (17) and its diagnostic accuracy is allegedly superior to other DDSS, nearly equal to general physicians (8). Users are asked for basic health information (sex, age etc.) and then for current symptoms. Depending on the answers given, further questions are asked, so that each symptom assessment is individual. The app suggestions are based on a Bayesian network, which is constantly updated (12). More detailed method descriptions involving authors from Ada can be found in previous publications (8, 12). Once symptom querying is over, a summary report is created, which can be saved as a pdf (**Supplementary Material 1**). This summary report includes a summary of (1) present, not present and unsure symptoms, (2) up to five disease suggestions including respective probability, triage advice (e.g., call an ambulance) and symptom importance and (3) basic information about the suggested diseases.

Rheport (www.rheport.de) is an online rheumatology referral system used in Germany to automatically triage appointments of new rheumatology patients according to the respective probability of an inflammatory rheumatic disease (IRD) (9, 10, 18). In contrast to Ada, Rheport is based on a fixed 23-item questionnaire and limited to rheumatic diseases. Furthermore, Rheport does not make any disease suggestions and "only" calculates the individual IRD probability, using an underlying weighted sum score. Based on the IRD probability the patient receives rheumatologist appointment proposals with varying urgency (4 levels). Total scores lower than 1 are transferred (back) to their treating general physician and do not receive rheumatology appointments. Patients with a minimum total score of 1 may book an appointment at a participating rheumatology center and the higher the total score, the earlier the appointment proposals get (total score >4= appointment within 1 week). Once the appointment is accepted, the respective rheumatologist receives a summary report of the questionnaire to guide the appointment (**Supplementary Material 2**).

Statistical Analysis

The multicentre prospective design with unequal variances of SUS may lead to heterogeneity of the data and bias the F-value when comparing means. Thus, data were analyzed using robust tests that trim 20% of scores and use a bootstrap procedure to obtain an empirically-derived critical value ($p < 0.05$) against which the test statistic is compared (19–21). The bootstrap procedure was the most effective remedy for non-normality because the critical value was empirically derived from the actual data (21).

The following statistical procedures were used:

- Descriptive statistics including means, standard deviations and quartiles. The percentile bootstrap procedure trimpb, with 2,000 bootstrap samples, was applied to compute robust confidence intervals for trimmed means (21).
- Yuen's test on trimmed means for dependent samples was carried out to calculate difference of SUS. To examine effect size, an explanatory measure of ξ which does not require equal variances and can be generalized to multiple group settings, was used. Values of $\xi = 0.10$, 0.30, and 0.50 correspond to small, medium, and large effect sizes (22).
- In order to assess within-subject effects (due to repeated measurements) and between-subjects effects (group comparisons), a robust two-way mixed ANOVA using trimmed means was applied by using bwtrim. This method provides a test value ("Q") which can be used to test null-hypotheses of main effects and interactions (21, 23). In order to conduct the analysis, the age factor was dichotomized using the median value that was detected of the whole sample.

Descriptive statistical analyses were carried out with the software SPSS 22.0. Robust statistical analyses were conducted with the software R 4.1.2 (http://cran.r-project.org) in conjunction with functions of the Wilcox' WRS, WRS2 Robust Statistics package (23).

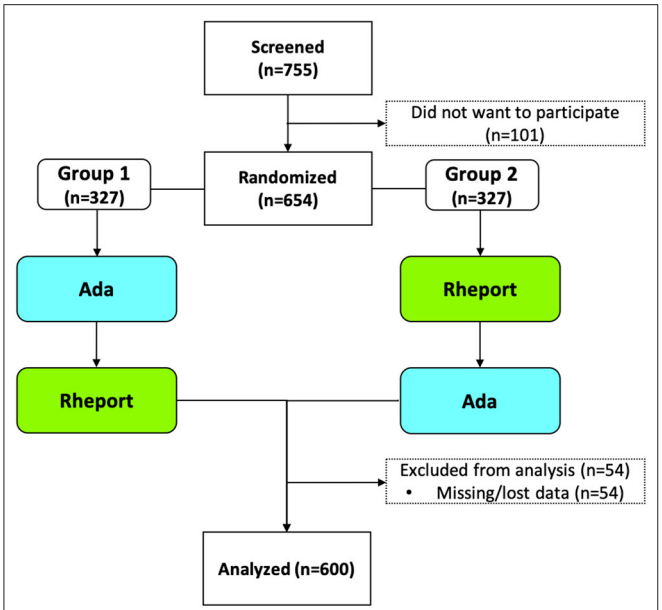

FIGURE 1 | Trial flow chart.

RESULTS

Participant Demographics

Seven hundred and fifty five consecutive patients newly presenting to three German recruiting rheumatology outpatient clinics with musculoskeletal symptoms and unknown diagnosis were approached between September 2019 and April 2021. Six hundred and fifty four agreed to participate, 54 patients were excluded due to major data missing (one of the DDSS not completed, or questionnaire not started), so that 600 patients were included into the main analysis, see **Figure 1**. The demographic characteristics are displayed in **Table 1**. Median age was 52 Years (37.0–61.0), 418/600 (69.7%) patients were female and 214/600 (35.7%) of the patients were diagnosed with an Inflammatory Rheumatic Disease (IRD) based on physician's judgment. 531/600 (88.5%) of the Patients regularly used a smartphone or tablet. 277/600 (46.2%) and 68/600 (11.3%) were using online search engines or dedicated symptom assessment websites/apps previous to their appointment.

Symptom Assessment Time and Perceived Helpfulness of Ada, Rheport and Online Search Engines

The median time (IQR) patients spent using online search engines to assess their symptoms was 180 min (120–360 min), compared to Ada with 7 min (6–10 min) and Rheport with 8 min (6–11 min). 111/275 (40.4%) patients rated the online search engine symptom assessment as very helpful or helpful, compared to 266/600 (44.3%) and 395/600 (65.8%) after having used Ada and Rheport, respectively.

TABLE 1 | Demographics according to final physician's diagnosis, reported on the discharge summary report.

Demographics	Value
Age in years, median (IQR)	52 (37.0–61.0)
Age in years, *n* (%)	
18–39	169 (28.2)
40–59	264 (44.0)
>60	167 (27.8)
Sex, female, *n* (%)	418 (69.7)
Diagnostic categories, *n* (%)	
Axial spondyloarthritis	31 (5.2)
Connective tissue disease	22 (3.7)
Crystal arthropathies	8 (1.3)
Peripheral spondyloarthritis	3 (0.5)
Polymyalgia rheumatica	16 (2.7)
Psoriatic arthritis	31 (5.2)
Rheumatoid arthritis	69 (11.5)
Undifferentiated arthritis	19 (3.2)
Vasculitis	8 (1.3)
Other IRDs	7 (1.2)
Osteoarthritis	71 (11.8)
Fibromyalgia	37 (6.2)
Other non-inflammatory	278 (46.3)
Regular usage, *n* (%)	
Smartphone and Tablet	233 (38.8)
Smartphone only	281 (46.8)
Tablet only	17 (2.8)
None	69 (11.5)
Previous digital symptom assessment, *n* (%)	
Online search engines	277 (46.2)
Dedicated symptom assessment websites / apps	68 (11.3)

IQR, inter-quartile range; IRD, inflammatory rheumatic disease.

Usability of Ada and Rheport

Bivariate Analysis

Patients rated the usability of Rheport significantly higher compared to Ada [79.3/100 vs. 76.7/100 ($p < 0.0001$)], see **Table 2**. This effect was independent of age and gender (**Supplementary Material 3**). However, this effect was small, (**Supplementary Material 4**) and converting the scores to traditional rating categories as previously described by Bangor et al. (16) results in "good" (SUS > 71.4/100 and <85.5/100) and above average (SUS > 68) (14) usability for both SUS. Older patients (>52 years) rated DDSS usability significantly ($p < 0.0001$) lower compared to younger patients (≤52 years), see (**Supplementary Material 3**). The effect of age was medium or close to medium with values of 0.35 and 0.29 for Rheport and Ada, respectively.

Multivariate Analysis

A robust two-way mixed ANOVA of usability (SUS) for the whole sample with DDSS and age as factors confirmed the effect of DDSS (**Supplementary Material 4**). Rheport was rated with a

TABLE 2 | Usability ratings of Ada and Rheport using the System Usability Scales (SUS).

	Ada		Rheport			
SUS Item	**Mean (SD)**	**Mean trimmed (95% CI)**	**Mean (SD)**	**Mean trimmed (95% CI)**	**ξ[a]**	***P*-Value[b]**
1-I think I would like to use the system frequently	1.9 (1.3)	2.0 (1.8–2.1)	2.1 (1.2)	2.2 (2.1–2.3)	**0.10**	**0.0004**
2-I found the system to be unnecessarily complex	3.1 (1.1)	3.3 (3.2–3.5)	3.2 (1.0)	3.4 (3.3–3.6)	0.05	0.0749
3-I thought the system was easy to use	3.2 (1.1)	3.6 (3.6–3.7)	3.3 (1.1)	3.7 (3.6–3.7)	0.04	0.1740
4-I think that I would need support of a technical person to be able to use the system	3.3 (1.2)	3.8 (3.8–3.9)	3.4 (1.1)	3.9 (3.8–3.9)	0.03	0.1581
5-I found the various functions in the system were well integrated	2.6 (1.1)	2.7 (2.6–2.8)	2.9 (1.0)	2.9 (2.8–3.0)	**0.11**	**0.0003**
6-I thought there was too much inconsistency in the system	2.6 (1.0)	2.5 (2.4–2.6)	2.7 (1.0)	2.7 (2.6–2.8)	0.09	**0.0009**
7-I would imagine that most people would learn to use the system very quickly	3.1 (1.1)	3.3 (3.2–3.4)	3.1 (1.1)	3.4 (3.3–3.6)	0.06	**0.0220**
8-I found the system very cumbersome to use	3.4 (1.0)	3.7 (3.7–3.8)	3.4 (0.9)	3.8 (3.7–3.8)	0.03	0.3623
9-I felt very confident using the system	3.0 (1.1)	3.3 (3.2–3.4)	3.2 (1.1)	3.5 (3.3–3.6)	**0.10**	**0.0003**
10-I needed to learn a lot of things before I could get going with the system	3.5 (1.0)	3.9 (3.9–4.0)	3.6 (0.9)	4.0 (3.9–4.0)	0.01	0.7859
Total Score (100)	74.4 (16.8)	76.7 (75.3–78.2)	77.1 (16.0)	79.3 (78.0–80.6)	**0.11**	**0.0000**

[a] *ξ, explanatory measure of effect size;* [b] *Yuen's test on trimmed means for dependent samples. Bold values indicate the at least small effect size and statistically significant.*

TABLE 3 | Usage of online assessment tools prior to visit and acceptance of DDSS according to respective age groups and in comparison to previous studies.

Age group	**Used online search engines previous to appointment (*N* = 600)**	**Used dedicated symptom assessment website/app previous to appointment (*N* = 600)**	**Healthwatch Enfield (24); "would use a symptom checker before seeking advice from GP" (*N* = 1,071)[a]**	**Miller et al. (12); "Extremely Likely/Likely to recommend Ada to a friend or relative" (*N* = 447)**	**would recommend Ada to a friend or other patient (*N* = 600)**	**would recommend Rheport to a friend or other patient (*N* = 600)**
18–24, *n/N* (%)	23/36 (63.9)	4/36 (11.1)	(74)	50/54 (92.6)	24/36 (66.7)	29/36 (80.6)
25–39 *n/N* (%)	78/133 (58.6)	17/133 (12.8)	(71)	125/147 (85.0)	95/133 (71.4)	98/133 (73.7)
40–54, *n/N* (%)	90/183 (49.2)	28/183 (15.3)	(69)	121/141 (85.8)	134/183 (73.2)	146/183 (79.8)
55–69, *n/N* (%)	82/194 (42.3)	15/194 (7.7)	(51)	64/72 (88.9)	144/194 (74.2)	156/194 (80.4)
70+, *n/N* (%)	4/54 (7.4)	4/54 (7.4)	(34)	25/33 (75.8)	43/54 (79.6)	46/54 (85.2)

[a] *n/N values are missing and only percentage is reported.*

higher total SUS score ($Q = 22.7$; $p < 0.0001$). In this analysis, we confirmed the significant effect of age ($Q = 32.7$; $p < 0.0001$) resulting in lower usability rating for older patients. There was not any significant interaction between effects of age and DDSS ($Q = 1.1$; $p = 0.31$).

However, if the analysis was conducted separately for each gender, the results were different. In the male subsample, the effects of DDSS ($Q = 5.4$; $p = 0.02$) and age ($Q = 8.3$; $p = 0.005$) as well as age by DDSS interactions ($Q = 1.1$; $p = 0.31$) were comparable to those described for the whole sample. In the female subsample, the effects of DDSS and age were both highly significant ($Q = 14.7$; $p = 0.0002$, $Q = 23.8$; $p < 0.0001$, respectively), but the effect of DDSS on usability ratings was different for younger patients than it was for older participants ($Q = 7.9$; $p = 0.005$), suggesting that younger women (<52 years) showed greater usability rating differences between Ada and Rheport.

Acceptability of Ada and Rheport

440/600 (73.3%) and 475/600 (79.2%) of the patients would recommend Ada and Rheport to friends and other patients, respectively. For both DDSS, a higher proportion of older patients (≥55 years) compared to younger patients (≥18–39 years) recommended the DDSS to friends and other patients (**Table 3**).

Potential Impact of Ada and Rheport

482/600 (80.3%) and 506/600 (84.3%) of the patients declared that they would not have done anything differently after having used Ada and Rheport, respectively, see **Table 4**. 68/600 (11.3%) and 61/600 (10.2%) stated that they would have consulted a physician earlier, whereas 7/600 (1.2%) and 6/600 (1.0%) stated that they would have consulted a physician later, having used Ada and Rheport, respectively. 17/600 (2.8%) and 14/600 (2.3%) would have worried less and 12/600 (2.0%) and 7/600 (1.2%)

TABLE 4 | Self-reported potential effects of diagnostic decision support system assessments[a].

Would you have done anything different having used the DDSS? *n* (%)		
	Ada	**Rheport**
No, nothing	482 (80.3)	506 (84.3)
Yes, seek a physician appointment earlier	68 (11.3)	61 (10.2)
Yes, seek a physician appointment later	7 (1.2)	6 (1.0)
Yes, seek no physician appointment at all	0 (0.0)	0 (0.0)
Yes, seek an appointment with a physician with a different specialty	11 (1.8)	5 (0.8)
Yes, worry less	17 (2.8)	14 (2.3)
Yes, worry more	12 (2.0)	7 (1.2)
Missing values	*3 (0.5)*	*1 (0.2)*

[a]*Answers were not mutually exclusive.*

would have worried more after having used Ada and Rheport, respectively. 526/600 (87.7%) patients would like to be able to choose an appointment directly from a list of qualified doctors in the surrounding area at the end of the symptom assessment.

DISCUSSION

To our knowledge this is the first and largest study directly comparing the patient perceived acceptability, usability and usage time of two digital symptom assessment systems including an artificial intelligence and chatbot-based symptom checker (Ada) and an online questionnaire-based self-referral tool (Rheport). Additionally, patient perceived helpfulness and usage time of these two DDSS was put in perspective, by comparison to previous conventional online search engine usage (if performed by patients previous to the appointment) and the potential impact of DDSS usage was investigated.

In line with previous studies (2, 3, 6, 7), our study showed that a significant proportion of patients consulting rheumatology services assessed their symptoms online prior to their appointment (46%). The proportion of patients using online search engines prior to their visit decreased with age (**Table 3**). One reason for this might be the decreasing eHealth literacy with age (3), with older patients not feeling confident looking for health-related information online.

In contrast to online search engines, only a minority used dedicated symptom assessment websites/apps (46 vs. 11%). In general, patients spent more time assessing symptoms online using search engines compared to the usage time of both DDSS (180 vs. 7/8 min). On the other hand, more patients stated that DDSS usage was helpful/very helpful compared to using search engines (44/66 vs. 40%), suggesting that using DDSS instead of conventional online search engines could save time and increase helpfulness.

In a recent online survey study Kernder et al. (2) could show that the COVID pandemic lead to an increased usage of symptom checkers by rheumatic patients and rheumatologists. 40.5% (121/299) of rheumatic patients stated that they already used a symptom checker, however this larger proportion of patients (40.5 vs. 11.3%) is probably due to the selection bias due to the online nature of survey study, suggesting that digitally active patients are more likely to use DDSS. In line with this, our study shows that with increasing age the proportion of patients having used online search engines or dedicated symptom assessment website/app previous to their appointment is steadily declining (**Table 3**).

Overall, 79 vs. 73% of the patients would recommend Rheport and Ada to friends and other patients, respectively. The preference for Rheport compared to Ada was largest in the youngest age group (80 vs. 67%) and particularly in female patients. Furthermore, we observed a higher symptom checker recommendation rate in older patients compared to younger patients, in contrast to previous studies (12, 24) (**Table 3**). Similarly, the usability (SUS) of questionnaire-based Rheport was rated significantly higher compared to AI-based Ada (77.1/100 vs. 74.4/100). However, the effect was weak ("small effect" with values from 0.10 to 0.29 in the bivariate analysis), which can be attributed to the large sample size. Translating these numeric results to categories, the usability of both DDSS was "good."

Similar to a previous observational study analyzing the potential impact of Ada (12), the majority of patients (already being at the healthcare facility) declared that they would not have done anything differently after having used the DDSS. In line with previous work that showed a general risk adversity of symptom checkers (4, 11), our results shows that DDSS suggestions would actually encourage patients to seek earlier care rather than turn to self-care or see a physician later. On the other hand, Meyer et al. (13) reported that 14/26 (54%) of symptom checkers users given advice to proceed to the ED actually did.

The large majority of patients would welcome the option to book an appointment directly from a list of qualified doctors in the surrounding area at the end of the symptom assessment. This feature is already implemented in Rheport. The AI-based Isabel symptom checker, for example also offers users to contact a doctor and "find a lab test" after symptom assessment (13).

A strength of this study is the large sample of patients, usage of a validated instrument to measure usability and the study's real-world nature. Furthermore, the fact that the same patient provided feedback on two DDSS and their previous online symptom assessment is a major strength of the study. The study also has several limitations. Although this study included three centers, the findings are limited to one country and patients referred to rheumatology services. Since the robust mixed ANOVA is actually limited to two-way design, the gender factor was not included in the calculation and the analysis was conducted separately for the male and female subsamples. We did not measure in how many cases patients needed help to use the DDSS, and we only asked patients about the "theoretical" impact of using the DDSS. As patients often used online search engines months before the appointment, this data is subject to recall bias and should be interpreted carefully. Furthermore, we did not differentiate between various available online search engines. No separate power calculation was carried out for the evaluation of the secondary outcomes investigated in this study. The risk-adverse setting, "where patients continue to receive standard care" was intentionally chosen as recommended by Fraser et al. (25). Furthermore, we did not assess the (e)health literacy of participants.

This study suggests that the majority of patients find both DDSS helpful and easy to use. From a physician perspective, the possibility to obtain a structured summary of the patient medical history, ready to guide the appointment and to be imported into the electronic health record appeals time saving and helpful as well. However, due to Ada's variable questioning approach, determining new questions on all previously supplied basic health information, Ada bears the risk of leaving out important questions compared to a fixed-questionnaire approach (Rheport). Whereas, Rheport uses pictures of typical symptoms (swollen joints), Ada does not. Pictures might aid to specify definitions to reduce interpretation differences of symptoms (26). Although we did not specifically ask patients about this difference, that could have at least partially have contributed to the better perception of Rheport by patients. Future qualitative research could complement the present findings by adding detailed reasons for the observed rating differences. Furthermore, a physician-based study could evaluate the time-saving potential and perceived helpfulness of DDSS.

CONCLUSION

Patients increasingly assess their symptoms independently online, however only a minority used dedicated symptom assessment websites or diagnostic decision support systems. DDSS are easy to use, well accepted among patients with musculoskeletal complaints and could replace online search engines for patient symptom assessment saving time and increasing helpfulness.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of the Medical Faculty of the University of Erlangen-Nürnberg, Germany. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JK, AH, GS, PB-B, WV, and MW: conceptualization. JK, DS, AK, SB, CB, and HL: methodology. FFu, JM, WV, MW, PB-B, and JK: software. JK, FFu, JM, FM, HM, YI, NV, MW, and AH: formal analysis. JK, FFu, HM, and JM: data curation. JK and FM: writing—original draft preparation. JK, FM, FFa, NV, YI, AH, and MW: writing—review and editing. JK: visualization. GS, AR, and JD: supervision. JK, MW, and AH: funding acquisition. All authors have read and agreed to the published version of the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.844669/full#supplementary-material

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METHODS
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Building Bridges for "Palliative Care-in-Place": Development of a mHealth Intervention for Informal Home Care

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Background: In Palliative Care (PC), family and close people are an essential part of provision of care. They assume highly complex tasks for which they are not prepared, with considerable physical, psychological, social and economic impact. Informal Caregivers (ICs) often falter in the final stage of life and develop distress, enhancing emotional burden and complicated grief. The lack of available and accessible in-person counselling resources is often reported by ICs. Online resources can promote early access to help and support for patient-IC dyads in palliative care. The primary aim of this research is to co-design, develop and test the feasibility of the Help2Care-PAL mHealth app that addresses the needs of ICs of palliative patients cared for at home. This Digital Health Intervention (DHI) in palliative care will be used for education, symptom management, communication and decision-making, to enhance Quality of Life (QoL) of patients and ICs, fostering anticipatory grief and the reach and efficiency of services.

Methods: This study will use an iterative co-design process and convergent mixed-methods design, following the MORECare consensus for developing a complex intervention. Construction of the DHI will follow four main phases: (I) a needs assessment (a cross-sectional survey, individual interviews with ICs and focus groups with professionals with community palliative care experience); (II) design and co-production of mHealth materials and interventions to support ICs; (III) the development of a mHealth app; and (IV) usability and feasibility of the mHealth app. The Help2Care-PAL platform seeks to build resources from the perspectives and needs of both family dyads and nursing professionals working in the field of community palliative care. User-centeredness will be ensured by the active participation of patient-IC dyads and professionals of the palliative care community.

Discussion: This mixed-method study will offer new insights on needs and expectations of patient-IC dyads and nurses in community palliative care regarding caregiving preparedness and online health resources. Through the implementation of an adaptive digital tool, we aim to improve access to palliative care family support, which is highly linked with the wellbeing of patients and especially new ICs.

Keywords: selfcare, chronic disease, mHealth, technology, palliative care, caregivers, communication

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INTRODUCTION

Community Palliative Care Services provide access to expert support by Healthcare Professionals (HCPs) for patients facing a life-threatening condition, irrespective of diagnosis, in all community care settings. The service teams comprise professionals with Specialist Palliative Care Competencies (National Hospice and Palliative Care Organization, 2021). In addition to clinical caseload, within agreed boundaries and protocols, these teams provide education and therapy, and perform consultancy services and research. Their strategies include 'symptom management, medication management, family support and training, advance care planning and goals of care facilitation, caregiver respite, and interventions for emotional and spiritual needs of patients and family' (Portz et al., 2020, p. 22).

The United Nations Sustainable Development 2030 Agenda (United Nations, 2015) set the goals of 'modern and effective care for all [and] conditions for all people to attain their fundamental rights to health and well-being' (Widberg et al., 2020, p. 2). Moreover, improving access to and quality of palliative care delivery is a healthcare priority in many countries. Information technologies, in particular, can help promote access to health information and care, particularly palliative care (Finucane et al., 2021). For instance, telehealth is an alternative form of palliative care delivery, which allows patients to spend more time or even remain at home, if they wish, throughout their illness (Steindal et al., 2021). However, Digital Health Interventions (DHIs) in palliative care must consider the patient's overall needs and preferences, while fostering a relationship that promotes dignity and is focused on the patient and caregiver's values and goals (Widberg et al., 2020).

Digital health, or eHealth, refers to applications of Information and Communication Technologies (ICTs) to all aspects of patient care and health services, including patient self-management, and encompasses a range of related concepts, such as 'telemedicine and telehealth, mobile health (mHealth), health informatics, and wearable devices' (Finucane et al., 2021, p. 1; Steindal et al., 2021). Digital resources are already part of routine healthcare practice in many countries, from simply maintaining electronic health records and using decision support software to using videoconferencing to remotely interact with patients. Mobile phones, apps, wearables and social media are already widely used by citizens/patients, and new technologies—such as 'augmented reality, virtual assistants, and artificial intelligence'—are increasingly applied in clinical management and patient self-care. As they become more affordable and widespread, these technologies are reshaping healthcare (Finucane et al., 2021, p. 1).

Palliative care is one area where these technologies are increasingly being deployed. Various eHealth applications enable patients to participate in and govern their own care, for example by self-reporting symptoms and needs (Cooley et al., 2017; Guo et al., 2017; Pinto et al., 2017; Vitacca et al., 2019; Finucane et al., 2021). The possibility of sending text messages to HCPs, for example, to give notice that medication needed refilling, is perceived by patients as a well-functioning alternative for traditional oral and synchronous communication. Using validated instruments, patients can provide HCPs with information, using eHealth technology, on physical, mental, social and existential symptoms, as well as Quality of Life (QoL), which can then be used to make care and treatment decisions (Hennemann-Krause et al., 2015; Tieman et al., 2016; Cooley et al., 2017; Pinto et al., 2017; Bonsignore et al., 2018; Vitacca et al., 2019). By enabling informal home care, eHealth technology can help ICs maintain their social relationships and contacts during their daily life. Participation in social contexts, in caring and supportive situations, despite troublesome symptoms and severe illness, provides a positive connection to life and loved ones. Furthermore, by enhancing the skills and psychological wellbeing of ICs, these technologies contribute towards improving the QoL, digital literacy and social inclusion of the care receiver (Widberg et al., 2020; Gomes et al., 2021).

As in other European countries, care for palliative patients in Portugal relies on ICs. However, due to financial hardships aggravated by the COVID-19 sanitary crisis, most family carers cannot provide care for their relatives (Parmar et al., 2021). Families often rely on the help of commodified care, benefiting from solutions proposed by social security services (Brito, 2019). There has also been an expansion of the private sector in end-of-life care. While this means more people might have access to palliative care, it also implies increased inequality (Gomes et al., 2020). To respect IC preferences for providing care at home, it is necessary to develop quality home-based palliative care services, focusing on training and the expansion of field teams. Despite this preference, home care for patients with palliative needs increases caregiving burden which usually increases as the patient's condition declines (Guerriere et al., 2016; Ahn et al., 2020). An estimated 10–60% of caregivers experience negative psychological and physical consequences, including anxiety, depression, grief and poor physical health (Ahn et al., 2020). These results highlight the importance of care for caregivers wishing to support death at home.

The rising need for palliative care services in Portugal, combined with the increasing use of DHIs in healthcare, calls for studies on how to adequately design such online resources. Although mHealth palliative care apps are available, these early apps did not offer family caregiving tools (Portz et al., 2020). Disease-specific apps are often too limited, as palliative care patients often have more than one condition. Moreover, current mHealth apps for palliative care do not offer comprehensive tools for coping with bereavement and grief, proving most useful early in the bereavement process (i.e., soon after the death of a loved one; Portz et al., 2020). While grief occurs throughout the course of serious illness (anticipatory grief; Nielsen et al., 2016), most apps are tailored for coping with bereavement after patient death. A recent review indicates that there are few commercial apps specifically for caregiving (Portz et al., 2020) and little usability evidence on caregiver apps (Grossman et al., 2018; Quinn et al., 2019).

Therefore, this study will generate a DHI that can be used by caregivers of palliative patients living in remote communities of Portugal. Despite long distances, patients could receive care through eHealth applications, in an accessible manner, without spending time or money on travel (Melton et al., 2017; Widberg et al., 2020). The Help2Care-PAL's purpose is to boost and

sustain the role of ICs in making the 'palliative care-in-place' imperative a sustainable reality in rural and remote areas. Furthermore, and compared with other digital solutions, this DHI will enable tailored care (specific information) according to patient and family needs, monitored and prepared by a health professional. All the information presented to the caregiver is validated by a professional, guaranteeing the carer does not get the wrong information (Gomes et al., 2021).

Theoretical Framework

The guidelines from the National Consensus Project (NCP) for Quality Palliative Care offer an opportunity to reassess the domains of care delivered at home, such as physical, psychological, social or spiritual aspects of care. Anderson et al. (2018) attributes particular importance to the family/caregiver domain. In this study, families described their role as care managers, but also reflected upon their families and personal transformations resulting from caregiving. The same authors considered two additional domains—financial/legal and legacy/bereavement—that reflect concerns about the preservation of assets and life transitions, respectively.

In addition, Social Convoy Theory (Antonucci et al., 2014) conceptualises social relations as a convoy that includes informal support from family members, friends and neighbours and formal supports such as professional caregivers. This model provides a framework for the complex relationships between individuals that give and receive social support. Social convoys have been shown to improve health outcomes and QoL among patients with serious illness, and reduce mortality in older populations (Portz et al., 2020). Palliative care should also follow a team-based approach with continuous reciprocal information flow between patients and care providers, rather than exclusive dissemination from one party (Portz et al., 2020).

Despite the evidence indicating social support as a critical construct in improving health behaviours and health outcomes, mHealth platforms are designed for individual users and usually do not integrate the patient's family, friends and professional support to maximise benefit (Portz et al., 2020).

Aim and Research Questions

The primary aim of the study is to co-design, develop and test the feasibility of a novel mHealth app that addresses the needs of ICs of palliative patients who are cared for at home. This study aims to contribute towards preparedness for end-of-life care and reducing potential negative effects for ICs. The following specific research questions will be addressed as:

a. What is the preparedness of ICs when facing the care of people with palliative needs?
b. How can a mHealth app be tailored to address the needs of carers regarding palliative care management?
c. How can a mHealth app be used effectively by ICs to learn and receive support in their caregiving role?

DESIGN

This study will use an iterative co-design process and convergent mixed-methods design, which 'involves simultaneously collecting and analysing qualitative and quantitative data and, as critically important, taking into consideration the iterative nature of mHealth technology development' (Alwashmi et al., 2019, p. 5). Additionally, we will follow the MOREC are consensus for developing a complex intervention in PC (Farquhar et al., 2013). Complex interactions between the intervention and its context determine and shape whether and how outcomes are generated (Skivington et al., 2021). Based on prior work of Rathnayake et al. (2018), this flexible approach will promote a comprehensive understanding of the phenomenon of interest, matching the design and evaluation of a multi-phase complex intervention.

mHealth Development

The DHI will be constructed in four main phases, implemented between April 2022 and December 2022, in Portugal. The research team has experience in both qualitative and quantitative research and holds advanced degrees in nursing (CL, AQ and MD) and software engineering (RM and RR).

The four phases are (I) a needs assessment; (II) design and co-production of mHealth materials and interventions to support ICs; (III) the development of a mHealth app; and (IV) usability and feasibility of the mHealth app (see **Figure 1**).

Phase I (Needs Assessment)

Phase I (needs assessment) will involve the identification of the target audience's needs through a cross-sectional survey, individual interviews with ICs and focus groups with professional experts with community palliative care experience. As much as possible, this phase will integrate the attitudes and knowledge of all potential users in the development of training materials and the design of the DHI.

a. The cross-sectional survey (including online or phone-based questionnaire) will assess the needs of ICs in their caregiving functions and the use of mHealth apps in health-seeking behaviours (Rathnayake et al., 2018). The participating ICs living in the community will be adults, unpaid primary carers, that provide informal care at home. Sample recruitment will be based on nationally representative data, based on the service list of the community support teams in palliative care from the Portuguese Observatory of Palliative Care. The surveys will draw from a random stratified sample of ICs based on gender, age range and geographical location. According to the Portuguese Strategic Plan for the Development of Palliative Care (2019-2020 biennium; Diário da República Portuguesa, 2019), there are an estimated 90,000 Portuguese people in need of palliative care, and 54 community support teams in palliative care with a regional coverage. To obtain enough data with a margin error of 5%, and a confidence level of 95%, we plan to recruit at least 400 ICs. A structured questionnaire divided into five sections will be used for data collection. The section "Introduction" will collect sociodemographic information of the caregiver and health condition of the care recipient, including the (i) Edmonton Symptom Assessment Scale (Chang et al., 2000) to rate the intensity of common symptoms

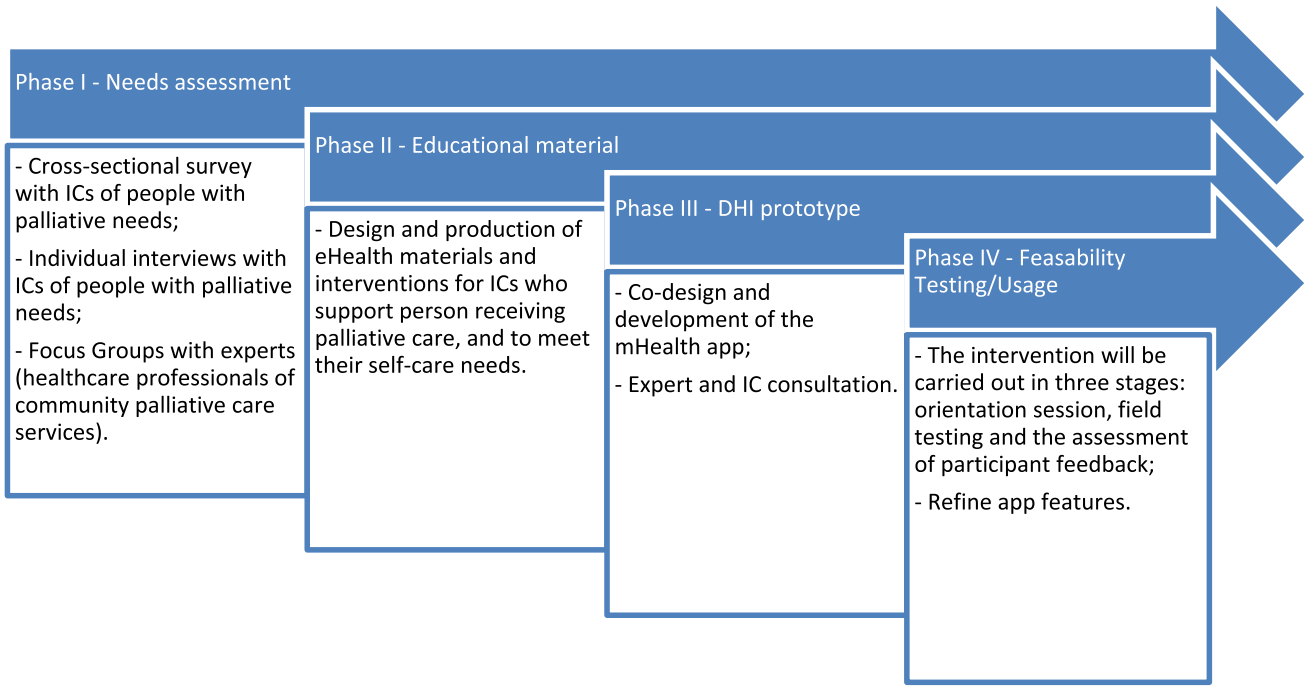

FIGURE 1 | mHealth app development process.

experienced by palliative patients and the (ii) Performance Palliative Scale (PPS) to estimate the survival time of palliative patients (Victoria Hospice Society, 2016). In section "Design", the health literacy level of carers will be assessed with three self-reported questions proposed by Chew et al. (2004), which show high specificity for detecting inadequate health literacy (Chew et al., 2004). Questions are answered using a five-point Likert scale (never-1 to always-5). Higher scores indicate a lower level of health literacy (Levin et al., 2014). In section "Ethical Considerations", the needs of the patient's family will access with Family Inventory of Needs (Kristjanson et al., 1995) validated in Portugal by Areia et al. (2016a). This instrument has 40 items and quantifies two concepts: the importance of family care needs and fulfilment of care needs. Regarding to internal consistency, a high Cronbach's alpha coefficient was obtained for the Importance of Needs subscale ($\alpha = 0.89$) and for the Needs Satisfaction subscale ($\alpha = 0.91$). Section "Dissemination Strategies" will assess the Caregiver Burden Scale, which was based on Zarit's Burden Interview Scale, and has been translated and validated in Portugal by Sequeira (2010). This scale assesses the objective and subjective burden of informal care and collects information on health, social life, personal life, financial situation, emotional situation and type of relationship. The instrument contains 22 items rated on a 5-point Likert scale ranging from 1 (never) to 5 (almost always), whereby the total score ranges between 22 and 100, with higher scores indicating a greater burden. A score of 56 or more was considered a high burden. This scale boasted an internal consistency of $\alpha = 0.82$. In section "Discussion", the pre-death grief will be assessed by the Marwit-Meuser Caregiver Grief Inventory Short-Form (MM-CGI-SF; Marwit and Meuser, 2005), validated in Portugal by Areia et al. (2016b). This form has 18 items rated on a 5-point Likert scale, thus a maximum score of 90. Before patient death, caregiver responses to perceived losses may include anticipation of future loss following physical death and mourning of present loss due to psychological death (Liew et al., 2018). The MM-CGI-SF had a good internal consistency ($\alpha = 0.89$).

b. Qualitative data collection using individual in-depth interviews with ICs of people with palliative needs (in-person or telephone/videoconference interviews) will explore perceived preparedness for different domains of caregiving, including communication with relatives and considerations about the IC's future, including bio-psycho-social-cultural and spiritual issues. Educational needs may include medical issues, such as symptoms and symptom relief; planning for the moment of death; and tracking IC's burden and risk of complicated grief. Interviews will investigate IC perspectives and challenges when caring at home and using mHealth apps in health-seeking behaviours (Rathnayake et al., 2021). Three broad questions will be used to stimulate conversation, 'Please, describe your preparedness to provide informal palliative home care'; 'What are the activities you find more difficult to perform for your care recipient?'; and 'Do you think a smartphone app would be helpful for you to manage the daily activities?', followed by further follow-up questions, depending on answers provided previously. Sociodemographic variables such as age, gender and education level will also be collected. Overall information will be used to design

the content and features of the proposed mHealth app. Participants from the cross-sectional survey who consent will be invited to participate in a qualitative interview. A purposive, maximum-variation sampling technique will be adopted to recruit 12 ICs. Each interview session will last for about 40–60 min and will be recorded digitally.

c. Qualitative data collection through virtual Focus Groups (FG) with professional experts in palliative care. FGs are suitable for eliciting attitudes, expectations and emotional arguments during the interactive group process (Richard et al., 2021). In line with the study of Rathnayake et al. (2018), the semi-structured interviews will collect expert opinions regarding the provision of palliative care (especially management of care) and about mHealth app for carers, including knowledge of existing smartphone-based interventions, attitudes towards mHealth educational interventions and possible constraints and challenges towards the development of a mHealth app. The interview guide will include some open-ended questions (e.g., 'What are the main difficulties you face when managing/planning daily activities for people with palliative needs?', 'What are your perceptions about mHealth apps as an educational and supportive resource for ICs?', 'What do you think are the most important smartphone features (for examples text, video, alert functions, calendar scheduling etc.) that should be included in a mHealth app for daily living activities?' and 'What are the potential difficulties and concerns associated with the development of a mHealth app for ICs?'). A convenience sampling method will be used to recruit 20 experts, including HCPs (e.g., nurses, therapists, social workers, physicians and psychologists) who work in a community support team and have three or more years of experience in palliative care. Two independent online FG sessions will be conducted with no more than ten participants per group. Each FG will last for approximately 60 min and will be moderated by one palliative care nurse and a software engineer with experience in apps development. All FG sessions will be digitally recorded.

Descriptive and inferential statistics will be used to analyse the sample data of ICs and of experts who participate in survey and interviews. All statistical analyses will be conducted using SPSS v.28 (IBM). In qualitative data analysis, audio files will be transcribed verbatim. Transcripts will be analysed using WebQDA® software. Thematic analysis will be conducted to identify the conceptual map of the core themes resulting from the interviews (Braun and Clarke, 2006). Themes will be inferred inductively by one researcher and discussed with the research team.

Phase II (Educational Material)

Phase II (educational material) includes the design and production of eHealth materials and interventions to support ICs. Data from phase I will inform the content of these materials and interventions. In this phase, an iterative co-design process (Rathnayake et al., 2018, 2021) will generate the educational material in the form of images, texts and audio/video that allow the IC to respond to the care of their family member and meet their self-care needs. The educational material, in Portuguese, will be presented at the Help2Care-PAL website, through videos and informative texts. To increase caregiving preparedness, the videos will show conversations, between ICs (played by actors) and different professionals (authentic), addressing intervention topics. The informative texts will deepen and broaden the topics raised in the videos. As a part of the intervention, the website will also host an online peer-support discussion forum, which can be used by ICs to communicate with others in a similar situation (Alvariza et al., 2020).

Phase III (DHI Prototype)

Phase III (DHI prototype) comprises the co-design and development of the mHealth app (Help2Care-PAL) to provide access to appropriate training materials, evaluate caregiver knowledge about these materials and collect feedback about their use, so that materials can be reviewed when necessary, offering a greater learning capacity and improved caring skills, especially for new ICs (Gomes et al., 2021). The health literacy concepts proposed by Broderick et al. (2014 cited in Rathnayake et al., 2018)—such as 'write actionable content', 'display content clearly', 'organize and simplify' and 'engage users'—will be incorporated. The web application will help manage users (administrators, health professionals and caregivers), patient needs and training materials. Among other features, questionnaires can be used to verify whether caregivers or self-care patients can perform a certain task or use a specific material (Gomes et al., 2021). Through the mobile application, the health professional will be able to provide the caregiver with training materials, according to patient needs. Besides, 'the caregiver will be able to communicate with the health professional, in case of doubts about their tasks' (Gomes et al., 2021, p. 222).

According to Portz et al. (2020, p. 28), specific palliative care issues typically not addressed by apps include care roles (e.g., defining and providing education on roles), skills and coping (e.g., time management, stress reduction, or anticipatory grief), and communication (e.g., planning family meetings, conflict resolution, or assertiveness training)'. Therefore, the DHI prototype will cover five main topics: (1) holistic approach to palliative symptom management; (2) preparedness for caring during dying process; (3) dealing with anticipatory grief; (4) feeling connected and supported; (5) valuing oneself as a caregiver and an individual; and (6) maintaining control of the caring situation and coordinating care (see **Table 1**).

Expert consultation will review content for readability. In this phase, six elements will be invited as: three experts from the expert consultation and three ICs who participated in the qualitative interview. The prototype content will be assessed for appropriateness and clarity. Experts will rate module content based on a 4-point Likert scale, from strongly agree (1) to strongly disagree (4). A Content Validity Index (CVI) greater than 0.80 will be considered adequate (Polit et al., 2007). If their rating is worse than 'agree', they will be asked to share their ideas for improvement. After this step, the prototype will

TABLE 1 | The content of the mhealth application.

Holistic approach to palliative symptom management	Overview of palliative care
	Overview of the illness trajectory and palliative care
	Pharmacological and non-pharmacological measures for symptom relief
Preparedness for caring during dying process	Reflection on the "road map" of the dying process and how to accompaing the patient in his/her journey
	Practice of gratitude, forgiveness and spirituality
	Management of daily living activities (ex-feeding/ nutrition; medication management; oral care; bathing; continence care; etc.)
	Dignity, last wishes fullfimlent and legacy
Dealing with anticipatory grief	Antecipatory grief symptoms
	Antecipatory grief stages
	Redefine hope and focus on quality of life
Feeling connected and supported	Peer support and carer support network
	Patient death and death rituals
	Advocate for better end-of-life care for everyone
Valuing oneself as a caregiver and an individual	Stress management
	Positive mental health strategies
	Self-care strategies
Maintaining control of the caring situation and coordinating care	Support services available
	Calendar planning and task reminders
	Connection to oneself and information sharing with the palliative care team

be concluded, and the software engineers will design the app. The app will be developed for both iOS and Android Operating Systems by computer science students undertaking a master's degree in Computer Science, under supervision by an experienced software engineer.

Phase IV: Usability and Feasibility of mHealth Application

The feasibility study will include user testing, specifically field testing in a real-world setting to assess user experience with the app (Rathnayake et al., 2018). Unlike statistical null hypothesis testing, feasibility studies do not require large sample sizes (Tickle-Degnen, 2013; Rathnayake et al., 2018). The sample size will be eight ICs of people with palliative needs, living in the Alentejo Region (Portugal) and having Internet access. Participants will be recruited through qualitative interviews, where they provide information about their digital skills. Participants unconfident in these skills will receive training. All participants will be given access to the app and a researcher will demonstrate how to use it. Participants will record the frequency of usage, challenges and constraints faced when using the app (Rathnayake et al., 2018).

After the 4 weeks of field testing, a phone survey will be performed to receive feedback from users. Direct observation of user testing will be adopted to perform the usability tests (Nielsen, 1994). Here, users will be asked to perform a pre-defined number of tasks in the app, thus providing statistical data about time of execution, number of erroneous interactions (e.g., wrong clicks) and rate of successful completion.

The quality of the mHealth app will be assessed by the Mobile App Rating Scale (uMARS; Stoyanov et al., 2015, 2016). This 20-item scale, rated on a 5-point scale from (1-Inadequate to 5-Excellent), includes five quality subscales: engagement, functionality, aesthetics, information and subjective quality. User satisfaction with the app will also be evaluated by one self-assessment question: 'How do you rate your satisfaction with this app?' based on a 5-point scale from very satisfied to very dissatisfied (Rathnayake et al., 2018).

ETHICAL CONSIDERATIONS

Ethical approval was obtained from the Unidade Local de Saúde—Baixo Alentejo and from the Polytechnic of Leiria. Participants will be assured that all information will be confidential and anonymous that participation is voluntary and may be suspended at any stage without penalty. Informed consent will be sought for each stage. Volunteers will receive no compensation for their participation. Coded information will be used in data management as a measure of privacy protection.

Data will be kept secure and confidential, according to institutional rules for data storage. The consent forms, data collection forms and verbatim transcripts will be kept for 10 years.

DISSEMINATION STRATEGIES

The main results will be disseminated on relevant social media and websites and through short reports to participating entities and stakeholders. Scholarly papers will also be submitted to relevant peer-reviewed publications. Additionally, public presentations will be delivered to relevant national and international conferences.

DISCUSSION

eHealth applications can provide palliative patient-IC dyads with access to convenient information and support contacts, thus empowering them to participate and govern their self-care, and enhancing their sense of security. 'At organizational and societal levels, eHealth may contribute to sustainable development and more efficient use of resources in palliative care' (Widberg et al., 2020, p. 12). eHealth should complement face-to-face meetings and not replace physical meetings. 'Human contact and human interactions are inherent to nursing, and relationships between patients and HCPs are important in palliative care'. Nonetheless, the tentative positive experiences of eHealth applications should not be discarded, namely, in our present uncertain time (Widberg et al., 2020, p. 11).

This proposed DHI will guide the development and testing of an educational and capacitating mHealth app for ICs of people with palliative needs, and generate knowledge contributing to health improvement (Skivington et al., 2021). The overall development method will be conducted throughout four phases, wherein ICs, nursing professionals and researchers will

be involved in software requirements elicitation, prototype validation, software development, testing and operation.

For each phase, specific validation/testing initiatives will be carried out to assess the effectiveness of this proposed mHealth app. The whole DHI will be performed under an incremental and iterative (agile) approach that foresees the execution and testing of phases, as well as the necessary adjustments to any of the main deliverables for each phase.

By integrating health literacy elements, we expect that this app will also aid groups with lower levels of health literacy. The developed mHealth app may help reduce carer burden and improve the wellbeing and QoL of care recipients (Rathnayake et al., 2018).

Potential limitations of this protocol should also be noted. Technology literacy and technical issues with the mHealth tools can pose challenges to this study. To address this, we will provide a one-day technology literacy workshop on basic skills with using mobile devices and mHealth tools. By only including participants with access to mobile telephones, 'there is a risk of social injustice by focusing on a select demographic with comparably better access to resources, sometimes referred to as the digital divide' (Rossing et al., 2016, p. 6). However, we have attempted to address this issue by defining mobile phone access in the widest meaning feasible. Given the limitation of study resources, initially the mHealth app will only be available in Portuguese, thereby excluding participants unable to read Portuguese. Lastly, this study will not determine the effectiveness of Help2Care-PAL, as this will be the focus of a further study.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by ULS-Baixo Alentejo and Polytechnic of Leiria. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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STUDY PROTOCOL
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A Clinical Decision Support System for Remote Monitoring of Cardiovascular Disease Patients: A Clinical Study Protocol

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Introduction: Cardiovascular diseases (CVD) are the leading cause of death globally, taking an estimated 17. 9 million lives each year. Cardiac rehabilitation is shown to reduce mortality and hospital readmissions, while improving physical fitness and quality of life. Despite the recommendations and proven benefits, acceptance and adherence remain low. Mobile health (mHealth) solutions may contribute to more personalized and tailored patient recommendations according to their specific needs. This study protocol aims to assess the effectiveness of a user-friendly, comprehensive Clinical Decision Support System (CDSS) for remote patient monitoring of CVD patients, primarily on the reduction of recurrent cardiovascular events.

Methods and Analysis: The study will follow a multicenter randomized controlled design involving two cardiology units in the Center Region of Portugal. Prospective CVD patients will be approached by the healthcare staff at each unit and checked for eligibility according to the predefined inclusion/exclusion criteria. The CDSS will suggest a monitoring plan for the patient, will advise the mHealth tools (apps and wearables) adapted to patient needs, and will collect data. The clinical study will start in January 2023.

Discussion: The success of the mHeart.4U intervention will be a step toward the use of technological interfaces as an integrating part of CR programs.

Ethics and Dissemination: The study will undergo ethical revision by the Ethics Board of the two hospital units where the study will unfold. The study was registered in ClinicalTrials.gov on 18th January 2022 with the number NCT05196802. The study findings will be published in international peer-reviewed scientific journals and encounters and in a user-friendly manner to the society.

Keywords: mHealth, cardiac rehabilitation, self-management, personalized care, clinical study

INTRODUCTION

Cardiovascular diseases (CVD) are the most common non-communicable diseases globally, accounting for an estimated 17.9 million deaths per year (1). They are the leading cause of mortality worldwide, with the number of deaths increasing by 14.5% between 2006 and 2016 (2). The reduction of CVD-related mortality and morbidity is a key global health priority for the World Health Organization (WHO) (3) and the United Nations (UN) Sustainable Development Goals (4).

The American Heart Association and the European Society of Cardiology suggest that cardiac rehabilitation (CR) is a Class IA recommendation for patients with CVD. Substantial benefits include reducing mortality by 20 to 47%, reducing hospital readmissions by 18%, improving physical activity, reducing cardiovascular risk factors and improving quality of life (5, 6). Despite the proven benefits, low rates of adherence (14 to 35.5%) in traditional CR programs continue to limit treatment impact, due to inadequate access, time conflicts and associated costs (5, 7).

Rapid advances in mobile wireless communications and wearable sensor technologies may bridge the gap between home- and center-based delivery models by combining availability, accessibility, and responsive individualized clinical oversight (8). These technologies have the potential to overcome some of these barriers and may be a valuable instrument for promoting adherence. Mobile technologies are recognized for benefits such as bridging time and distance barriers to clinical oversight and increasing accessibility to care that is traditionally delivered face-to-face (9).

Particularly in relation to CR, studies reveal that technology-mediated interventions are equally effective in improving health outcomes compared to conventional care, dissipating fears referred by both clinicians and patients in relation to achieving similar results with virtual methods (10, 11). Studies specifically evaluating the effectiveness of mHealth-mediated CR interventions have revealed positive impact on composite and combined scores involving cardiovascular morbidity (e.g., worsening heart failure), hospitalizations or readmissions due to cardiovascular causes (e.g., unplanned revascularization) and cardiovascular mortality (12).

The COVID-19 era has been of enormous importance for the clinical implementation of digital health and wearable devices (13). Due to this pandemic, outpatient visits of chronic patients have been replaced by virtual visits to limit disease transmission. Health-related mobile apps (mHealth) have many advantages such as enabling continuous monitoring of patient health status, receiving health-related knowledge and automated feedback, and improving quality of life (14–17). Studies have shown that the use of mHealth interventions increases motivation and participation in CR programs (8, 18). In 2017, there were an estimated 3.7 billion mHealth app downloads (19), highlighting their practicality and convenience.

However, there is still a lack of qualitative data about which mobile app features are more engaging over time, thus contributing to behavior change and increasing treatment adherence (1). The heterogeneity of features in these apps leads to the need of identifying which of them can better contribute to disease self-management (20).

Wearables may also provide a benefit through increased health awareness, democratization of health data and patient engagement (13). The widespread use of heart rate and fitness tracking technologies provides unparalleled opportunities for capturing physiological information. While the number of patients meeting healthcare providers with wearables is rapidly growing, the European Society of Cardiology (13) highlights that there are few clinical guidelines on how to use these data and that technical aspects of heart rate tracking need to be further validated. The use of continuous monitoring may allow early risk detection, thereby becoming novel applications in both prevention and clinical research (13). A recent systematic review (5) evaluated the effects of eHealth CR on health outcomes, showing a significant promotion of physical activity, daily steps, quality of life (QoL) and a reduction in rehospitalization.

Time constraints, patient overpopulation, and complex guidelines require alternative solutions for real-time patient monitoring. Rapidly evolving e-health technology combined with clinical decision support systems (CDSS) provides an effective solution to these problems (21). There are several computerized CDSS for chronic diseases management, however, to the best of our knowledge, there are none for the management of CVD patients.

Scoping the literature on remote monitoring of cardiovascular patients through mHealth tools, a few clinical study protocols can be found in recent years, aiming at determining the effect of these resources on both clinical (e.g., cardiovascular events) and process outcomes (e.g., hospital readmissions) (22, 23). Although overlapping the effect aimed through the mHeart.4U, the current study protocol adds to the previous as it builds on existing mHeath tools for monitoring and rehabilitation of cardiovascular patients with the integration of AI for personalized selection of the rehabilitation plan. Accordingly, the mHeart.4U trial will aim to reinforce the evidence on outcomes that inform clinical decision-making, such as rehospitalizations and health-related QoL, while following a sustainable approach to intervention research, wherein existing evidence and resources are pragmatically adapted and adopted to fit the real-world practice (24).

The current study protocol will innovatively explore CDSS for management of CVD patients building on existing mHealth-based interventions for cardiac monitoring and rehabilitation. We hypothesize that an mHealth intervention supported by a CDSS will reduce recurrent cardiovascular events, will promote QoL, treatment adherence, adoption of a healthier lifestyle, and Body Mass Index (BMI) reduction. Therefore, the objective of the mHeart.4U clinical study will be to determine the effectiveness of an intervention using a CDSS for remote patient monitoring, selecting the best mHealth tools (apps and wearables) according to the needs of each CVD patient and managing clinical data.

METHODS AND ANALYSIS

The mHeart.4U trial is designed in accordance with the methodology adopted for mHealth-based interventions for remote monitoring and rehabilitation trials involving CVD patients (5). Accordingly, the study will follow a pragmatic, multicenter, two parallel arms (1:1), prospective, randomized controlled design with blinded endpoint assessment, involving two cardiology units in the Center Region of Portugal. This study is a pragmatic trial because it examines the outcomes of the experimental intervention compared with a standard intervention under circumstances which closely approximate the real world (25). Additionally, personnel undertaking outcome assessment will be blinded to group allocation. The Standard Protocol Items: Recommendations for Interventional Trials reporting guidelines were used to write this protocol (26).

Participants

Eligible participants will be adults (18+ years old) attending these cardiology outpatient clinics after the onset of an acute cardiac event, or those engaged in a structured CR program. Inclusion criteria also consider the need to be able to communicate with the researcher. Participants will be excluded if they have New York Heart Association class III/IV heart failure, terminal disease, or significant non-CVD exercise limitations.

Procedures

Sample recruitment will have the support of the clinical staff of the outpatient clinics based on inclusion and exclusion criteria. All eligible participants will be asked to fill out the informed consent. Participants will be randomized at a 1:1 ratio to receive usual care composed by CR alone (control group) or the mHeart.4U program (intervention group). Treatment allocation will follow a computer-generated schedule prepared by a biostatistician. The randomization schedule will be stratified by gender and trial center and will use random permuted blocks (**Figure 1**). The control group will follow the standard treatment protocol (27), while the Intervention group will, additionally, participate in the mHEART.4U intervention (**Figure 1**).

Intervention

The mHEART.4U intervention will include the use of an online CDSS for remote patient monitoring. The CDSS rule sets will be developed according to the knowledge on: (a) self-management and monitoring needs and difficulties of CVD patients and requirements of healthcare professionals, and (b) functional and technical characteristics of available mHealth tools for promoting CR.

According to the patient's needs and profile, the CDSS will suggest a monitoring plan accordingly. The mHEART.4U intervention kit will include mobile apps and wearables, such as heart rate, blood pressure, peripheral oxygen saturation (SpO2), sleep and step trackers, symptoms, lifestyle self-monitoring tools, medication reminders or motivational resources. The resources composing each intervention kit will be defined upon initial assessment of the patient's needs and in a shared decision-making process according to co-established therapeutic goals (**Figure 2**). Smartphones and/or wearables may be lent if necessary.

Intervention length will be 6 months and will take into account the most recent guidelines on CR (27, 28).

Outcomes and Measurements

Outcome measurements will be carried out at the 3-month (T1) and the 6-month interventions (T2) (**Table 1**).

The primary outcome will be the reduction of recurrent cardiovascular events, which is a composite of (i) cardiovascular rehospitalization or urgent visit; or (ii) unplanned revascularization; (iii) cardiovascular mortality; or (iv) worsening heart failure (29, 30).

Secondary outcomes measures will include:

a) Quality of Life, assessed through the MacNew Heart Disease Health-related Quality of Life (HRQL) questionnaire (MacNew) (31).

Acknowledging the importance of including patient's perspectives on health outcomes, the MacNew is a self-reported questionnaire that has been validated and used with both patients with experience of a myocardial infarction, and patients with experience of angina. The measurement instrument is composed of 27 items, scored from 1 (poor) to 7 (high), to assess global HRQL, physical limitations, emotional and social functions. The MacNew is currently validated to many languages including Portuguese, where it appears to be a reliable, valid and moderately responsive instrument to evaluate HRQL of people after a diagnosis of acute coronary syndrome (32);

b) Adherence to treatment, assessed through the Therapeutic Self-care Scale (TSC) (33).

The TSC includes 12 items to be answered on a 5-point Likert scale, from 0 (no) to 5 (yes) in relation to the level of knowledge during situations related to therapeutic self-care management, with higher scores corresponding to high level performance in therapeutic self-care. The measurement instrument is composed of four domains to assess patients' ability to engage in self-care activities related to: (1) taking medications as prescribed by the doctor; (2) identifying and managing symptoms; (3) performing activities of daily living; and (4) managing changes in condition. The instrument can be administered either to patients admitted to hospital with a variety of acute medical and surgical conditions, or to home-based care patients. The TSC has been widely used and is validated to various cultural contexts, including Portugal (34). The original scale has a strong internal consistency (Cronbach's α 0.93), also replicated in the Portuguese version (Cronbach's α 0.979);

c) Nutrition and Physical Activity, assessed through the Health-Promoting Lifestyle Profile-II (HPLP-II) (35).

The HPLP-II is a self-reporting instrument composed of 52 items to be answered on 4-point Likert scale (never, sometimes, often, routinely) in order to assess health-promoting behaviors as a multidimensional pattern of self-initiated actions and perceptions that serve to maintain or increase the level of wellbeing, self-fulfillment, and self-satisfaction. Nutrition (N,

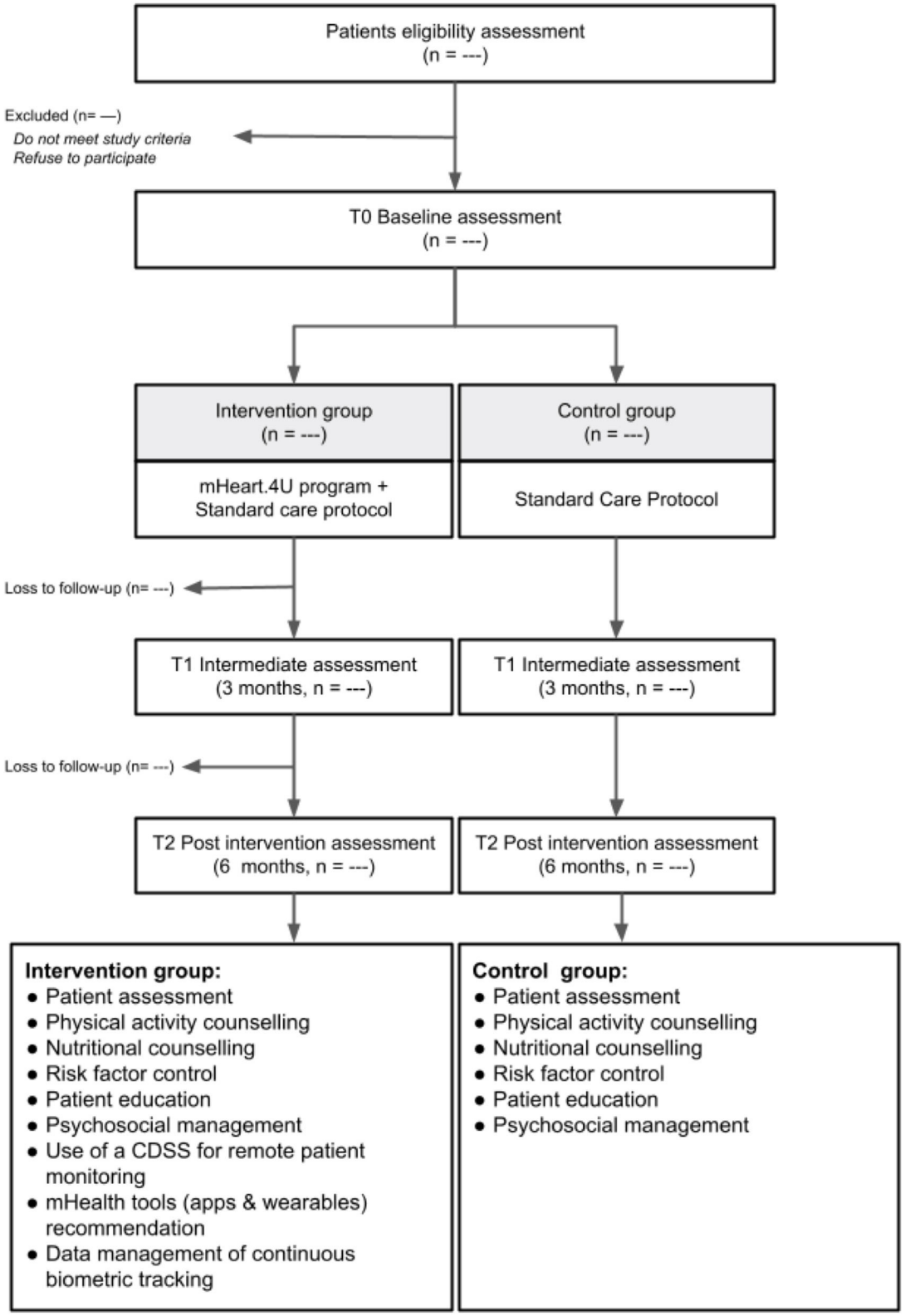

FIGURE 1 | Participant's flowchart.

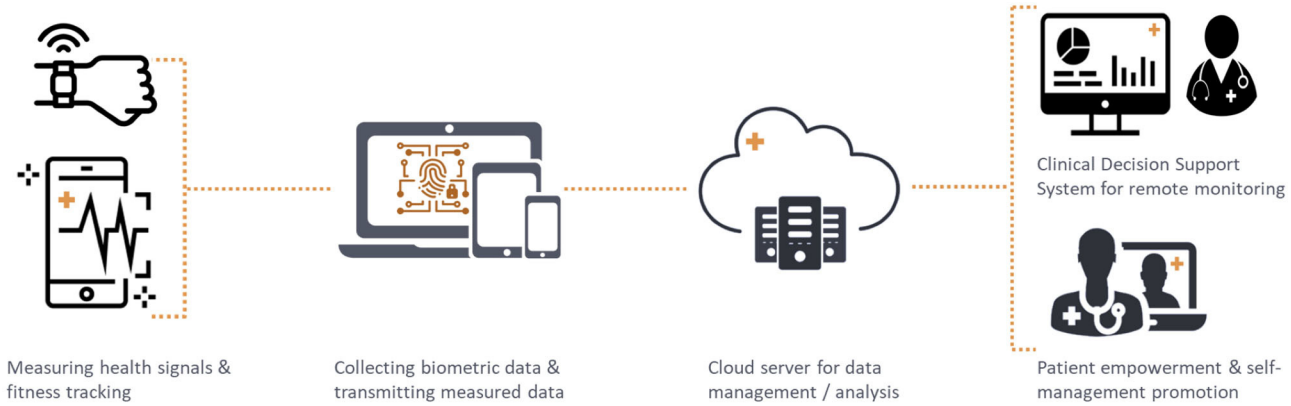

FIGURE 2 | Overview of the mHeart.4U framework and functioning.

TABLE 1 | Schedule of assessments.

Assessments	Measure	T0	T1	T2
Recurrent cardiovascular event				
Cardiovascular	Patient health records		x	x
Rehospitalization	Death certificates			
Cardiovascular urgent visit				
Unplanned revascularization				
Cardiovascular mortality				
Worsening heart failure				
Quality of Life	MacNew heart disease health-related Quality of life questionnaire	x	x	x
Adherence to treatment	Therapeutic self-care scale	x	x	x
Anthropometric measures	Patient health records (BMI, waist circumference)	x	x	x
Nutrition	Health-promoting lifestyle profile-II	x	x	x
Physical activity	Health-promoting lifestyle profile-II	x	x	x
Clinical data	Patient health records	x	x	x
Blood pressure, heart rate, blood biomarkers, pathological history, cardiovascular risk	Systematic coronary risk evaluation			
Sociodemographic Data	Sociodemographic questionnaire	x		
Gender, age, academic qualifications, profession				
mHEART.4U usage	Utilization rate, consulted resources, self-monitoring data		x	x

T0, Baseline assessment; T1, 3-month intervention assessment; T2, 6-month intervention assessment.

nine items) and Physical Activity (PA, eight items) are two of the six domains assessed, the others being: health responsibility (HR), spiritual growth (SG), interpersonal relations (IR), and stress management (SM). The original measurement instrument was tested with an α coefficient of 0.943. It has been used and validated to several languages and cultural contexts, including Portugal with psychometric results showing an adequate fit to a 52-item, six-factor structure and global Cronbach's α of 0.925 (α of N = 0.726; α of PA = 0.835) (36);

d) Anthropometric measures (Body Mass Index, waist circumference).

Other measures used during the randomized controlled trial include:

a) Sociodemographic characterization, gender, age, academic qualifications, and profession, which will be collected through questionnaires;
b) Clinical data, to be collected through questionnaires and patient records analysis, blood pressure, blood biomarkers, pathological history, and cardiovascular risk assessed through the Systematic COronary Risk Evaluation (SCORE) (37).

Sample Size Calculation

The sample size calculation for the multicentre clinical trial will be performed in order to allow for a statistically significant comparison between control and intervention groups at each center with a 95% confidence level, two-tailed analysis and aiming at a reduction in the effect variable, i.e., recurrent cardiovascular events, which is a clinically relevant composite of (i) cardiovascular rehospitalization or urgent visit; or (ii) unplanned revascularization; (iii) cardiovascular mortality; or (iv) worsening heart failure (29, 30). The G Power software was used to determine *a priori* sample size according to the evidence reported in a previous systematic review (5), which showed that eHealth CR was effective reducing rehospitalization [RR = 0.49, 95% CI (0.27, 0.89), $p = 0.02$]. Accordingly, a proportion of 6% in the intervention group was rehospitalized compared with 13% in the control group 1 year after the intervention terminus, resulting in an effect size of 7% (5). Departing from this evidence-based measure of effect size, power (1 -β) of 80%, a significance of 0.05 and accounting for 20% loss to follow-up, a sample of 330 patients per arm will be included.

Statistical Analysis

The patient characteristics in the two arms at baseline will be compared descriptively using chi-squared tests for the binary and categorical variables and an unpaired Student's *t*-test for the continuous variables. One-sample *t*-test will be performed to measure the differences within the same group.

The primary outcome will be analyzed using a generalized linear mixed model, adjusting for the stratification variables (i.e., gender, hospital unit). Logistic regression will be conducted in order to explore predictive relationships of the baseline categorical variables (e.g., age, clinical variables) on the primary outcomes in both groups.

Analyses to determine the study primary outcome will be performed on the principle of intention-to-treat. Accordingly, assuming there will be a reasonable amount (>5%) of missing data, analyses to determine the primary outcome will be conducted using a multiple imputation model. A per-protocol analysis will be conducted with complete cases to test the robustness of intervention effects under different assumptions. Subgroup analyses will be conducted to determine intervention effects by gender and trial center. All statistical tests will be 2-sided at $\alpha = 0.05$. The biostatistician will remain blinded throughout the analysis of treatment effects.

DISCUSSION

The current study protocol aims to assess the effectiveness of a user-friendly, comprehensive CDSS for remote patient monitoring of CVD patients, primarily on the reduction of recurrent cardiovascular events. To that end a multicentre randomized controlled design involving two cardiology units in the Center Region of Portugal will be conducted involving patients living with CVD and receiving care at these Units. The CDSS will recommend a personalized monitoring plan for each patient through mHealth tools, and provide self-management recommendations adequate to the patient's needs and preferences.

Along with the WHO key global health priority (3) and UN Sustainable Development Goals (4) of reducing CVD-related mortality and morbidity, the mHeart.4U has the potential to contribute to sustainable and person-centerd CR, with low-effort added to the healthcare services and without jeopardizing quality of care (38). The mHeart.4U will be conducted at two cardiology units, which will allow to gain insight concerning contextual differences to the adoption of the intervention. The recruitment and intervention delivery might however entail minor differences that need to be investigated in a *post-hoc* analysis for their potential to induce bias.

Technology-mediated CR has been shown to have equal impact on health outcomes as conventional programmes delivered at the clinic (11). The mHeart.4U trial will primarily study the impact on recurrence of cardiac events, with effects on quality of life being secondarily explored. Along with the increasing importance of meaningfulness of life as a quality indicator for people living with chronic disease, recent trials have had the contrary approach [e.g., (23)]. Although it might be seen as a limitation, the evidence concerning this primary outcome is of paramount importance to ascertain the added value of the mHeart.4U in relation to the existing mHealth-based interventions for cardiac monitoring and rehabilitation, which will integrate the current trial. However, the mHeart.4U trial design does not allow for analyzing the separate effects of different mHealth resources included in the intervention.

Drop-out rates are recognizably higher in intervention studies involving mHealth resources (10, 15) and the mHeart.4U trial is not immune to that potential limitation. Attempting to mitigate the risk, evidence highlights the importance of attending to psychosocial variables that are related to adherence to mHealth interventions, and contextual factors related to adoption by healthcare professionals (39). As the mHeart.4U will entail personalized recommendations of mHealth resources complementary to standard-of-care, to be used according to the patients' preferences on daily living, the adherence to the intervention is expected to be reinforced.

To the patient participating in technology-based CR, the mHeart.4U is likely to empower to take action while recognizing his/her own resources beyond the disease (23). The patient will naturally become part of the therapeutic partnership in a more equitable role as the healthcare professionals, and his/her agency will be reinforced by the self-monitoring and adherence to self-management recommendation. In such a way, the patient will be more prepared to participate in processes of clinical decision-making (40).

From the healthcare professional's perspective, bridging the gap between the hospital and patient's home is a criterion of

quality of care, contributing to enhancing accessibility and care continuity. Among many other advantages, mHealth resources allow to reduce access and continuity inequities related to geographical location and financial constraints. They additionally allow safety of care and treatment along with their telemonitoring resources, with healthcare professionals having access to disease and illness indicators during patient's daily life functioning (17).

The integration of mHealth resources, and particularly the mHeart.4U, into CR will therefore make it possible to personalize the intervention parameters, facilitate monitoring and tracking according to patient's personal preferences and clinical needs, which is expected to improve the patient's recovery and health status (17). This flexibility aspect related to tailoring in mHealth programmes is a valuable feature compared to conventional programmes. Particularly in CR programmes, tailoring is likely to go beyond prompting adherence as the person closer relates to the intervention content and format, to embrace intervention effectiveness as specific e-management recommendations are determined upon the patient's clinical profile.

The success of mHeart.4U intervention will be a step toward the use of technological interfaces as an integral part of CR programs. Altogether, these programmes are likely to facilitate the management of resources for healthcare professionals and reduce inequality of access to healthcare for CVD patients. In the western world healthcare systems, the complementarity of mHealth solutions to the treatment, care and rehabilitation along the chronic diseases pathway is mandatory if aiming for sustainable, integrated healthcare systems that endorse patient's willingness to be part of their treatment journey, while assisting them at distance.

ETHICS STATEMENT

The project will be reviewed by the Ethics Committee of both hospital units where the study will unfold. The study was registered in ClinicalTrials.gov on the 18th January 2022 with the number NCT05196802.

The study findings will be published in international peer-reviewed scientific journals in accordance with Consolidated Standards of Reporting Trials, including the extension for non-pharmacological treatment interventions (41). Dissemination through scientific meetings will also be conducted. Workshops will be organized to disseminate the results to healthcare professionals and other stakeholders. Furthermore, citizen-friendly reports will be elaborated to disseminate the results to the end-users in the society.

AUTHOR CONTRIBUTIONS

PS led the design of the study protocol and will coordinate the RCT. FV led the writing of the study protocol. SD contributed to elaborate the data analysis protocol and will assist in the statistical analysis of the RCT data. JM and LG provide advice on key study issues. PS, PF, and MA contributed to design the intervention. All authors contributed with important intellectual content to the study protocol and approved the final version for publication.

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STUDY PROTOCOL
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Baropodometric Assessment of the Podiatric Profile of Nursing Students in Clinical Settings: A Study Protocol

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Introduction: Nursing students are exposed to increased risks of developing foot and ankle disorders due to prolonged standing and walking positions during clinical settings. This can lead to high dropout rates from nursing degree, thus contributing to a future shortage in nursing professionals. This protocol aims to develop a study to understand the influence of prolonged standing and walking positions on nursing students' foot health, and specifically to study the relationship between the podiatric profile (regional force and pressure exerted on the foot) and related signs and symptoms.

Methods and Analysis: A prospective observational cohort study will be conducted with 194 nursing students. Participants will be asked to walk through a baropodometric platform before and after a 5-month clinical training session. Assessment will focus on the change in podiatric profile, namely foot posture and foot function, at 5 months, and changes in foot health at 5 months. The study will start in January 2022 and it's expected to end by June 2022.

Discussion: The study aims to perform an innovative assessment of nursing students' podiatric profile, which will allow for a comprehensive description of foot/ankle changes and their relationship with prolonged standing and walking contexts.

Ethics and Dissemination: The study was approved by The Ethical Committee of the Health Sciences Research Unit: Nursing (UICISA: E), of the Nursing School of Coimbra (ESEnfC), with the approval code nr. P799_07_2021. The study was also recorded in ClinicalTrials.gov on the number NCT05197166. Findings will be used to publish articles in peer-review scientific journals and oral communications and posters at scientific meetings.

Keywords: foot health, ankle injuries, nurses, nursing, standing position, occupational health, baropodometric gait analysis

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INTRODUCTION

Nurses are one of the healthcare professionals most exposed to occupational health risks, mostly due to prolonged standing and walking contexts (1, 2). Evidence has suggested that prolonged standing is associated with the development of adverse health outcomes (3), particularly lower-limb disorders. One of the most common disorders concerns the ones in the foot/ankle region (4, 5).

Stolt et al. (6) state that prolonged standing is considered the second work-related factor hindering foot health, increasing the risk for the development of significant disorders, and affecting the quality of life. However, these disorders are a large and often unrecognized group of diseases (4, 6) having poor evidence based on the scarcity of related research. As so, the biomechanics of many foot disorders remain poorly understood (7), particularly the influence and relationship between biomechanical variables and external stressors, such as, prolonged standing or walking positions.

According to Bakker et al. (8), the increase in physical demands while in clinical settings is an important contributor to nursing students' late-dropout, thus contributing to the future professional shortage. Data from a recent prospective cohort study (9) shows that musculoskeletal complaints, including foot/ankle disorders, accounted for 39.9% of intention to leave nursing education and an actual dropout rate of 3.4% among nursing students. In fact, many authors state that the foot and ankle regions are the most commonly affected and reported locations for the development of disorders in nursing students (10–14).

In this sense, to effectively prevent future disorders, and for an adequate foot self-care promotion among nurses and nursing students, a suitable evaluation and description of the podiatric profile are necessary. Furthermore, a categorization of the most important foot/ankle variables that are affected by standing environments, as defined by Bernardes et al. (15), as potentially aggressive contexts in the nursing profession, often implying continuous static-bound positions (while standing) or continuous dynamic movements (with long built-up walking distances throughout the shift time), is deemed important for the development of preventive interventions.

An evaluation and assessment of foot and ankle dynamic variables, while in static or dynamic positions, can be performed by various means. One of the most reliable method to determine the podiatric profile and respective variables, namely plantar pressure, is baropodometry (16). It's usually used to analyze the pressure areas exerted by the body in both motion and static positions, providing a dynamic gait analysis, distribution of loads during walking, peak pressures, and contact time with the ground, and also detection of areas in risk on the foot. Many previous studies have used plantar pressure assessments to identify foot pathologies and risk factors (17), with important results, namely detecting altered regional loadings (18), significant differences in foot kinematics (19) and pronated foot function (20).

Therefore, this paper aims to describe a protocol for a prospective observational study on the influence of prolonged standing and walking positions on nursing students' foot health, and relationships between the podiatric profile (regional force and pressure exerted on the foot) and related signs and symptoms.

METHODS AND DESIGN

Study Design and Setting

A prospective observational cohort study will be conducted between January 2022 and June 2022 in a Nursing public school in Portugal. Data collection will take place at the end of January and in the first days of February.

Participants and Recruitment Process

The study will enroll nursing students from a Portuguese Nursing School, and which are exposed to standing environments during acute clinical settings (e.g., hospitals). The recruitment process will be developed according to the following inclusion criteria: (i) nursing students enrolled, at the moment of the study, in a Nursing degree; (ii) nursing students that, at the moment of the recruitment phase, are not enrolled in a clinical learning setting; and the following exclusion criteria: (i) diagnosed chronic systematic diseases (e.g., rheumatoid arthritis); (ii) diagnosed metabolic disorders; (iii) visible lower limb swelling; (iv) presence of contraindications for baropodometric-related measurements; (v) history of orthopedic neurological and/or musculoskeletal problems likely to affect gait; and (vi) students that, at the moment of the recruitment phase, are also committed to a professional working activity or involved in high competition sports, which might influence foot health (e.g., waitress, door-to-door delivery, among others).

Participants will first be addressed in a project presentation session, where informed consent will be provided for their analysis and signature. Subsequently, the days for data collection will be scheduled, taking into consideration the most convenient periods for students and the research team. In this sense, a convenience sample will be recruited, as students will voluntary show up to participate in the study. This sampling method was chosen, rather than randomization, due to time constraints regarding project schedule, and also the need to achieve a representative sample. As we are performing the study only in one Nursing School, due to researchers' availability and ethical approvals, randomization could include students that wouldn't be able or didn't want to be part of the research in progress. In this sense, the research team opted to include volunteers, also helping decrease potential loss to follow-up.

In the Nursing School involved in this study, clinical training has an average duration of 4 to 5 months for students in the third and fourth year of the Nursing degree. Thus, the study will depend on this timeframe for the respective follow-up period.

According to the defined criteria, all undergraduate nursing students at the third year will be recruited as participants. Each academic year, an average of 300 students are enrolled, and for a confidence interval of 95% and a margin of error of 5%, the sample size needed is 169 participants. Also, an a priori 0.05 significance level is defined and a response distribution of 50% is assumed. To prevent potential losses, we've added an additional 15% of the total sample size, thus aiming to recruit 194 students.

All data collection will take place inside the Nursing School, in specifically chosen places, previously tested for the study, and will be performed by two researchers, which will be different from those responsible to analyze data.

Exposures, Outcomes and Confounders

The exposure under study consists of a particular environment that poses particular biomechanical risks to the foot/ankle region. According to Bernardes et al. (15), standing environments include those of prolonged standing and prolonged walking,

TABLE 1 | Specific podiatric profile variables.

Category	Variables	Definition
Kinematic variables	Forefoot width/spreading	Distance, in millimeters, between two straight lines perpendicular to the Chopart joint and tangential to most medial and most lateral points of the heads of first and fifth metatarsals, respectively.
	Foot angle at contact (sagittal plane)	Dorsiflexion angle at contact, in relation to the sagittal plane.
	Foot eversion	Or pronation, is an angular movement where the foot moves away from the medial plane.
	Foot adduction	Is the angular movement were the foot moves toward the medial plane.
	Foot external rotation	Rotation of the joint away from the midline, measured as an angle.
	Ankle inversion	Angular movement toward the medial plane.
	Medial longitudinal arch (MLA)	Located between the heel proximately and the medial three metatarsophalangeal joints anteriorly. Runs through metatarsals 1-3, sesamoid bones, cuneiform bones, navicular, talus, and calcaneus bones; the plantar aponeurosis, spring ligament, talocalcaneal ligament, and deltoid ligament; the flexor *hallucis longus*, flexor *digitorum longus*, *abductor hallucis*, flexor *digitorum brevis*, tibialis posterior.
	Ankle plantarflexion ROM in late stance	Refers to the angular distance of the movement around the ankle joint during the late stance of gait, characterized by a single limb support, and occurring before the swing period.
Kinetic variables	Initial peak vGRF	vGRF consists of the ground reaction force during walking, this is, the force exerted by the ground on the body (the sum of all forces that exist between a body and the supporting surface). Abnormal peaks or loading values can lead to overuse injuries. vGRF can be measured in different gait phases, like initial, breaking or propulsive stances. It's measured in Newtons (N).
	Breaking vGRF	
	Propulsive vGRF	
	Peak plantar pressure	Foot plantar pressure is described as the distribution of forces exerted in the field between the sole of the foot and the ground. It's measured in kilopascal (kPa).
	COP displacement (medio-lateral)	In biomechanics, COP is the specific point where the vGRF vector is applied. Its displacement consists of an oscillation, which might be identified in different axis of the body in relation to the ground.
	COP displacement (anterior-posterior)	

ROM, range of motion; vGRF, vertical Ground Reaction Force; COP, center of pressure.

which can be defined as spending at least 5% of occupational time standing or walking (21).

The first primary outcome of interest is related to the change in podiatric profile at 5 months and will be evaluated at month 0 and month 5, being an objective and quantitative outcome. In this case, specific foot-related variables while walking will be recorded, illustrating the actual behavior of the foot during activity. The assessment of the podiatric profile follows the important premise that the medial longitudinal arch is one of the most important and highly variable structural characteristic of the human foot (22).

The relevant variables that describe this outcome are summarized in **Table 1**.

This outcome includes foot posture and foot function assessments, which are relevant biomechanical measures, that can be extracted from the plantar pressure scans acquired previously.

Foot posture can be characterized using the modified arch index (MAI), which is calculated by the division of the foot length, minus the toes, in three equal portions, and also the division of pressure in the middle third by that of all three regions.

Foot function is characterized by the center of pressure excursion index (CPEI), which is a measure of foot function throughout the gait cycle, being defined as the distance between an imaginary line drawn from the first and last points of each foot's center of pressure (COP) trajectory and the COP as the distal third tertile of the foot. This value is usually normalized by foot width and multiplied by 100, to obtain a percentage excursion of the COP.

Following previous similar studies (7), CPEI and MAI's distribution are divided into quintiles. For the first, feet in the top and bottom quintile will be considered as having a supinated and pronated foot function, respectively, and for MAI, the top and bottom 20% will be considered *pes planus* and *pes cavus*, respectively.

Another variable of interest to characterize the podiatric profile is plantar loading characteristics. As there is no current consensus in the literature for the definition of adequate foot segments, this study will consider the templates of similar studies, which showed good reliability for plantar forces and pressures during barefoot walking in healthy adults (23). Namely, the regions to assess and compare are: lateral heel, medial heel, midfoot, 1st metatarsophalangeal joint (1MPJ), 2nd−5th metatarsophalangeal joint (2–5MPJ), hallux and the lesser toes.

The second primary outcome concerns the change in foot health at 5 months, a subjective evaluation by the participant, and is related to observed clinical parameters, signs and symptoms, namely skin, nails, foot structure, as well as presence and location of the pain. The Portuguese adaptation of the Self-Administered Foot Health Assessment Instrument (S-FHAI), a Likert-type instrument with four dimensions, will be used. It will be applied at month 0 and month 5. The majority of observed foot disorders will be recorded as either present or absent.

The study also includes the following secondary outcomes: (i) Foot Self-Care Knowledge, which is assessed between month 0

TABLE 2 | Primary and secondary outcomes assessment.

			Assessment	Timeframe		
				Month 0	Month 3	Month 5
Primary Outcomes	Change in Podiatric Profile at 5 months*	Kinematic variables	EMED® software	x		x
		Kenetic variables		x		x
		Foot posture	MAI analysis	x		x
		Foot function	CPEI analysis	x		x
	Change in Foot Health at 5 months	Skin health	Portuguese adaptation of the self-administered foot health assessment instrument [S-FHAI; (24)].	x		x
		Nail health		x		x
		Foot structure		x		x
		Foot pain		x		x
Secondary Outcomes	Foot self-care knowledge	Skin: structure, problems and care	Portuguese adaptation of the Nurses' Foot Care Knowledge Test (NFKT)		X	
		Nails: structure, problems and care			X	
		Foot structural deformities: identification and care			X	
		Disease specific foot problems: identification and care			X	
		Footwear: properties and suitability			x	
	Students' Perceptions	Perceptions on the influence of clinical settings and potential foot disorders in quality of life.	Focal groups			x

**global evaluation through the Emed® platform; MAI, Modified Arch Index; CPEI, Center of Pressure Excursion Index.*

and month 5, through a four-dimensional questionnaire, where specific interventions for the promotion and prevention of foot and ankle disorders are evaluated; and (ii) Students' perceptions about the influence of foot health in their quality of life. It is evaluated through focus groups after exposure time (month 5).

Regarding potential effect modifiers and confounders, we expect that different nursing activities and ward typology (e.g., surgical units, intensive care) might produce diverse baropodometric patterns.

The primary and secondary outcomes, respective instruments for evaluation and timeframes for assessment are summarized in **Table 2**.

Study Layout

After recruitment, at month 0 (before exposure) and month 5 (after exposure), the participants will undergo a four-phased procedure:

- Preparation: the trials will be explained to the participants and consent will be retrieved; any questions will be properly addressed;
- Familiarization: a test procedure will be performed where participants walk freely over the platform, without recording baropodometric gait analysis (BGA), to achieve the greatest possible freedom of movement. Participants will be asked to always walk barefoot.
- Trials: three types of gait protocols are usually applied in this type of study (one-step, two-step and mid-gait protocol). The choice should be based on both the variable of interest and the site of the foot to be studied. According to some authors (25, 26), there are few differences between the mid-gait (the *standard* protocol) and the two-step protocol, with similar values provided by both. An important criterion is using the same protocol throughout all studies, including follow-up.
In this study, we chose to use the mid-gait protocol (**Figure 1**), particularly because the two-step termination protocol method is usually more appropriate for collecting joint kinematic data, which is out of the scope of this study, and also because the two-step initiation and termination protocols might delay acquiring the usual walking velocity during the trial (25, 26). In this sense, subjects will walk, at a self-selected pace, along an 8.0 m walkway. An initial position will be pre-established, to allow the right foot to hit the pedography platform at the middle of the walkway, with the fourth step, also avoiding gait alterations. After striking the platform, subjects will continue walking for 4.0 m until de end of the walkway.
Additionally, participants will perform three valid trials per foot, as it has been previously found to be sufficient to ensure adequate reliability of force and pressure data (27–29) and will perform at least three steps before and after the pedography platform, as stated by Cousins et al. (27), that gait protocols should ideally involve a minimum preamble of at least three steps for a representative gait pattern to be obtained.
It should be noted that a valid trial of a foot scan is defined as the participant hitting with the whole foot over the platform, without gait pattern alterations. A trial will be excluded, and should therefore be repeated, if a participant: (i) targets the borders of the platform with any part of the foot; (ii) alters gait to ensure full contact of the foot; and (iii) pauses on the mat.
- Self-Assessment of Foot Health: at the end of the BGA, participants will be asked to answer a self-assessment

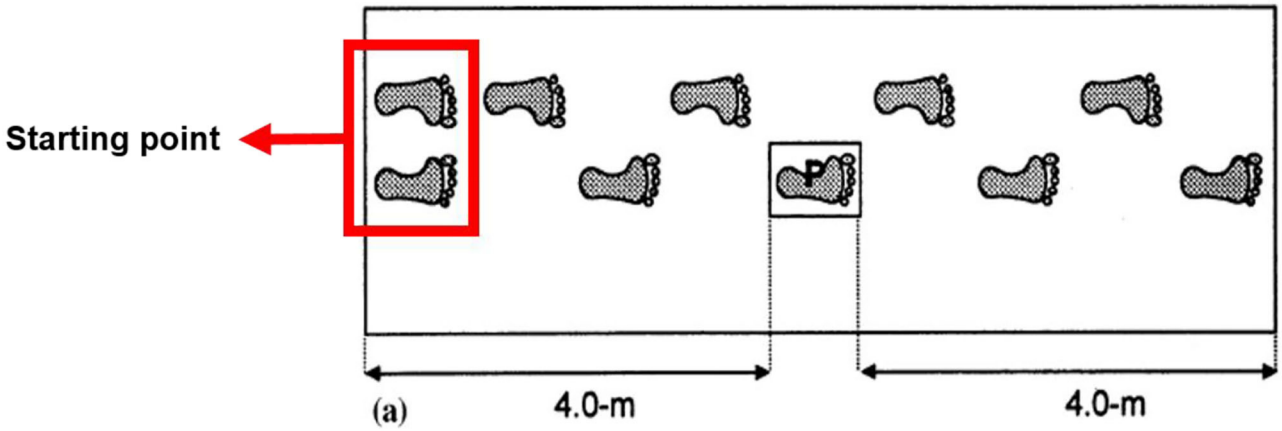

FIGURE 1 | Midgait method. Participants start 4.0 m from the platform (P) [Adapted from Wearing et al. (25)].

instrument about their current foot health, including skin, nail and presence of pain and will participate in a focus group together with another 5–10 participants from the study to discuss the influence of foot health in quality of life.

Instruments

To record the desired data, the Emed® platform from *novel.de* will be used. It consists of a pedography platform to measure pressure distribution under the foot, containing calibrated capacitive sensors, with the potential to accurately measure foot pressure in static and dynamic positions.

The main variables measured (throughout time) are: maximum pressures, pressure/time, force exerted, contact area and COP line.

According to the provider, the sensor platform has an area (mm) of 475 × 320 with a total of 6,080 sensors, with a resolution (sensor/cm^2) of 4. The recording frequency is set at 50 Hz, with a pressure range (kPa) of 10–1.270. The pressure threshold is 10 kPa and the maximum total force is 193,000 N.

Statistical Analysis

The primary outcomes and the Foot Self-Care Knowledge (secondary outcome) will be analyzed using SPSS Statistics v25, namely with descriptive statistics (average; standard deviation; medians) with an *a priori* significance value of $p < 0.05$.

After verifying the type of distribution of the sample, using the Kolmogorov-Smirnov (KS) with Liliefors correction (suitable for samples with more than 30 subjects) (30), either the independent samples *t*-test (normal distribution) or the Mann-Whitney (test non-normal distribution) will be used to compare changes in outcomes before and after the exposure.

To relate variables of interest, namely podiatric profile variables and specific foot-health parameters, a Multiple Linear Regression will be computed and multivariate analysis of variance with repeated measures to detect significant interactions between variables.

To control confounding effects, we'll perform a stratification of variables, and evaluate the exposure-outcome association, also using Mantel-Haenszel (M-H) estimator for an adjusted result. Additionally, the Analysis of Covariance (ANCOVA) will be computed to assess the effect of certain factors on the outcome variables.

The secondary outcome, related to the students' perceptions, will be analyzed using ATLAS.ti v7 software, based on the content analysis as defined by Bardin (31). The different phases of analysis are: (i) pre-analysis; (ii) exploration of the material; and (iii) treatment of results, inference and interpretation. The categorical organization of the content will be performed *a posteriori*, through the following codification steps: (i) cutting—choice of units; (ii) enumeration—choice of counting rules; and (iii) classification and aggregation of chosen categories and units.

Potential missing data will be handled using marginal mean imputation, this is, computing the mean of the missing value, *X*, using the non-missing values and use it to impute missing values of *X*.

Regarding loss to follow-up, all data belonging to participants that choose to opt-out or are lost during the study, will be erased from storage, as explained in the informed consent document.

DISCUSSION

We have described a protocol for a prospective observational cohort study, that aims to understand the influence of prolonged standing and walking positions on nursing students' foot health. This study will also explore the potential relationship between nursing students' podiatric profile and reported signs and symptoms.

Nursing practice is physically demanding, causing high loading forces, namely to the lower extremities. Additionally, common factors for increased risk for the development of foot/ankle disorders are footwear, constant standing and neglected foot care (6).

Currently, the study of injuries has been the subject of several studies, and some (31, 32) report that further investigations should be carried out into the circumstances and factors

that cause problems at the level of foot/ankle region in this population.

Although several studies identify this problem, few describe in detail the causes of pain and discomfort. On the other hand, the podiatry evaluations conducted are poor (31), which limits a more detailed knowledge of the phenomenon under study. Moreover, and although some researchers suggest some solutions, namely the development of ergonomic and personalized footwear (33–35), there seems to be no adequate interventions to improve foot health in nursing students (4, 13).

Therefore, this study has the potential to comprehensively map significant foot/ankle changes caused by prolonged walking or standing positions, experienced by nursing students in clinical settings. Such data will be essential to establish a potential relationship between those factors. The conclusions will lead to a better understanding of the phenomena, thus allowing for better prevention. Additionally, the conclusions will lead to a better understanding of the phenomena, thus allowing for a better prevention, particularly through the development of guidelines and preventive tools.

Some limitations of the study are related to the convenience sample, which is recruited from a Nursing School in Portugal, reducing the external validity of the study. On the other hand, the follow-up time of 5 months, may be insufficient to elicit important signs and symptoms.

ETHICS STATEMENT

The study was approved by the Ethical Committee of the Health Sciences Research Unit: Nursing (UICISA: E), of the Nursing School of Coimbra (ESEnfC), with the approval code no. P799_07_2021. The study was also recorded in ClinicalTrials.gov on the number NCT05197166. Participants will first be addressed in a project presentation session, where informed consent will be provided for their analysis and signature.

AUTHOR CONTRIBUTIONS

RB, SC, and AG led the writing of the original protocol. PP, LS, and PS-C contributed to the statistical analysis section. RB, SC, AG, IA, and FP-S contributed to the qualitative analysis section. RB, SC, and PS-C were responsible for the final review of written English. PP, RB, and AG were responsible for the recruitment and exclusion/inclusion criteria sections and initially wrote a draft of the study layout, which was later validated and corrected by SC, LS, FP-S, and IA. RB, SC, PP, IA, and AG outlined the major outcomes of interest and, with the contribution of LS and PS-C, described them for the present study. The global administration of the project is led by RB, SC, and AG.

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Wearable Walking Assistant for Freezing of Gait With Environmental IoT Monitoring: A Contribution to the Discussion

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Parkinson's disease (PD) is the second most common neurodegenerative disease, significantly increasing in the last three decades. Worldwide, seven to ten million people are affected by PD. In people living with PD, freezing of gait (FoG) significantly impacts activities of daily living, potentially leading to falls, injuries, and loss of autonomy. FoG prevalence rates vary widely, reaching at least 50% of patients with PD. Current therapeutic options have limited effectiveness, and their complement with innovative technology-based solutions in the real world is demanded to enhance daily functioning for people living with PD. This article provides a narrative review of current technological developments for people living with PD and, derived from that evidence, presents a perspective on integrating wearable technology and IoT to support telemonitoring and self-management of people living with PD in their daily living environment. Complementing current therapeutic options with technology-based solutions in PD patients' real-world environment is crucial to enhancing the quality of life of people living with PD. In that way, wearable technology and IoT might constitute resources of excellence in seamless monitoring and self-management in people's home environments.

Keywords: Parkinson's disease, freezing of gait, internet of things, self-management, wearables

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INTRODUCTION

Parkinson's disease (PD) is a neurological disorder with evolving layers of complexity. It has long been characterized by the classical motor features of Parkinsonism associated with Lewy bodies and the loss of dopaminergic neurons in the substantia nigra (1). The parkinsonian symptoms include bradykinesia, muscular rigidity, rest tremor, and postural and gait impairment (2).

In Europe, the estimated prevalence of PD is 1.0% in people with 60 or more years and 3.0% in people older than 80 years, with prevalence rates estimated between 65 and 12.500 per 100.000 and incidence between 5 and 346 per 100.000 person-years (3).

Regarding the global burden of PD, Klietz et al. (3) found a mild increase in caregiver burden in 1 year, highlighting that it is time-consuming and a risk factor for developing depressive symptoms. Economically, PD also has a significant impact worldwide. Yang et al. (4) note a significant economic burden of PD in the United States, with direct medical costs of $25.4 billion and $26.5 billion in indirect and non-medical expenses.

Clinically, a consensus on the classification of PD subtypes has not yet been established. Still, empirical observations suggest two significant subtypes: tremor-dominant PD (with a relative absence of other motor symptoms) and non-tremor-dominant PD (which includes phenotypes described as akinetic-rigid syndrome postural instability gait disorder). People living with PD typically present at least one of four major motor symptoms: Bradykinesia or hypokinesia, resting tremor, rigidity, and postural instability (5). Non-motor symptoms include psychiatric disorders (e.g., hallucinations and delusions, mood disorder), cardiovascular disorders (e.g., orthostatic hypertension, fatigue), neurocognitive disorders, and visual disorders.

Figure 1 summarizes the main signs and symptoms related to PD. The classic motor symptoms are frequently mentioned by authors (6). PD can also be evidenced by non-motor symptoms, which include psychiatric disorders (e.g., hallucinations and delusions, mood disorder), cardiovascular disorders (e.g., orthostatic hypertension, fatigue), neurocognitive disorders, attention deficit, sexual dysfunction, visual disorders, among others (7, 8). However, a combination of these symptoms poses a more significant impact on the person's quality of life with PD. As for diagnostic purposes, Morgan et al. (9) highlight that diagnostic criteria should also include asymmetry and cogwheel rigidity. Other advances regarding the diagnostic of PD have been observed, with Alpha-synuclein oligomers and small nerve fiber pathology in the skin as potential biomarkers, as well as analysis of presynaptic dopaminergic terminals and the severity of the putamen involvement through ^{99m}Tc-TRODAT-1 SPECT Imaging, presenting as potential diagnostic markers of PD (10, 11).

Motor and non-motor signs and symptoms are usually treated using doses of carbidopa/levodopa, depending on the disease's stage. Pharmacological treatment is an important strategy to manage chronic symptoms and increase independence at an initial stage. Yet, several non-pharmacological interventions are available. For example, Church (6) mentioned a technological device, i.e., the red-light-helmet, which uses Light-emitting diodes (LEDs) to alleviate motor symptoms. Morgan et al. (9) state that deep brain stimulation (DBS) is the most effective treatment for motor symptoms. Exercise and neurorehabilitation are increasingly reported as essential measures to fight against motor symptoms. Isernia et al. (12), following the discussion on motor and non-motor interventions, highlight telerehabilitation's efficacy, including physical and cognitive interventions being delivered at a distance.

The social and psychological issues in PD-affected patients should also be considered and might vary in individual patients. Therapies, such as deep brain stimulation and surgical lesioning, should be explored. Further research should be encouraged to better understand the disease's characteristics and etiology.

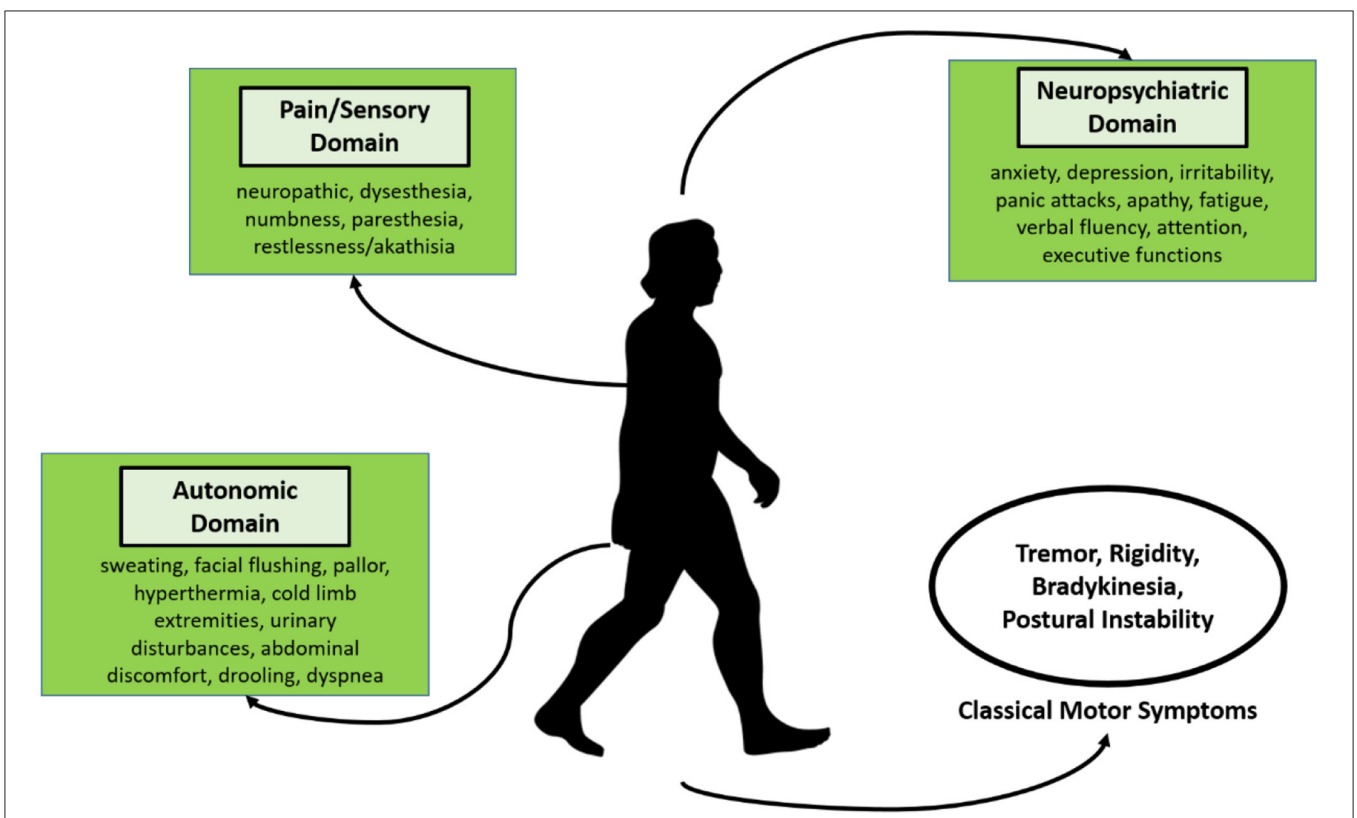

FIGURE 1 | Clinical presentation of PD, according to the motor and non-motor signs and symptoms.

TABLE 1 | Treatments for motor and non-motor symptoms.

Symptom domain	Associated symptoms	Pharmacologic	Non-pharmacologic
Pain/sensory domain	Neuropathic, dysesthesia, numbness, paresthesia, restlessness/akathisia, visual impairments	Anticholinergic, dopamine agonists, trihexyphenidyl, analgesics, opiates	Physical therapy and exercise programs,
Autonomic domain	Sweating, facial flushing, pallor, hyperthermia, cold limb extremities, urinary disturbances, abdominal discomfort, drooling, dyspnea	Fludrocortisone, acetylcholinesterase inhibitors, dopaminergic treatments, anti-muscarinic anticholinergic drugs, β-3 adrenergic agonists	Sex therapy
Neuropsychiatric domain	Anxiety, depression, irritability, panic attacks, apathy, fatigue, verbal fluency, attention, executive functions	Tricyclic antidepressant drugs (TCA), selective serotonin reuptake inhibitors (SSRI), buspirone	Deep brain stimulation (DBS), cognitive behavioral therapy
Others	Sleep disorders, weight loss, malnutrition, osteoporosis, fatigue	Dopamine agonists, gabapentin, pregabalin, vitamin D, calcium	Multiple sleep latency test, mini-nutritional assessment, dual-energy X-ray absorptiometry (DXA), Parkinson's fatigue scale (PFS-16)

Future scientific research involving Parkinson's disease might enlighten our knowledge of disease onset and progression and deliver some added aspects/components to help find more effective therapies to improve patients' quality of life with PD. As for non-motor symptoms, the latest research trends point to the need to better understand the pathophysiology mechanism before developing new therapeutic approaches (13). However, with pharmacology interventions being insufficient for the management of the person with PD, a clear trend toward developing client-centered interventions that personalize care is becoming more noticeable (14).

According to recent studies, **Table 1** provides an overall perspective of the most common pharmacologic and non-pharmacologic treatments for motor and non-motor symptoms (6, 9–15).

As one of the most common and incapacitating PD symptoms that severely compromise patients' quality of life, freezing of gait (FoG) occurs in about 50% of patients with PD (2). Clinically, FoG is characterized by sudden, relatively brief episodes of inability to produce effective forward stepping and typically occur during gait initiation or turning while walking. These gait blocks significantly interfere with daily life, also being on the list of common causes of falls (1). Importantly FoG is now recognized as the leading cause of falling, fracture risk, and activities of daily living disability (16). This risk is compounded because FoG often co-occurs with substantial balance problems and cognitive deficits, mainly frontal executive (17). Associated gait abnormalities affect step calling, step symmetry, and step time consistency before and in-between FoG episodes.

The prevalence of FoG increases with a longer disease duration. It has been reported that 81% of people with PD experienced FoG after a disease duration of 20 years (18). Nieuwboer and Giladi (7) point to four potential mechanisms for FoG events that may explain this time-dependent increase in the prevalence. According to these authors, FoG may occur due to: a motor breakdown associated with the accumulation of various motor deficits (threshold model); an inability to deal with multiple sensory and motor inputs leading to the interruption of locomotion (interference model); behavioral indecision (cognitive model); a cleavage between introductory programming and the intended motor response (decoupling model).

Regardless of the potential model that leads to FoG, the multiple dimensions and systems implicated in this phenomenon highlight FoG management as a significant therapeutic challenge in clinical practice (19). The variety and heterogeneity of existing solutions are a consequence of the complexity of the pathology. However, new and emerging approaches have been developed in recent years, which allow the possibility to enrich and deepen the discussion that has been made in recent times. In this sense, this article intends to contribute to this discussion, highlighting some current gaps and proposing some innovations in the research processes.

CURRENT THERAPEUTIC TRENDS AND CHALLENGES IN FoG EVALUATION: THE CASE OF ENVIRONMENTAL IoT MONITORING

The most common form of treatment to manage the motor symptoms of PD is Levodopa (LD). LD is the metabolic precursor to dopamine and is used to replace endogenous dopamine at the striatum (2). The medication cycle between two consecutive intakes is roughly divided into two periods, the ON period in which the LD is adequate and the OFF period in which the influence of the medicine has subsided (2). The development of involuntary movements and the ON/OFF phenomenon, i.e., motor response fluctuations uncorrelated with the expectation from the daily medications intake schedule, can limit mobility and complicate dosing.

Gait deficits and FoG are often resistant to pharmacologic treatment. Therefore, effective non-pharmacologic therapies are needed as an adjunct therapy to relieve symptoms and improve mobility (2). There are various approaches to FoG treatment, one of them being non-pharmacological. Previous work has shown that gait performance in PD can be improved by applying continuous external rhythmic auditory, visual or somatosensory

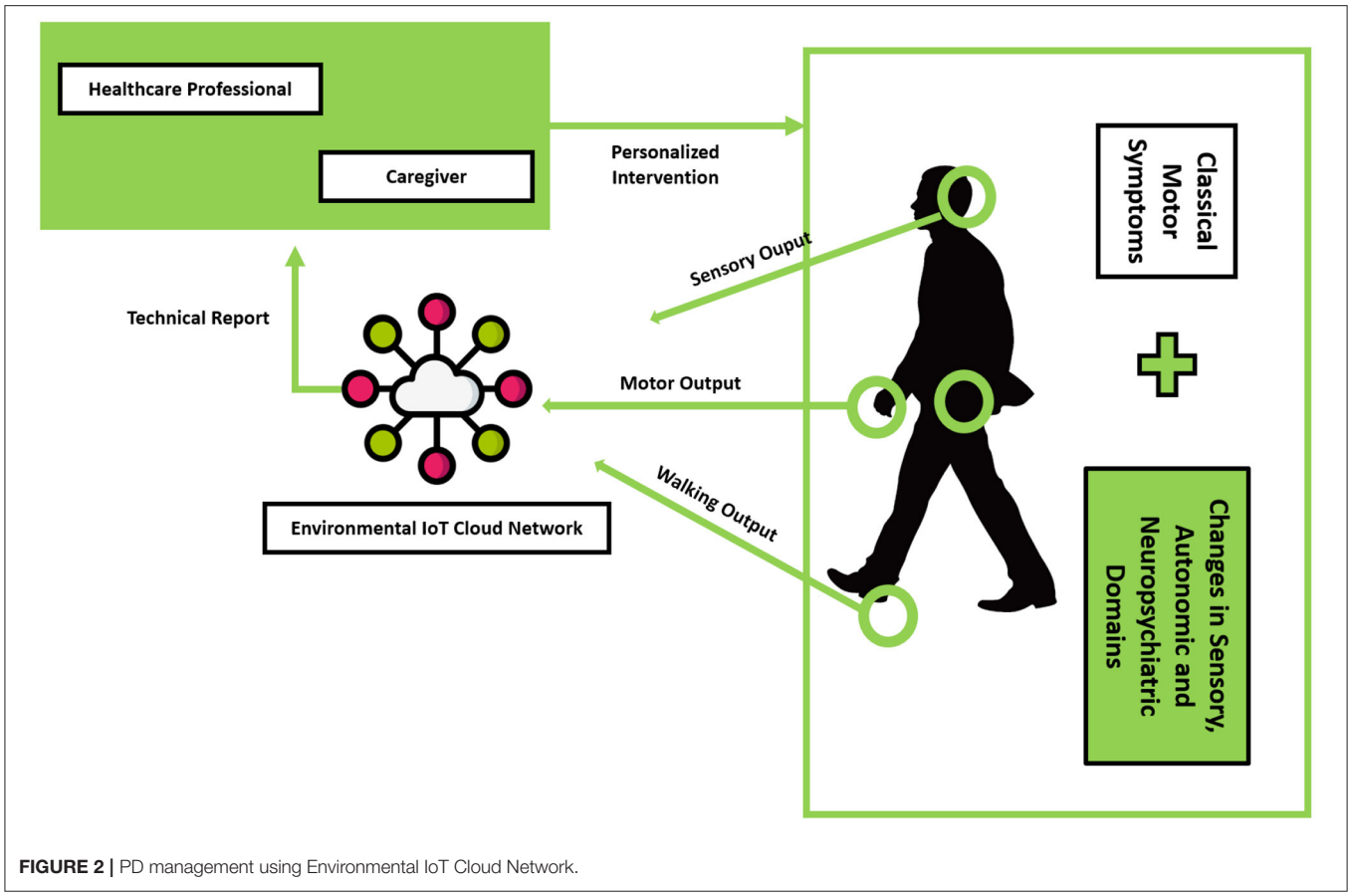

FIGURE 2 | PD management using Environmental IoT Cloud Network.

cueing (1). Eskofier et al. (19) noted that the constant, automatic monitoring of sensor-based information on walking ability and mobility is increasingly exploited to support objective assessment for preventive and proactive disease management. The Internet of Health Things (IoHT) is remarkably making its way within healthcare interventions and markets worldwide to answer complex and chronic pathological frameworks, just like PD.

As an initial step to further developing IoHT devices, it is vital to understand how IoT works in a healthcare environment, mainly how it contributes to monitoring external environmental stimuli. Usually, IoT consists of a complex connection between devices, machines, and servers with ample data storage (internet), functioning through a network shared between different stakeholders (20). IoT is an exciting topic inserted in the so-called Industrial Revolution 4.0, which aims to connect things and objects anytime and anywhere.

Following the previous description, we could argue that people with PD are surrounded by several stimuli, internal and external, generating a complex relationship between variables, and making it difficult to perform efficient disease management. This problem is evidenced in **Figure 2**, with the possible association with Environmental IoT Management.

One of the advantages of Environmental IoT Management is the likely decentralization of the healthcare structure, allowing for a smoother and more efficient interaction between healthcare professionals, caregivers, and patients (21). One of the challenges posed by PD is the chronic and variable nature of signs and symptoms, which are difficult to monitor (21).

CURRENT WEARABLE DEVICES ADDRESSING FREEZING OF GAIT IN PARKINSON'S DISEASE

A recent systematic review of new assessment methods on PD concludes that there is a particular need for standardized and collaborative studies to confirm the results of preliminary initiatives, assess domains that are currently under-investigated, and better validate the existing and upcoming assessment of PD with technology. Another systematic review (22) has identified and described different wearable insoles with the capacity to recognize patterns, namely stride time, step length, foot clearance, postural sway, gait kinematics, and plantar pressures. Marcante et al. (23) specifically addressed wearable pressure sensors to detect FoG. Some common limitations of these solutions are that their intervention ends in prevention or identification. The ability to associate a personalized intervention by receiving, processing, and sending data with advanced algorithms for health professionals or caregivers is usually not present or requires other devices.

Cueing is a well-established technique that has been shown to improve gait in PD patients in terms of increased walking speed,

step length, cadence (total number of steps taken per minute), and reduced number of FoG episodes (24).

Cueing can be defined as using external stimuli which provide temporal (related to time) or spatial (related to space) information to facilitate movement (gait) initiation and continuation. The literature extensively reported three cueing modalities: visual (25), auditory cueing, and somatosensory cueing. The precise mechanism(s) underlying the effectiveness of cueing to ameliorate FoG is unclear. However, previous studies (24) have suggested cueing may compensate for the defective internal rhythm generator of the basal ganglia, consequently affecting the coordination and execution of movement. In this way, PD patients may use auditory, visual, or somatosensory cueing to provide temporal information (i.e., external rhythm) to which movement can be associated. Another hypothesis is that people suffering from PD may use visual cueing to provide spatial information to scale and guide movements, allowing the patient to bypass their defective basal ganglia during gait.

Previous studies (26) have also suggested that cognitive/attentional mechanisms might explain the positive effects of cueing on FoG. Namely, auditory, visual or somatosensory cueing may shift the patient's attention to the task of walking, helping them to consciously think about the next action to be undertaken.

Studies indicate that enhanced proprioceptive information processing could be the mechanism underlying the positive effects of cueing on FoG (27). In this way, the patient may use visual or somatosensory cueing as an artificial means to stimulate the proprioceptive inputs, providing enhanced information on limb position and movement during gait.

Table 2 summarizes current devices and registered patents on cueing technology to treat FoG, describing the main trends on this topic.

Although several wearable devices have increased for patients with Parkinson's, few seem to use technologies such as environmental IoT, as described and defined earlier in this article. It is interesting that some projects and devices mentioned in **Table 2** use techniques such as health education and learning, namely by training specific exercises. Others have developed stimulation devices with a concrete therapeutic objective. This type of resource—education for health, day-to-day devices—due to its proximity and usability for the end-user, is a competitive advantage among the various devices developed or under development.

Despite this, and given the novelty of environmental IoT, particularly the collection of data, learning of personal patterns, machine learning, and generation of outputs personalized to the context, some projects and devices manage to fulfill the proposed purpose. Still, they would have the capacity to be more effective and satisfactory for people if they integrated all systems discussed so far.

Thus, the reflection proposed here contributes to broadening the discussion on the subject and revealing the importance of making fundamental and clinical investigations interdisciplinary, proposing more cooperation and synergies between the various disciplines of knowledge. In the case of PD, the participation of nurses in the construction of medical projects and devices can be very significant due to their thorough understanding of the person's adaptive capacity to the health-disease situation being experienced. But, it is not only nursing which benefits from cooperation with robotics, electronics, mechanics, medicine, and occupational therapy, among others.

INTELLIGENT SHOES FOR DIGITAL HEALTH MANAGEMENT

Generally, wearable health assistants aim to reduce the number and length of motor blocks, thus increasing safety while walking (2). Even assuming that this is a core function of the developed devices, Maetzler (36) indicates that, currently, there are no technology-based tools available that: (a) provide valid and accurate parameters of clinically relevant features of PD; (b) provide evidence of an ecologically relevant effect on specific clinical applications; (c) a definition of a target range, wherein the parameter reflects the adequate treatment response; (d) simple implementation allowing for repetitive use.

Within this scope, the development of smart shoes for managing complex health conditions is not new (37). Namely, this technology has already been applied to situations like degenerative spinal cord disabilities (37), frailty syndrome (38), diabetes (39), or even glaucoma (40). In terms of non-pharmacological treatment, previous work has shown that gait performance in PD can be improved by applying continuous external rhythmic auditory, visual or somatosensory cues (1). Accordingly, various behavioral "tricks" were developed by clinicians and patients to overcome freezing events. These tricks include marching to command, stepping over a walking stick or cracks in the floor, walking to music or a beat, and shifting body weight.

Mobility monitoring technologies demand research in sensor-based data acquisition and subsequent analysis to support objective and clinically relevant gait analysis (41). To undergo research in this field, Eskofier et al. (19) have already bulleted the main elements to take into consideration:

1) Remote gait assessment with smart shoes requires a data acquisition system that will collect sensor data;
2) An efficient management of power is essential to reduce the frequency of required charging of devices.

The variety of sensors that are applicable in the context of smart shoes are:

- Relative location and orientation determination using inertial-magnetic measurement units (e.g., accelerometer, gyroscope, magnetometer);
- Absolute location determination using satellite navigation systems (e.g., GPS, Glonass, Galileo);
- Foot plantar pressure determination using various forms of pressure sensors, which provide information regarding how effectively and efficiently individuals control the distribution of the body weight during gait;
- Ambient environmental sensors, such as atmospheric pressure sensors for altitude-dependent activities (e.g., stair climbing), light and sound sensors;

TABLE 2 | Current cueing devices and registered patents for FoG treatment.

Authors	Device	Method and description	Performance
Mazilu et al. (28)	GaitAssist	Personalized wearable system for FoG support and gait training in unsupervised environments. The two functionalities of the GaitAssist are (1) gait support during daily-life activities to avoid or reduce FoG episodes; (2) training support—as a personal assistant for the gait exercises. It provides audio feedback at critical moments throughout walking when FoG appears.	• Tested with five patients; • FoG real-time hit rate was equal to 97% (99 out of 102), with a detection delay of 0.25s; • FoG events shorter than that period could not be detected; • A decision in the algorithm regarding the FoG event is performed in at most 1 ms. • The system can be continuously used in the assistive mode for up to around 4 h.
Bächlin et al. (2)	Wearable Assistant for Online FoG Detection	A tiny computer for recording data and online signal processing. Customized platform based on an Intel XScale family processor and uses a Linux operating system.	• The device successfully identified 237 FoG events in eight patients (0–66 per patient). • The length of the FoG events ranged from 0.5 to 40.5 s, and over 50% of the FoG episodes lasted longer than 5 s. • Specificity ranged from 39.7 to 88.9%, and sensitivity from 34.1 to 99%.
Van Gerpen (29)	System and method for alleviating freezing gait and gait hypokinesia in users with extrapyramidal disorders	Visual cue for a user of a walker or walking aid device. Provide a constant or recurring stimulus to reduce or substantially eliminate the occurrence of FoG, gait hypokinesia, or stride reduction in a user, such as one suffering from parkinsonism.	Patent (n/a)
Buated (5) McCandless (30)	LaserCane	External cues improve walking ability in PD patients, stating that it significantly enhances FoG, specifically by increasing patients' stride length and velocity immediate improvements during gait initiation when using the Laser Cane over other interventions.	• Buated et al. (5) applied an external cue with a laser cane in 30 patients, significantly reducing time, the number of freezes (steps) from 0.33 ± 0.84 to 0, and increasing stride length (cm) from 6.82 ±_18.54 to 90.05 ± 19.44. • McCandless et al. (28), in their study with 20 participants, the visual cue with the laser cane reduced the percentage of freezing episodes from 81.58 to 27.50%, increasing velocity (m/s) from 0.335 to 0.455.
Mcloul et al. (31)	Movement initiation device used in Parkinson's disease and other disorders which affect muscle control	A portable wearable device produces rhythmic stimuli in auditory, visual, tactile, and/or vibratory activity that initiates or assists in the continuing movement of the body's muscles that tend to become rigid and immobile. Includes a housing, a clinician-accessible controller, a user-accessible controller, a transducer for producing sound or vibratory signals, and a computer interface.	Patent (n/a)
Shim et al. (32)	Walking assistance method and apparatus	Walking assistance method and apparatus, in detail, a control device that may estimate a gait motion of a user based on pressure data indicating information on a pressure applied to a sole of the user, and provide a feedback corresponding to the gait motion to the user by controlling a vibrator to apply vibration to the sole of the user, is provided.	Patent (n/a)
Akay (33)	Intelligent wearable monitor systems and methods	An intelligent wearable monitoring system includes a wireless personal area network to monitor a patient's motor functions. The private wireless network consists of a smart accelerometer unit, a personal server, and a remote access unit. The intelligent accelerometer unit measures the acceleration data of the patient in real-time. Motor function information is transmitted to a remote access unit for statistical analysis and formatting into visual representations.	Patent (n/a)
Chun et al. (34)	Wearable vibratory stimulation device and operational protocol thereof	The wearable stimulation device includes a measuring instrument for obtaining data relating to a body motion of a user who wears the vibratory stimulation device, a walking pattern database for storing normal walking pattern data collected by measuring general persons having standard walking patterns, and information about an inherent walking pattern analysis result of a specific user, a controller for analyzing the body motion information of the user, transmitted from the measuring instrument.	Patent (n/a)
Miyake (35)	Walking Aid System	The walking aid system comprised of a sensor section for sensing the motion rhythm of a walker, a recording section for recording values of measurements of the motion rhythm felt with the sensor section, a target setting section for setting a target value for the motion rhythm of the walker, a timing generating section for generating a timing signal according to the difference between the measurement and the target value, and a stimulus generating section for generating rhythm stimulus that is recognizable by the walker, according to the timing signal generated with the timing generating section.	Patent (n/a)

- Two major applications of algorithmic methods are to be used:
- Activity pattern recognition;
- Gait signature derivation for medical diagnostic and treatment contexts.

When we mention "smart shoes," we are necessarily restricting the discussion to intelligent footwear, but, in a broader sense, to wearable devices which support people with PD during walking. Such technology is not new nor under-studied, mainly because of the importance of FoG treatment, as stated before. The application of wearable walking assistants can include several features and present different treatment goals. For example, Pardoel et al. (42) have employed a conjoint precision analysis of PD motor symptoms using IMU and plantar pressure, successfully identifying Total-FoG (pre-FoG, FoG Transition, and FoG). The authors conclude that the developed system could lead to appropriate prevention of freeze or help to exit the episode. This is an example of an early detection and prevention wearable assistant device.

For PD, it is utterly important, at some point, to estimate gait patterns and recognize important gait events, particularly FoG subtypes. In this sense, Eskofier et al. (19) state that gait event recognition technologies compare the incoming sensor data, preprocessed time-series or computed gait features to reference characteristics of important gait events.

EUROPEAN PROJECTS: AN EFFORT TOWARD AN EFFECTIVE SOLUTION

In the last years, there has been an effort to develop and structure new interventions and technological devices to manage and treat FoG, which can be found in the European database CORDIS (cordis.europa.eu).

Main technological advances have been focused on wireless technologies with high-resolution tracking of gait patterns in PD patients, dimensioning time-varying biomechanics related to locomotion, like the project *"Decoding impairments of gait and balance from local field potentials in patients with Parkinson's disease (gaitCODE)."*

Some projects were interested in developing portable devices for people living with PD, delivering non-invasive neurostimulation signals, as in the *Automated Mechanical Peripheral Stimulation for motor rehabilitation in people living with Parkinson's Disease (GONDOLA)*, which specifically provided physical neurostimulations on specific points in both feet. These neurological stimuli allow for increasing afferent inputs from the peripheral nervous system to the spinal cord, inducing a better functioning of the central pattern generator (the mechanism that regulates movements in the body). Similarly, *Industrial Academic Initial Training Network toward the focused treatment of age-related motor symptoms* project aims to study specific basal ganglia pathways and stimulate balance and postural control through virtual reality, body-worn movement monitors, therapeutic cues, and individualized training.

Portable and wearable devices seem to be the most common strategy to address FoG, particularly when it is necessary to monitor related motor symptoms in real-time, to support clinical decisions. This is the case of the project *Unobtrusive, Continuous and Quantitative Assessment of Parkinson's disease: Hard Evidence for Optimal Disease Management with Information Technologies (Stat-On TM, Park-IT)*, which developed a small wearable device to continuously monitor movement patterns, being total autonomous and comfortably worn in patient's waist. An exciting and noteworthy addition is the possibility to transfer the motor assessment data to an external mobile device, which then, through machine learning, provides an identification of specific PD symptoms.

Treatment-related projects have also been developed, like a *Closed-loop system for personalized and at-home rehabilitation of people with Parkinson's Disease (CuPiD)*, designed to meet optimal rehabilitation of PD patients with personalized training at home. It's based on an ICT-enabled solution, with a tailored solution to target mobility, cognitive function, and debilitating symptoms like FoG.

The way has been drawn to reach a more person-oriented treatment, with the ultimate goal of achieving autonomy and independence. This is the project's logic *PROPHETIC: An innovative personal Healthcare Service for holistic remote management and treatment of Parkinson's patients*, which exploits miniature information systems to manage the disease, with remote and continuous monitorization of patients and sharing management plan data between caregivers and health professionals. This project, similarly to others, applied virtual reality to enhance treatment with gamification features at home.

Other projects, like the one developed by *Kinetikos* or *TecaPark*, in addition to presenting the features of the previous projects, include a more subjective assessment with a biopsychosocial dimension and address quality of life as part of the treatment of FoG.

DISCUSSING FUTURE TRENDS

With IoT and the increase in the ability to computationally collect and process data, devices anchored in this technology will quickly become part of our daily living activities. Thus, it is no surprise that most client-centered devices developed a focus on wearable technology. However, this aspect adds a layer of complexity, as questions of comfort, usability, and aesthetics need to be considered.

With this shift to a self-care paradigm, where the relationship between client and healthcare provider will change, the key to developing future viable solutions will imply including dimensions that were not previously considered when using technology. The presence of wearable devices in patients experiencing FoG will most certainly become a reality, with the client as an active part in demanding this technology and choosing which option fits their personal preferences (43). Among the wearable devices that will become mandatory for people with PD experiencing FoG, smart shoes will most certainly be one, if not the most present technology (44).

The potential associated with smart shoes is immense. Not only will PD patients be able to understand what happens before and during the FoG event, but the data collected throughout

the whole process will help researchers and healthcare providers develop personalized interventions and new technologies, like domotics, that will significantly decrease the burden associated with FoG (45).

Smart shoes will most certainly be data-collection-based. The potential to help the patient to focus the attention on the task of walking by restoring internal cueing and internal driving is a dimension that can be associated with a machine-learning algorithm with the potential to significantly reduce the risks associated with the FoG (46).

These devices will further assist healthcare providers and researchers in understanding how the real-world environment influences controlled interventions. Until now, clinical research has been associated with limited control of variables. Data collected during clinical trials represent only part of how people deal with their health conditions and how the intervention affects (positively or negatively) the client's quality of life.

Data collection will become more complex, with IoHT allowing machine-learning algorithms to help the client understand what is happening in real-time (47, 48). They will also help address FoG causes and consequences by preventing them through the individualized establishment of cueing strategies and alert systems that will allow a quicker and better response to a fall, namely through an intelligent environment (49).

Future trends portray the need to engage all the actors in this phenomenon: the FoG. Understanding how wearable technology can be part of this new self-care paradigm will significantly impact how patients deal with this condition. Thus, assuring citizen engagement in developing IoHT strategies will be a requirement for every device, with new variables being integrated into how these are built (50).

CONCLUSIONS

FoG is a complex episodic motor symptom that significantly affects the quality of life and activities of daily living. Despite the existing pharmacological treatments to alleviate PD symptoms, namely tremors and bradykinesia, there are limited resources to treat FoG. Accordingly, technology has been consecutively applied, concomitant with conventional approaches, namely external cueing, either visual, auditory, or somatosensory.

This perspective successfully presented and described current therapeutic options in PD, eliciting their advantages and limitations. One of the major conclusions is that complementing the standard treatment with innovative technology-based solutions is helpful for enhancing the daily life of people with PD. Wearable technology and IoT might constitute important assets for monitoring and self-management in homecare. Existent solutions still need further development to address the need to deliver a personalized intervention by receiving, processing, and sending data with advanced algorithms for health professionals or caregivers.

Regarding cueing devices, one of the most recent and modern approaches is wearable technology embedded in footwear, which increases neurological stimuli in PD patients and thereby their motor functions. Smart shoes have been developed for many pathologic signs and symptoms and are currently being tested for PD.

State of the art aims to apply IoHT and virtual reality to monitor patients and increase their autonomy, also propelling caregiver abilities through personalized programs. Future trends seem to be reaching a person-centered approach, focusing on comfort, usability, and aesthetics, namely in footwear development.

Some limitations have been identified: the unsystematic review might have implied the loss of previous important works on the topic; the focus on wearable shoes provided a more narrowed review, thus contributing to less enriched work.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

RB and PS led the design of the manuscript. HN and FV assisted in drafting the manuscript. MF provided advice on key study issues. All authors contributed equally to the narrative literature review and evidence synthesis. All authors contributed important intellectual content to the manuscript and approved the final version for publication.

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How Far Can Conversational Agents Contribute to IBD Patient Health Care—A Review of the Literature

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Modern societies are facing health and healthcare challenges as never seen before. The digital world in which we are living today considers digital health interventions such as "internet-delivered" therapy (e-Therapy) or mobile apps as an integrated part of healthcare systems. Digital transformation in health care requires the active involvement of patients as the central part of healthcare interventions. In the case of chronic health conditions, such as inflammatory bowel disease (IBD), it is believed that the adoption of new digital tools helps to maintain and extend the health and care of patients, optimizing the course of the treatment of the disease. The study goal was to undertake a literature review associating the use of chatbot technology with IBD patients' health care. This study intends to support digital product developments, mainly chatbot for IBD or other chronic diseases. The work was carried out through two literature review phases. The first one was based on a systematic approach and the second was a scoping review focused only on Frontiers Journals. This review followed a planned protocol for search and selection strategy that was created by a research team discussion. Chatbot technology for chronic disease self-management can have high acceptance and usability levels. The more interaction with a chatbot, the more patients are able to increase their self-care practice, but there is a challenge. The chatbot ontology to personalize the communication still needed to have strong guidelines helping other researchers to define which Electronic Medical Records (EMRs) should be used in the chatbots to improve the user satisfaction, engagement, and dialog quality. The literature review showed us both evidence and success of these tools in other health disorders. Some of them revealed a huge potential for conversational agents as a part of digital health interventions.

Keywords: artificial intelligence, chatbot, conversational agents, digital health, IBD, machine learning

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INTRODUCTION

Digital health is an umbrella expression that joins health areas allied to digital technology usage. It involves a wide technology landscape and standardized health design for better customized healthcare services. Digital health has an important role in supporting healthcare systems and public health, aiming for more equity in public access, and reaching toward universal health coverage. It uses different delivery systems that connect and interpret data (1, 2).

One of the delivery systems based on computational dialogs is the conversational agents. The conversational agents' era has now become a reality. It is a digital tool that includes software and hardware, "that uses machine learning and artificial intelligence methods to mimic human-like behavior and provide a task-oriented framework involving dialogue" (3). Considering the technologies that are behind conversational agents, otherwise known as chatbots, it is worth noting that machine learning (ML) is the study of computer algorithms that automatically improve the virtual communication experience and is seen as a subset of artificial intelligence (AI), defined as the intelligence demonstrated by the machines.

Looking back to half a century ago, there emerged the programmable natural language ELIZA, developed at the MIT Artificial Intelligence laboratory by Joseh Weizenbaum. It may be considered the first chatbot therapist (4). Years later, the employment of this tool made it possible to build commercial conversational agents, such as Google Home and Amazon Echo. The technology has also been advancing to the point where chatbots incorporate a natural language processing capacity for speech, dispensing with the need for a keyboard, as anyone who uses Siri knows.

In the healthcare environment, these digital tools may offer particular advantages because conversational agents are always available when patients need to interact with them. This programmed machine is never distracted by other issues and always remembers everything (5). This issue enables us to predict patients' needs based on their conversations, purchasing, or browsing behaviors. It is also considered a way of improving value in health care because it promotes the exchange of quality healthcare services and, consequently, better health outcomes for all.

Recent research (3) and media information (6, 7) has shown increasing evidence of conversational agent contributions since 2017, in particular regarding mental health. They are being used in the prevention of suicide and cognitive-behavioral therapy. Considering this type of usage, it should be evident that clinical requirements are well suited to the existing e-Therapy digital tools. This is because a conversational agent involves a dialog system that responds automatically using human language. In addition, e-Therapy provides both internet-delivered data and simple online self-help resources.

Authors such as Gratzer and Goldbloom (5) have classified how e-Therapy offers guidance to physicians on three levels:

- Low—Those patients who are told about websites and/or apps or find them on their own to aid their health condition;
- Medium—Patients are given self-directed tools by their physicians;
- High—Internet-delivered therapy or apps which are integrated into traditional health care systems followed by discussions between patients and physicians.

With reference to the above, it is clear that conversational agents involve high levels of interactions such as programmed dialogs that e-Therapy does not include. It is important therefore to understand the "starting point" of chatbot technology and how it has been introduced into the field of health care.

The way patients are using healthcare mobile apps nowadays is similar to the early days of conversational agents. Within the chatbot technology, Torous et al. (4) have discussed several issues related to chatbots that have been incorporated into mobile apps. First, they have highlighted that there is an increasing number of apps. They said that only one in four revealed a quality standard. Second, when patients download a mobile app, it does not mean that they are necessarily going to use it. Third, downloading a mobile app involves challenges for patients in finding the right app at the right time. Fourth, the majority of users do not understand the ethical issues associated with mobile apps which do not offer the right to privacy (8).

The usage of ML and AI technologies in gastroenterology has been carried out since 2018 (3–11). Only one experimental study was found (12), which was published in May 2020. It was a retrospective cohort study where the authors explored the use of chatbots for patients with IBD. It had also been developed from a poster previously published (12), which was found during the systematic literature review process conducted for this research. These findings demonstrate a huge potential to explore and consider other medical chatbots since there are many different systems where they can be used for multiple purposes, e.g., dementia (13)—the chatbot acts through voice recognition, working as a companion for patients with short-term memory loss, helping physicians to identify signs of the patient's condition; insomnia[1] – acts through conversations *via* text, working as a companion for insomniacs when they are awake at night; pediatric issues (14)—chatbots are designed to help pediatric patients get appropriate medicine for certain ailments; childhood obesity[2]—acting as a peer companion, using an app interface, for obese teens to keep them engaged through text messages; and psychiatry[3]—to help patients think about their critical situations[4] (6, 12).

The goal of this study is to systematically review the literature regarding the use of chatbot technology in the healthcare of patient with IBD. This study aimed to support future developments in digital health, mainly chatbot for IBD or other chronic diseases. To this end, several research questions were posed:

- How do academics describe the use of chatbots by healthcare professionals and patients with IBD?
- Who are the researchers that are studying this topic?
- What are the patient profiles that are targeted for using this digital tool?
- What are the implications of using chatbots in the health care of patients with IBD and healthcare professionals?

This document is divided into 5 sections: first, the Introduction, where a summary of the context is given; second, Materials and methods, setting out the search strategy adopted through two different phases and the selection criteria used to filter the articles in both phases: (a) systematic literature review and (b)

[1]https://insomnobot3000.com/ (Accessed January 04, 2022).
[2]https://mobilecoach.com/ (Accessed January 04, 2022).
[3]https://woebot.io/ (Accessed January 04, 2022).
[4]http://www.prisma-statement.org/ (Accessed January 04, 2022).

scoping review; third, Results, where the global outcomes are shown through the (a) PRISMA (see text footnote[4]) method and (b) description method. In this section, the selected studies are analyzed using the narrative research approach; fourth, the Discussion, in which the impact of using digital tools such as a conversational agent is examined; finally, the Conclusion, with implications for further research.

MATERIALS AND METHODS

This literature review study was developed into two phases. First, it was carried out by a systematic approach and the second effort was a scoping review on Frontiers Journals. These are detailed below.

1st Phase—Search Strategy and Selection Criteria

First, the team shared their different experiences and perspectives on the subject. This resulted in a title, "How far can conversational agents contribute to IBD patient healthcare—A review of the literature." Following this, the principal goal was established, "to understand the current implications and possibilities for a chatbot in IBD as a channel of communication for physicians and patients." This implied the need for a systematic literature review to be carried out. Another point of discussion was a future goal that our team would establish: the development of a pilot scheme for an online platform for IBD management/control that uses ML or AI frameworks, enabling the chatbot to interact virtually with a patient. The purpose of adopting this technology would be, for example, to predict automatically, disease complications, and to support physicians, clinicians, and others.

Following a period of initial discussions, the research team decided to investigate the literature published from 1 January 2014 to 31 December 2019. This task was performed in February 2020 on ACM, PsycINFO, PubMed/NCBI, Scopus, and WOS, using a team of three researchers for the validation process. After that, Parsifal was chosen as the online tool to plan, structure, gather, register, and screen the studies.

The initial brainstorming process of the research team was supported by Parsifal online tool[5], and it was divided into different phases. First, a plan was carried out that was structured by protocol, objectives of the study, population, intervention, comparison, outcomes, and context (PICOC); research questions; related keywords and synonyms; search string definition; database sources; inclusion and exclusion selection criteria. Second, the research team kept Parsifal and conducted a phase composed of study selection, quality assessment, data extraction, and data analysis.

It is worth mentioning that keywords and synonyms were broadly discussed by the three researchers. Another Parsifal feature that contributed to the aforementioned task was an automatic generation control of a research string. Regarding the brainstorming of keywords (**Table 1**), synonyms and the PICOC field previously referred to, the "Parsifal" software queried that we included in the databases search the following:

- ("IBD*" OR "Crohn's Disease*" OR "Inflammatory Bowel Disease*" OR "Ulcerative Colitis*") AND ("Chatbot*" OR "AI*" OR "Artificial Intelligence*" OR "Chat*" OR "Conversational Agent*" OR "Conversational Assistant*" OR "Conversational Interfaces*" OR "Machine Learning*" OR "Messaging Applications*" OR "Natural Language Processing*" OR "NLP*" OR "Question Answering System*" OR "Robot*" OR "Service Automation*" OR "Virtual Agent*" OR "Virtual Assistant*").

TABLE 1 | Brainstorming of keywords, synonyms, and field.

Keyword	Synonyms	Related to (PICOC)
Chatbot	AI	Outcome
	Artificial Intelligence	
	Chat	
	Conversational Agents	
	Conversational Assistants	
	Conversational Interfaces	
	Machine Learning	
	Messaging Applications	
	Natural Language Processing	
	NLP	
	Question Answering System	
	Robot	
	Service Automation	
	Virtual Agents	
	Virtual Assistants	
IBD Patients	Crohn's Disease	Population
	Inflammatory Bowel Disease	
	Ulcerative Colitis	

The criteria of inclusion and exclusion were defined by discussion between members of the research team. It was decided that studies should be included in the review if they met at least three of the criteria referred to below, and two of them should be "Focused on IBD" and "Focused on the patient." Criteria for inclusion were as follows:

- Focused on IBD and;
- Focused on the patient and;
- Involved technology related to a chatbot, ML, or AI;
- Involved interventions such as non-pharmacological therapies, multi-component interventions such as complementary strategies to increase adherence to treatments;
- Multiplatform technology (software developed for multiple operating systems);
- Prospective communication studies involving Electronic Medical Records (EMRs).

Studies were excluded if they matched at least two of the criteria referred to below and one of them should be "Study Design." Duplicated studies, or those which were not written in English, were also excluded, as well as studies whose outcomes did not

[5]https://parsif.al/ (Accessed April 30, 2022).

TABLE 2 | "Airtable" tabs.

Label name	Screening number	Description of the method	Not meeting the inclusion criteria	Not meeting the exclusion criteria
01_1stPhase_LRCycles	7,586	Title and abstract screening		
02_2ndPhase_LR_53SelectedArticles	53		X	
03_3rdPhase_LR_30SelectedArticles	30	Full-text screening		X
04_4rdPhase_LR_9ArticlesIncluded	9	Describe the included studies		

match the purposes of this investigation. Criteria for exclusion, therefore, were as follows:

- Duplicates or not in English;
- Study design (e.g., the design of clinical trial);
- Clinical experiences;
- Clinical intervention;
- Description of the chatbot for other purposes (conversational agents used without intervention proposes) or future research;
- Focused only on clinical issues (e.g. nutrition, gut microbiota, and immunity).

1st Phase—A Strategy Adopted for Data Extraction

As mentioned above, Parsifal helped the research team with both brainstorming and conducting processes until all the data had been collected. After that, it became necessary to register all phases of data extraction (**Table 2**). Given the complexity of data, the team decided to use Airtable[6] which is an online tool that is used as a complement to Parsifal. The Airtable sheets were used to globally organize all the research. Each tab corresponds to one research phase and is presented in **Table 2**. Below, each phase will be explained in detail.

The first phase of the data extraction was registered in tab "01_1stPhase_LRCycles." This phase was conducted to retrieve articles that could inform us about the background and discussion in general. Each study has its title and the abstracts that were double screened by three researchers in a random way. When a decision on inclusion or exclusion could not be made based on the defined criteria, the full text was retrieved. If any question persisted, a fourth person made a final decision. From this primary stage, 53 articles were extracted and manually registered in the tab "02_2ndPhase_LR_53 SelectedArticles" with some guideline notes included.

Second, these 53 articles were filtered by reading again the title and the abstract, and also the introduction and the conclusion. The process also involved two people, with one investigator's opinion being validated by the other. Out of 53 articles, 23 of them were excluded. The process of registration was similar. All titles were manually registered in a new tab, the "03_3rdPhase_LR_ _30SelectedArticles," including other information in subtabs such as if it was rejected or accepted and what were the criteria of exclusion.

A total of three previously rejected articles were checked again and were included in this review. This is because the research team considered that these articles revealed an interesting and detailed technological approach regarding new IBD strategies for patients' behavioral changes. These three articles are as follows: (a) "Challenges in using real-world clinical practice records for validation of clinical trial data in Inflammatory Bowel Disease: Lessons learned" (15); (b) "Decision-making process in colon disease and Crohn's disease treatment" (16); and (c) "Digital health apps in the clinical care of Inflammatory Bowel Disease: Scoping review" (17).

In short, nine articles were included in this research and were read. Only one researcher manually recorded the findings with reference to the inclusion criteria defined earlier by the team. In the tab, "04_4rdPhase_LR_9ArticlesIncluded", data relating to title, date of publishing, and the disease or conditions involved with it, were also manually registered.

In the following section, the results will be displayed. First, a global perspective is presented of the outcomes using the PRISMA method, and second, a narrative characterization of the studies is given combining the authors' analyses with the research team's overview. Finally, they will be discussed in Section 4.

2nd Phase—Search Strategy and Selection Criteria

With the COVID-19 pandemic declared in March 2020 (18), new challenges in the healthcare systems domain emerged. After researchers concluded the first phase of the literature review, they decided to update this original study and include more recent studies.

Another decision regarding the feasibility of this second phase of the search was to focus only on the Frontiers Journals database. The reason being "Frontiers ranks as the 3rd most-cited publisher among the 20 largest publishers with an average of 4.8 citations per article, an increase from 3.9 citations in the previous year." (19). Regarding the queried referred before, a few doubts emerge when researchers tried to apply that queried: Should the "IBD" word or "Inflammatory Bowel Disease" expression be used in this second phase of the search? Thus, they decided not to use them as a string setting, but to extend it, reducing the initial query to a unique keyword arrangement, in this case: "conversational agents" or "chatbot." The reason being the selected range data criteria was "past year." Following this approach, we would like to focus only on the year 2021 collecting the most recent studies published. After, researchers filtered only articles associated with health topics. The titles were screened through a double review discussion. In case of any questions, they kept an abstract analysis.

[6]https://airtable.com/ (accessed April 30, 2022).

2nd Phase—Strategy Adopted for Data Extraction

The research team established inclusion criteria through a remote discussion based on discoveries that were found out in the Frontiers website. Unfortunately, any article referring to the IBD topic with a chatbot was not found. Thus, the researchers decided to extend this initial scope and include any article related to other chronic diseases. The title and abstract analysis had the following inclusion criteria:

- Articles related to any chronic disease.

The exclusion criteria were as follows:

- Articles only related to methods assessment.

RESULTS

1st Phase—Systematic Literature Review

The detailed PRISMA diagram in **Figure 1** further outlines the number of studies excluded per criteria and matches them with the data presented in **Table 2**.

In summary, **Figure 1** presents the database search retrieved from five databases with a maximum achieved in Scopus $N = 5{,}708$ and a minimum in PsycoINFO $N = 12$. After that, two researchers' readings went through a more in-depth review process and $N = 7{,}392$ articles were excluded. From this point, 23 were excluded for not meeting the inclusion criteria "Focused on IBD" and "Focus on the patient," which is the main context of the review. After a full-text screening of the 30 articles, 21 were rejected for meeting the exclusion criteria detailed in **Figure 1**. In the end, only nine studies were included in the systematic review. They will be described in detail in part 3.3, Characterization of the studies included.

2nd Phase—Scoping Review

This search phase, conducted between 4 January 2022 and 7 January 2022, identified 30 articles without any interval date limitation. The application of two filters resulted as follows: first, 22 articles were published in 2020; second, and after selecting health topic as a domain area, 11 articles emerged as a final result. In the end, this material was spread across these different Frontier Journals categories: digital health ($N = 7$) (20–26); public health ($N = 2$) (27, 28); and psychiatry ($N = 2$) (29, 30). All 11 titles were analyzed through a double review discussion. In case of any issues, the researchers followed the criteria of abstract analysis. There were three articles related to chronic diseases: sickle cell disease ($N = 1$) and mental health ($N = 2$). The last two were related to method evaluation. Therefore, only one article could be added to the first review study.

Characterization of the Studies Included

In the current section, studies included in the systematic literature review are presented. They come from domains such as computer science, health information, and live science. The presentation of the findings is structured as follows: first, the criteria for inclusion in the study are stated, and second, a narrative review is given. This approach helps the research team to accomplish purposes, such as understanding the results of other studies that are closely related to the one being undertaken and establishing the importance of the findings recognizing where the gaps to be filled may exist.

As a complement to the discussion part, it was decided to create a literature map (**Table 3**). The goal was to summarize the relevant details of each article not considered in the narrative review.

- Cohn et al. (31)—The criteria to be included in the study were "Focused on IBD," "Focused on the patient," and "Involved technology related to chatbot, ML, or AI."

This study, presented in poster form, aimed at predicting patients' responses to immunosuppressive therapy by capturing subtle characteristic patterns of the disease in magnetic resonance enterography images. What is interesting in this study, even involving a small sample of participants as few as 11 patients, is the fact that the authors used an ML framework for calculation, by "reading" magnetic resonance enterography images, according to whether the patients were responding, or not, to the immunosuppressive therapy. Their findings showed good feasibility compared with the manual process of analysis conducted by physicians.

In summary, they argued that this method did not represent a risk and could be adopted as a support tool.

- Afzali et al. (15)—The criteria to be included in the study were "Focused on IBD," "Focused on the patient," and "Prospective Communication Study involving EMRs."

The goal of this USA study was to show, through several case studies, what the challenges were regarding the accuracy and the implementation of EMRs. The first case presented in the study pointed to an interesting issue: the source of the data collected is from the Veterans Health Administration (VHA) database; this is restrictive and reveals critical challenges: restrictive, because the type of sample involved did not include women, and challenging because the authors argued that the data collected coming from only one gender. This issue may have produced inconsistent results. Another point was the diagnoses and the treatments of this population were conducted outside the VHA system. This means that there existed more than one database presenting different IBD categories and the systems were not connected between them. Regarding this scenario, some specific data which were not well defined were recorded manually on the VHA database.

The second case reported was PRECISE 3 (38), a study from the Czech Republic. This open-label safety type of clinical trial, in which information is not withheld, aimed to study which were the clinical factors that predicted short-term and long-term efficacy of anti-TNF therapies. PRECISE lasted 7 years and screened 867 patients with IBD. However, the screening process failed in 91.8% of cases because only a small number of participants were eligible. The authors assumed that they believed that these clinical records were initially documented using inadequate clinical variables from heartbeat interval (HBI). In this particular example, it was assumed that there were no differences between the type and the

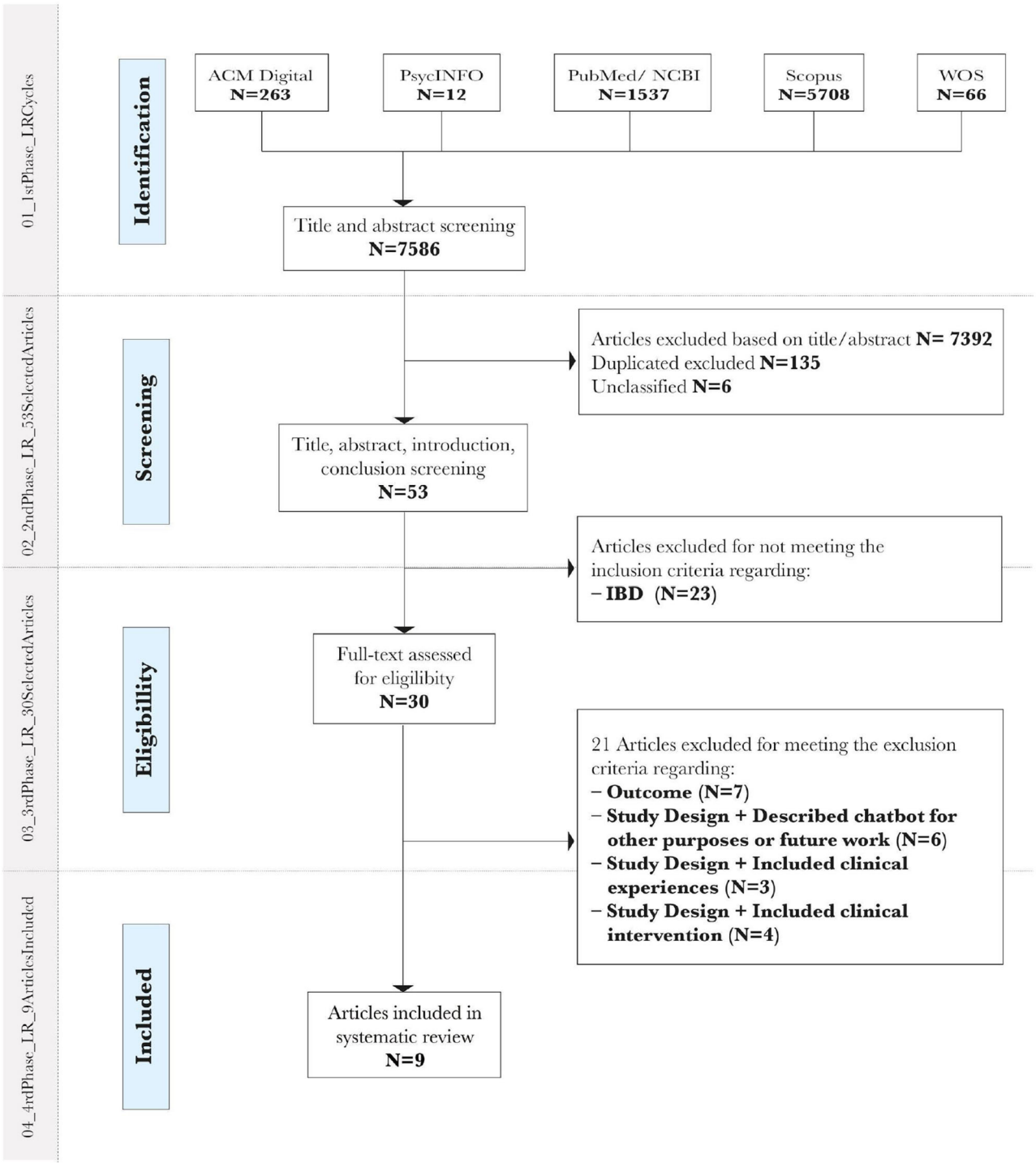

FIGURE 1 | PRISMA flow diagram for systematic review.

size of the sample considering the percentage of, or reason for, screening failure.

The last case presented was a piece of research conducted by the authors of the article (15), and it was considered an opportunity to reveal more consistent results. It was a retrospective cohort from eight academic and large community practices. It also referred to the challenges with the accuracy of EMRs regarding the high degree of variability in the completeness

TABLE 3 | Literature map of the included articles.

References	Study type	Participation	Study duration	Intervention and/or methods	Outcomes
Cohn et al. (31)	Experimental study	11 CD patients who underwent MRE between 2010 and 2015	Not applicable to the type of study	CD patients who underwent MRE between 2010 and 2015 and for whom there was at least 6 months of follow-up or an outcome of interest, were retrospectively identified. An expert radiologist demarcated regions of interest (ROI) based on accepted MRE criteria	Radiomics-based ML analysis of MRE (resonance heterography) images of CD patients can be used to develop a personalized risk score to predict response to IS (immunosuppressive) therapy
Afzali et al. (15)	Case studies	867 IBD patients were screened	Not applicable to the type of study	Data from EMRs extracted manually	The screen rate failed in 91.8%
Mossoto et al. (32)	Experimental study	287 children with PIBD	Not applicable to the type of study	Mathematical model assembled different techniques of supervised ML to classify IBD diagnosis in patients with pediatrics	Clinical IBD potential of ML models
Roccetti et al., (33)	Longitudinal study	Crohn's disease experts with a specific pharmaceutical treatment, the infliximab	2 years[a]	Participants post[b] were read and analyzed by human beings and automatic tools in order to understand their mood when infliximab treatment was mentioned (positives, neutral, or negative term exist in a given discourse)	Gastroenterologists tends to express more positive considerations than the OponionFinder. The non-medical experts tend to return a large number of negatives
Dardzinska and Kasperczuk, (16)	Experimental study	IBD patients	Not applicable to the type of study	The presented model predicts the probability of IBD with malignancy or benign tumors	Classification model tool to find symptoms that affect whether the patients is ill or not[c]
Ashton et al. (34)[26]	Case studies	This study phase is not included in the inclusion of participants	Not applicable to the type of study	Literature review to the analysis of the current management of pediatric IBD applying personalized medicine	AI and ML for personalized medicine[d]
Ashton and Beattie, (35)	Case studies	400 patients in remission until 12 months		Model to predict disease outcome	Identify the potential to translate clinical data from diagnosis into a clinically accurate model predicting the response of medications, complications and others
Borland et al. (36)	Experimental study	This study phase is not included in the inclusion of participants	Not applicable to the type of study		Integrative visualization tool enabling users to explore patients generated research questions or topics
Zand et al. (37)	Experimental study	1712 IBD patients	Do not have this information	Electronic dialog data collected between 2013 and 2018 from a care management platform (eIBD) at a tertiary referral center for IBD at the University of California, Los Angeles (UCLA)	Algorithm showed 94% similarity in categorization compared with our three independent physicians

[a] *The 261 posts analysis range was between October 2013-October 2015.*
[b] *Group A – Experts gastroenterologists; Group B – Non-medical experts; OpinionFinder – Standard values into the integer interval (−1,1) based on the algebraic sum of provided scores.*
[c] *IBD doesn't present a precise diagnosis.*
[d] *This is the only study founded that refer the potential of personalized medicine within crossing multi-omics data with clinical data (bloods, complications, outcomes, relapse, etc.).*

of EMRs in terms of information resembling data collected during clinical trials.

One of Afzali's team's conclusions was the need for a standardization process to evaluate and document IBD EMRs. Regarding this issue, The American Gastroenterological Association (AGA) has established a document where it documents community practices for IBD regarding the quality and performances to be followed[7]. The authors argued that this orientation was not clear enough on the way IBD EMRs should be carried out.

- Mossoto et al. (32)—This is the first of three selected studies on the subject of personalizing medicine in pediatric inflammatory bowel disease (PIBD) conducted by the same research group. The criteria of inclusion met "Focused on IBD," "Focused on the patient," "Involved technology related to chatbot, ML, or AI," and "Prospective Communication Studies involving EMRs." This study was published in one of the most prestigious research journals, Nature, in the scientific reports section.

The goal of this study was to present a workflow that aided the accuracy of PIBD diagnostics through a unique experimental approach, being the application of a mathematical model that used different techniques of supervised ML, diagnosing Crohn's disease (CD), or ulcerative colitis (UC) through endoscopic and histological data.

[7] https://gastro.org/practice-guidance/quality-and-performance-measures/ (accessed January 07, 2022).

The study involved 287 patients, 178 with CD and 80 with UC, and 29 patients with unclassified diseases from Genetics of Pediatric Inflammatory Bowel Disease at Southampton Children's Hospital in the UK. From this sample, EMRs were collected using a standard platform not identified by the authors. The purpose of this phase was to observe how far clinical features of analysis could induce the development of two data clusters, one for CD and the other, for UC. Concerning classification, the groups identified by each cluster were assessed with reference to "age of onset and C-reactive protein levels at diagnosis, disease subtype, gender, family history and personal history of autoimmune disease (…)" (p. 2). After that, an ML framework was applied to these EMRs aiding initial diagnosis with endoscopy and histology data.

The endoscopic and histological data were collected from 287 patients, but the ML framework was applied only to 239 patients (CD = 143, UC = 67, IBDU = 29) because the model verified that there existed unlabeled data from the validation dataset of 48 participants. The female gender represented 37% ($N = 107$) of the sample in the dataset. The average age was 11.5 years (range from 1.6 to 17.6 years). About 9% ($N = 26$) of patients diagnosed were below 6 years of age (very-early onset of IBD). The remaining 48 patients (CD = 35, UC = 13, the average age of onset being 13.2 years) were used to validate the model.

In summary, the outcome model demonstrates high accuracy in distinguishing CD from patients with UC with a total average of 83.3%: 71.0% through endoscopy data (duodenum, ileum, D-colon, rectum, perianal); 76.9% in histology (ileum); and 82.7% combining both (duodenum, ileum, D-colon, rectum, perianal, esophagus, ileum, and A-colon).

- Roccetti et al. (33)—This article met the inclusion criteria of "Focused on IBD," "Focused on the patient," and "Multiplatform technology."

It is an Italian longitudinal study that aimed to investigate the Facebook posts written by patients with Crohn's disease with particular reference to the effects given by Infliximab treatment.

Over 2 years, 216 posts were analyzed using a social media multiplatform tool. They exhibited opinions written on networking groups with particular reference to the reactions given to Infliximab treatment. The relevance of the findings is that the human side of patients and sentimental issues were investigated in the posts from three different perspectives: group A, composed of experts, e.g. gastroenterologists; group B, by generic assessors without any specific medical competence, and group C with an analysis conducted by a digital tool, OpinionFinder, which is one of the best known and tested ones (34).

The results of the categorization of the posts conducted by the two groups and the software revealed an interesting gap: the expert group tended to assign a negative evaluation to patients' comments on Infliximab with a lower frequency. Only 13% of the posts were assessed as negative by Group A, and 34% of the posts were negatively scored by Group B. Still, the gastroenterologists classified 45% of the posts as neutral in comparison with 42% for the machine result and 25% for non-experts. The values for positive posts were similar between the two groups (Group A—42%; Group B—41%) but, compared with the machine 30%, they were higher.

In conclusion, non-medical experts tend to interpret patients' dialogs with reference to social media posts, more negatively than gastroenterologists. Surprisingly, machines were inclined to agree with the medical experts. This scenario reveals that both types of analyzers, the gastroenterologists and the machine, are only focused on the positive side effects regarding IBD treatments.

- Dardzinska and Kasperczuk (16)—This research met the inclusion criteria of "Focused on IBD," "Focused on the patient," and "Involved technology related to chatbot, ML, or AI."

This Polish experimental study consisted of two phases where a logistic regression method with computerized extraction data was used to classify the CD and UC diseases. One of the two experiments involved ML. The main goal of the study was to present a retrospective analysis of symptoms discovered in medical data that could differentiate UC from CD as quickly as possible in the diagnosis process.

The retrospective analysis of medical data where the authors applied the logistic regression method (a statistical technique to predict values in defined categories) reported interesting results. With a sample of 152 patients with IBD (UC—men $N = 54$ and women $N = 32$; CD—men $N = 34$ and women $N = 32$), researchers used mathematical formulae based on the construction of logic models to classify symptoms that identified if the patients were ill or not. In their investigation, they assumed that the "classification model of the patient is not clear." Results indicated that even selected attributes from the data did not have a significant impact on the classification of patients' diseases. For these reasons, the authors decided to conduct another phase of analysis using a statistical and ML framework to build a new and improved model, which could more accurately classify a patient's disease. The second case referred to involves a small sample, $N = 11$ patients. Even so, it is a good example of what computerized extraction of data using ML can accomplish. The accuracy of this small mathematical experimental test was 90.9%, whereas a radiologist medical physician could not determine visual differences in the disease that appeared in the image screened because the visualized radiomic features used by radiologists, in almost all digital tools, appear to be marked differently for both scenarios (patients that did and did not respond to treatment).

Briefly, it is hard, using the method explained above, to achieve accuracy regarding disease identification.

- Ashton et al. and Ashton and Beattie (34, 35)—Both studies meet the criteria of inclusion "Focused on IBD," "Focused on the patient," and "Involved technology related to chatbot, ML, or AI."

We decided to include these studies in the same discussion because both cover the same topic. This is an evolutionary process conducted by the same research team regarding the topic of personalized therapy for IBD in children.

The first study (34) reinforced the fact that sophisticated mathematical models and innovative cutting-edge ML techniques give the potential to integrate EMR developing

algorithms for personalized clinical care to treat patients more effectively. According to the authors, this process can reduce the "toxicity" existing in the data collected, improving new clinical outcomes and exploring how the future management of IBD may be revolutionized by personalization of clinical care. This study starts by summarizing the current management strategies of treatments used in PIBD.

It helped us to understand how far ML or AI can go if multi-omics data are applied to personalized medicine in IBD. It means introducing biological analysis into the data sets coming from multiple "omics," such as genomics, proteomics, transcriptomics, epigenomics, metabolomics, and microbiomics.

The aforementioned computational medical challenge regarding personalized IBD therapy is a topic also found in the second study (35). This short paper presents only a reflection on the topic explained before. The authors argue that despite the performance presenting the modeling of single data types, they believed that there is room for improvement by merging diverse data. This means achieving greater power in detecting new IBD subtypes categories using ML.

In summary, with each data type representing a different characteristic of a single patient, ML algorithms can simplify the representation of higher complexity. As a direct consequence, this framework identified a new stratum, which might reflect important clinical outcomes and enable the personalization of therapy based on new groups of multi-omic data.

- Borland et al. (36)—This study met the inclusion criteria of "Focused on IBD," "Focused on the patient," and "Multiplatform technology."

This American experimental study explored how patients think about their health. The goal was to identify, in an online forum and using data visualization, which was the most popular search topic suggested by patients with IBD.

The authors created a website with a discussion forum feature for patients to talk about their IBD experiences. They also created an initial ontology with topics to organize the content in this forum. Crohn's and Colitis Foundation of America (CCFA) was a partner in this project. The foundation was interested in developing efficient approaches to identify new IBD topics of concern for patients and to recognize which search questions were most frequently discussed by them. Regarding the main goal of the study referred to, 97 research topics were identified, and 121 user comments were made by fellow patients on proposed questions, up to a total of 17,322 words.

It is worth mentioning that the initial method of creating the IBD ontology involved a quantitative analysis of the forum data, calculating the frequency of words and phrases. The authors revealed that this method did not effectively capture the nuance of specific lines of research in which the patients were interested. Their solution to overcome this issue was to manually analyze the content by a single person using spreadsheet software and manual data entry.

In total, 165 classes from the Ontology for Adverse Events (OAE)[8] and 36 from the Disease Ontology (DO) were included. During the ontology creation, IBD partner CCFA was consulted to ensure whether that structure seemed appropriate. The results described a hierarchy of 337 total classes divided by seven top-level groups:

- Comorbidity;
- Diagnosis/monitoring method;
- IBD course—Pre-diagnosis time period, diagnosis event, post-diagnosis time period.
- Quality of life;
- Risk factor—Demographic factor, environmental factor, lifestyle factor, physiological factor, psychological factor.
- Symptom—Gastrointestinal manifestation, extra-gastrointestinal manifestation,
- Treatment method—Alternative therapy, holistic treatment, medication, surgery.

In conclusion, the discussion previously presented helps us to understand which, even in an embryonic phase, are the ontologies created by the authors considering the sample of patients available and the project on its own.

- Zand et al. (37)—This study met the inclusion criteria of "Focused on IBD," "Focused on the patients," and "Involved technology related to chatbot, ML, or AI."

This American study, from UCLA, aimed to explore the use of a conversational agent for IBD health care. It is a short study presented as a poster that demonstrated that the authors were trying to categorize electronic dialog data from patients and healthcare providers through a care management platform including a mobile app.

Regarding the electronic dialogs mentioned, these data were collected from 2013 to 2018. Initially, this information was reviewed manually and after that, the authors created an ML algorithm to categorize the content. The accuracy of this technique was validated by three independent physicians that labeled, manually, 100 lines of randomly picked dialog. Next, they compared the manual process with what the algorithm collected. There was a 94% correlation between the algorithm and the results processed by the three independent physicians. These results show that ML frameworks can achieve similar accuracy, or even higher, compared with a non-automated process of labeling content.

Recently, in May 2020, the same group of authors published a JMIR article (12) where they explained in detail the study stated earlier, highlighting the feasibility of using natural language processing (NLP) for the categorization of IBD EMRs to be used in the development of a chatbot. Although this study is outside the systematic literature review process, some topics will be outlined in the Discussion section because the results inform our research questions in some respects.

- Issom et al. (20)—This study met the inclusion criteria of "articles related to any chronic disease" defined in the second search phase.

The aim of this study was to test the usability and perceived usefulness of the high-fidelity prototype chatbot "TREVOR" which is a part of a mHealth coach app for patients with sickle cell disease (SCD). SCD chronic illness is a genetic blood disorder. It encounters an increasing number of comorbidities. The authors

[8]http://www.oae-ontology.org/ (accessed January 04, 2022).

of this article argue that "To our knowledge, no work has been done to design chatbots for the specific self-management needs of people with SCD" (p. 3). This is why they decided to develop "TREVOR" and test the system's usability and usefulness.

The article presents two study phases of robot coach patients' experiences: first, a mixed-methods design research, combining qualitative and quantitative analysis; second, a qualitative survey to understand which was the patients' satisfaction levels and if there were specific recommendations for better conversational agent designing. The sample was composed of 33 SCD participants and 23 were women (medium age is 38 years old). In total, 70% ($N = 23$) of participants were active, whereas 64% ($N = 21$) were affected by the most clinically severe SCD genotypes.

TREVOR was developed using Chatfuel[9] technology and has been designed to deliver text-based messages and media objects to patients with SCD. The authors of the article explore how this automated health coaching chatbot can improve patients' self-management and support health behavior changes, to understand how to avoid triggering vaso-occlusive crises.

The tests measure the system usability as well as if the robot interaction was empathetic. Its results show us that 73% ($N = 24$) commented positively on how easy it was to use and how fun it was when interacting with the "TREVOR" chatbot. About 82% of patients ($N = 27$) thought the SDC content was useful or interesting. Only 12% ($N = 4$) of patients did not consider the information useful. A total of 18% ($N = 6$) of participants liked how empathetic the chatbot was "It looks like we are communicating with someone who understands our health status" (p. 6). The final survey listed interesting observations: 9.1% ($N = 3$) felt that the content visibility displayed was not optimal; 30% ($N = 10$) requested more flexibility in the choice of answers; 12% ($N = 4$) requested to add more SCD content; 12% ($N = 4$) participants wished to be able to modify their answers more easily.

DISCUSSION OF PRINCIPAL FINDINGS

AI or ML With Multi-Omics—A Different Paradigm for IBD EMRs

As seen before, after concluding the systematic literature review, the usage of frameworks such as AI and ML is not new in the IBD environment (32, 34, 35, 37). It has served several purposes but always with the same goal, to help with the classification of the disease, CD or UC.

The other relevant finding in the literature was a growing body of how ML algorithms are being applied to EMRs and how it is changing the accuracy of the data collected (16, 36–38). With reference to this scenario, as seen in the Introduction section, the ML framework can be used in digital tools as a conversational agent. But, to reach this goal, first, it is necessary to analyze the patient profile from different perspectives such as patients' appointments, clinical settings, and others. For us, the literature review was not clear enough about which are the best strategies to adopt since some authors (12, 37) have argued that IBD outcomes can vary. But we found some guidelines that may help us in the future: most of the IBD EMRs differ in certain aspects (12, 15) such as record style, patient behavior, and physician experience from clinic to clinic, as previously explained.

The course of events presented above reflects also that the nature of the data collected is not robust (32). This is because, in the majority of experimental studies reviewed by the research team (15, 32), the IBD EMR collected was categorized manually by experts. Most of these studies did not detail the method used to validate these data and the way experts conducted the process. Only one study (12) mentioned that "doctors evaluate the appropriateness of the categorization by manually categorizing 100 lines of randomly picked dialogue" (p. S244), but we lack more details.

The third finding was the importance of screening the information collected before, identifying which class contents are to be included to define the IBD ontology. Only one study (36) reveals how the authors created an IBD ontology. Furthermore, they argued about the importance of IBD communication being based on different perspectives, patient-to-provider, and patient-to-patient. The authors of the study said, "this is the first such ontology incorporating concepts of using linked views that automatically highlight relationships between selected ontology terms and research topics; the researcher can gain insights into concepts of importance to the forum participants" (p. 384). Apart from this study, IBD ontology is well studied, for example, in the contexts of the nutritional field (39), but no literature was found on IBD ontology for conversational agents. What we discovered was architecture information developed as an initial proposal for a prototype related to semantic technology for IBD. This initial proposal was developed by a group of Chinese researchers (40), but the study presented was at an early stage.

Finally, creating the semantic categories will be important to support intelligence features for the verbal interaction between a conversational agent and patients. With reference to the process of creating semantic categories, the literature (12, 34, 35) indicated that this involves two types of ML: the supervised ML which means that the algorithm predicts the class to which data elements belong, or the unsupervised ML, which uses data which is not classified, categorized or labeled, allowing a more complex analysis than using supervised ML. Even so, we did not discover a detailed list of semantic categories regarding European patients with IBD.

Conversational Agent—Is It a new Paradigm for Chronic Disease Patients' Care?

As seen, AI and ML frameworks open new opportunities in IBD by improving the accuracy of EMRs manually managed after being collected. An example of this is what Z and his research team (12, 37) are trying to do. Their study from 2020 collected and analyzed 16,453 lines of dialog extracted from the UCLA

[9]https://chatfuel.com/ (accessed December 20, 2021).
Chatfuel is the leading chatbot development platform for Facebook Messenger that allows to design fully automated and script-based conversational agents.

IBD database and processed manually on a common sheet. After that, 8,324 messages from 424 patients were studied. The first 400 lines of each were manually reviewed defining seven categories by their frequencies:

- Medications (38.70%);
- Communications (34.89%);
- Laboratory investigations (34.01%);
- Symptoms (32.83%),
- Appointments (24.51%);
- Miscellaneous (10.08%);
- Procedures (9.96%)
- Finance or insurance (7.22%).

The keywords used in the algorithm come from these 400 lines—a simplified bag-of-words model. Roughly 90.00% of dialogs that came from patients fell into only seven categories, which shows potential for developing a chatbot with a Neuro-Linguistic Programming (NLP) algorithm that can handle the most relevant IBD patients' questions and concerns. This study presented an interesting flowchart explaining the inclusion and the categorization of dialog, but it revealed something critical that helps us to comprehend why it is so hard to create patterns for IBD ontology: their patient sample was fairly homogeneous, consisting mostly of young (mean age 42 years) and white patients, which limits the extrapolation of our results to other populations.

Sickle cell disease (20) article reveals contributions to IBD study. Chatbot technology for chronic disease self-management can have high acceptance rates and usability scores. The more patients interact with a chatbot, the more knowledge and information the chatbot can support, increasing the self-care practices in an empathetic way.

Principal findings show us that delivery systems, such as chatbots, could be created to have an empathetic personality, and their communication could be more personified as a digital health strategy to improve user satisfaction, engagement, and dialog quality.

CONCLUSION AND IMPLICATIONS FOR RESEARCH

Regarding the research questions that guided the systematic literature review presented and after concluding the process, our team concludes that the academics are not yet discussing vigorously the use of chatbots by health professionals and patients with IBD, as seems to be happening in other clinical fields such as dementia (13) and pediatric issues such as obesity (14). Considering the IBD topic, only one study was found (12). The authors from UCLA Center For Inflammatory Bowel Disease published an exploratory study in May 2020 about the feasibility of using NLP for the categorization of electronic dialogs. This study reveals how hard it is to define linguistic patterns because the collected data from several dialog sources may influence how these patterns are defined.

We conclude that it will be a challenge to create the IBD ontology because there are no strong guidelines to help researchers to define which IBD EMRs should be used effectively to define linguistic patterns. We have discovered that biological data should be included and also that experts such as gastroenterologists must be included in the data validation process.

Conversational agents in IBD patient care show promise: e.g., in automating requests regarding booking and cancellations, or even by playing an instrumental part in disease triage; following the same guidelines as nurses; and saving the provider team valuable time that could be redistributed to better patient care. However, more experimental studies are needed to achieve meta-analysis and to determine the effectiveness of this digital tool in IBD.

We challenge the research communities to focus their studies on identifying the class content and the linguistic patterns to be included in conversational agents in the IBD ontology, and on creating the semantic categories supporting intelligence features for verbal interaction between a conversational agent and patients with IBD in the digital world.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article material, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

CP and IS contributed to the planning, conducting of the study, and approved the final version to be published. CP, IS, and JD was carried out the search procedure and reporting of the manuscript. All authors contributed the analytic strategy to achieve the final classification of assessment criteria and critically wrote and revised the manuscript providing insights into the review discussion. All authors contributed to the article and approved the submitted version.

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Promoting Physical Activity in Older Adults With Type 2 Diabetes *via* an Anthropomorphic Conversational Agent: Development of an Evidence and Theory-Based Multi-Behavior Intervention

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Introduction: Anthropomorphic conversational agents (ACA) are a promising digital tool to support self-management of type 2 diabetes (T2D), albeit little explored. There is a dearth of literature on the detailed content of these interventions, which may limit effectiveness and replication. Our aim is to describe the development of an evidence and theory-based intervention to improve physical activity in older adults with T2D, subsumed in a multi-behavior intervention *via* a mobile application with an ACA.

Methods: Overall decisions on the multi-behavior intervention design, such as the use of standardized behavior change techniques (BCTTv1), guided the development of the physical activity component. Firstly, recommendations on ambulatory activity were used to select the target behavior (walking). Meta-research on effective behavior change techniques (BCTs) was then identified. One meta-analysis linked effective BCTs with the three basic psychological needs of the self-determination theory (SDT). This meta-analysis, taken together with additional evidence on SDT, led to the selection of this theory to inform the design. BCTs were extracted from meta-research; we selected the most appropriate to be operationalized *via* the conversational agent through multidisciplinary discussions. Rules governing the dialogue flow and BCTs tailoring, taking the form "if some conditions hold then execute some action," were derived based on the Basic Psychological in Exercise Scale (competence, autonomy, and relatedness scores), in conjunction with published evidence and multidisciplinary discussions.

Results: Thirteen BCTs were implemented in the prototype *via* the ACA (e.g., goal setting behavior 1.1). Six if-then rules were derived and depicted in the dialogue steps through process flow diagrams, which map how the system functions. An example of a rule is "If competence score ≤ 10 then, apply BCT 1.1 with 500 steps increments as options for the daily walking goal; If competence score > 10 then, apply BCT 1.1 with 1,000 steps increments as options for the daily walking goal."

Conclusion: Evidence and SDT were translated into a mobile application prototype using an ACA to promote physical activity in older adults with T2D. This approach, which includes 13 BCTs and six if-then rules for their tailoring, may leverage the efforts of others in developing similar interventions.

Keywords: conversational agent, older adults, type 2 diabetes, physical activity, intervention development, behavior change techniques, self-determination theory

INTRODUCTION

The sustainability and quality of healthcare provision in many countries is threatened by a constellation of factors, such as aging, the rising burden of non-communicable diseases and shortage of health professionals. It is estimated that the number of older people in the European Union (EU) will increase significantly, from 90.5 million at the start of 2019 to 129.8 million by 2050 (European Union, 2020). Public expenditure on health and long-term care has been increasing over the last decades in all EU Member States (European Union, 2020). These factors have driven the reengineering of health care delivery and the role of digital health technology.

Diabetes is one of the fastest growing health issues. Globally it affects around 537 million adults; type 2 diabetes (T2D) accounts for over 90% of all diabetes cases and has an increasing prevalence by age (International Diabetes Federation, 2021). Cardiovascular diseases are the leading cause of morbidity and mortality for individuals with diabetes accounting for an estimated cardiovascular-related cost of $37.3 billion per year, associated with diabetes (American Diabetes Association, 2018).

Furthermore, additional common metabolic conditions often coexist with T2D (e.g., hypertension and dyslipidemia) confers an increased health risk in this specific group (American Diabetes Association, 2021a). Diabetes-related health expenditures, irrespective of being borne by people living with diabetes, their families, or the health system, grew globally from USD 232 billion in 2007 to USD 966 billion in 2021 for adults aged 20–79 years, representing a 316% increase over 15 years (International Diabetes Federation, 2021).

Sustained hyperglycemia in persons with T2D also increases the risk of other complications, such as renal failure and retinopathy (International Diabetes Federation, 2021). T2D may also engender distress, understood as "negative emotional or affective experience resulting from the challenge of living with the demands of diabetes" (Skinner et al., 2020), and impaired health-related quality of life (Cannon et al., 2018).

It has been estimated that persons with diabetes spend fewer than 6 h per year consulting with healthcare professionals (Holt and Speight, 2017), which illustrates the importance of empowering and supporting these persons to actively self-manage the condition. Physical activity and other lifestyle behaviors fall under the remit of self-management, as they are dependent on the daily role taken by persons living with diabetes (American Diabetes Association, 2021b). Such behaviors, as regular physical activity and healthy eating are the cornerstone of T2D management (American Diabetes Association, 2021b; Kanaley et al., 2022).

Physical activity and exercise have been endorsed as a treatment or adjunct therapy for T2D and, at least, 25 other health conditions, including some T2D cardiometabolic comorbidities (Pedersen and Saltin, 2015; Shah et al., 2021). Sound evidence-based recommendations for physical activity and exercise for persons with T2D have been released (American Diabetes Association, 2021b; Kanaley et al., 2022). Simple physical activity behaviors such as walking one mile per day, or more (≥1.6 km/day), may provide a two-fold reduction in adjusted risk of all-cause mortality and a five-fold reduction in adjusted risk of non-coronary cardiovascular disease (CVD) death in older adults with diabetes (Smith et al., 2007).

Digital Behavior Change Interventions are a coordinated sets of activities or products designed to change specified behavioral patterns (e.g., physical activity) of individuals through digital technology, such as mobile applications, wearable technology (e.g., activity trackers), or websites. Digital Behavior Change Interventions are a promising approach for empowering diabetes self-management, as they have the capability to deliver personalized solutions to influence complex and challenging health behaviors (Michie et al., 2017). These digital interventions can support persons with diabetes to engage in physical activity, healthy eating, and overall disease management behaviors, intended to improve health outcomes and reduce complications (Fleming et al., 2020). Although T2D has a growing prevalence in older people, it has been recognized that mobile applications have limited usability for this group, which may hinder their use (Arnhold et al., 2014; Berenguer et al., 2017).

A meta-analysis of mobile applications for T2D, included 6 randomized controlled trials, with a total of 1,022 participants, and found an overall efficacy in reducing glycated hemoglobin (HbA1c), with a mean 0.40% decrease (95% CI 0.11 to 0.69%;

Cui et al., 2016). Typically, a change in glycated hemoglobin of 0.5% is considered clinically significant (Little and Rohlfing, 2013). As for the cost-effectiveness of T2D digital interventions, a systematic review, included seven full economic evaluations, three of which comprised self-management support, albeit non-automated. Of these, the two studies that reported cost per quality-adjusted life-year (QALY) gained were cost-effective (Rinaldi et al., 2020). Although economic evaluation of these interventions is still in a nascent stage, it shows encouraging results, favoring resource allocation to digital diabetes self-management interventions.

Conversational agents, defined as computer programmes designed to simulate two-way human conversation using language (speech and/or text), potentially supplemented with non-language modalities are regarded as a promising approach to support diabetes self-management (Guerreiro et al., 2021). They may, for example, be more user friendly for people with lower literacy. These agents can be integrated in multiple devices, including mobile phones. Virtual human is another term to describe anthropomorphic conversational agents. A meta-analysis demonstrated the effectiveness of virtual humans in patient-facing systems, based on 26 controlled studies. Future accumulation of research may help to overcome the moderate heterogeneity in study results (Chattopadhyay et al., 2020). Notably, no trial involving long-term self-management support in T2D was included in this meta-analysis.

More recently, Luo et al. reported a dearth of research on conversational agents targeting physical activity in persons with T2D. In particular, published interventions do not always rely on behavior change theory (Luo et al., 2021), which may curtail their effectiveness, nor explicitly present their active components, which limits replication and knowledge transfer.

One example of the use of conversational agents in T2D management is the VASelfCare project (2018/01-2020/03).[1] This project developed a multi-behavior change digital intervention for older people with T2D, *via* an anthropomorphic conversational agent and a connected web-based dashboard for health professionals. Vitoria, a 3D female virtual human, was designed as a coach for three target behaviors: medication taking, physical activity, and healthy eating, resorting to design principles for older adults. The overall intervention has been described previously (Balsa et al., 2020; Guerreiro et al., 2020) and the development of the medication taking component detailed elsewhere (Félix et al., 2019). The current paper focuses on the development of the physical activity component, a key behavior in diabetes management in older adults (Bellary et al., 2021).

The Medical Research Council (MRC) framework (Skivington et al., 2021) for developing and evaluating complex intervention, which guided the VASelfCare project, recommends an accurate process of development drawing on existing theories, modeling of process and outcomes, followed by feasibility assessment.

The importance of theory-based interventions for promoting physical activity in persons with T2D has been recently underscored (Konerding and Szel, 2021). Theory-based interventions are recommended as it provides assumptions about why interventions differently affect health behavior (Gourlan et al., 2016). The effectiveness of the intervention depends on the theory selected and how design and implementation of the intervention fits to the theoretical constructs. Additionally, only a small proportion of interventions publish the link between theory and behavior change techniques (BCTs), despite the recommendations to improve the transparency of theory-based interventions (Michie and Abraham, 2004; Abraham et al., 2014; National Institute for Health and Care Excellence, 2014). To enable interventions to be evaluated and implemented, BCTs should be well specified, increasing their accurate replication.

Enhancing the importance of adequate description of the interventions, the MRC endorses the publication of the intervention development process as it allows others to establish links between this process and the subsequent success of interventions and learn about the endeavors of this approach, which may be useful for developers (O'Cathain et al., 2019). Currently, there are limited examples in the literature of detailed descriptions of how systematic processes of developing digital health behaviors change interventions (Encantado et al., 2021), including in physical activity.

This paper describes the development of an evidence and theory-based intervention to improve physical activity in older adults with T2D, subsumed in a multi-behavior intervention *via* a mobile application with an anthropomorphic conversational agent.

MATERIALS AND METHODS

The design of the VASelfCare intervention is described below, focusing firstly on the overall design, and then on the procedures to design the physical activity component, as part of the multi-behavior intervention (medication-taking, physical activity and healthy eating). The overall design of the intervention framed the development of the physical activity component and is therefore critical to its understanding. These procedures for the latter detail the use of theory and evidence for deriving the content of the physical activity component and rules to tailor them.

Overall Design of the Multi-Behavior Intervention

The anthropomorphic conversational agent, Vitoria, developed within the VASelfCare project, was designed to support behavior change through daily interactions with users. Based on the literature (e.g., Bickmore et al., 2010), users are offered the possibility of interacting with Vitoria once a day only. Vitória is capable of speaking European Portuguese and expressing emotions through facial and body animations; verbal content is supplemented with subtitles to help reduce potential communication barriers such as hearing deficits. User's input consists of a set of options depicted in response buttons or through values recorded. For details on the IT development of the anthropomorphic conversational agent prototype refer to Balsa et al. (2020) and Guerreiro et al. (2020).

An overall design choice, regardless of the component, was to address each target behavior in two stages: in the evaluation stage Vitoria collects data to tailor the intervention content in the subsequent follow-up stage, which purports to promote or maintain the behaviors.

[1]https://vaselfcare.esel.pt

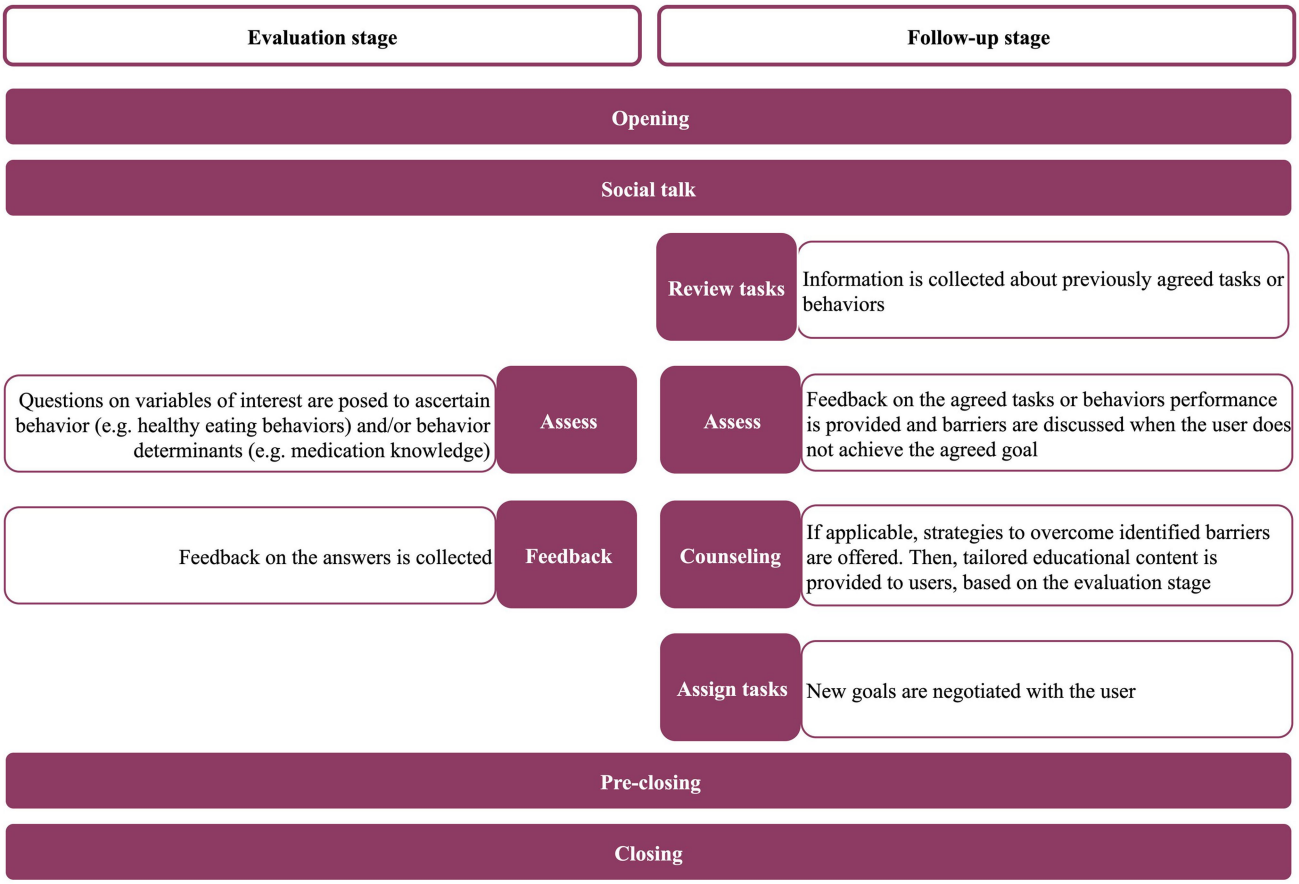

FIGURE 1 | Steps of each daily interaction in the evaluation and follow-up stages across the three components (medication taking, physical activity and healthy eating).

Tailoring is employed in this paper as "any combination of information and behavior change strategies intended to reach one specific person based on characteristics that are unique to that person related to the outcome of interest and derived from an individual assessment" (Kreuter et al., 2000). Across the three components of the VASelfCare intervention, tailoring relies not only on data from the evaluation stage, but also from previous interactions, and addresses both general information about diabetes, to improve health literacy, and the selection of BCTs, as explained later in this section.

Each daily interaction was structured in sequential steps based on the literature (Bickmore et al., 2005). In the evaluation stage, the sequential steps are depicted in **Figure 1** (opening, social talk, assess, feedback, pre-closing and closing). The "opening" and "social talk" steps involve greeting the user and inquiries about the general emotional and physical state, respectively. Finally, the content of the next interaction is described in the "pre-closing" step and a farewell is delivered ("closing"). The dialogue in the follow-up stage has three additional steps, "review tasks," "counseling," and "assign tasks," also described in **Figure 1**.

A critical design decision was how to combine the physical activity component with the remaining components of the intervention: medication taking and healthy eating. There is little guidance on the best approach to design digital multi-behavior interventions; general recommendations indicate that interventions targeting behaviors requiring inaction (such as not eating high fat food) and those requiring action (such as increasing physical activity or taking medication) should not be pursued concomitantly (Albarracín et al., 2018). From a practical standpoint, pursuing three behaviors at the same time from the outset of the intervention would increase the length of each interaction to a point that was deemed detrimental for engagement. Taken together, these two aspects determined a stepwise approach, in which medication taking is firstly addressed, then the physical activity component added, while reducing the intensity of the medication taking component; as depicted in **Figure 2**, the same approach was employed for the healthy eating component. A less intensive intervention in each component, designated as "lite" (**Figure 2**), comes up after firstly, addressing each target behavior more intensively. "Lite" interventions have reduced number of dialogue steps and provide feedback to users based on weekly data (e.g., average medication taken in the last week). They encompass repeated collection of evaluation data, such as on medication knowledge and

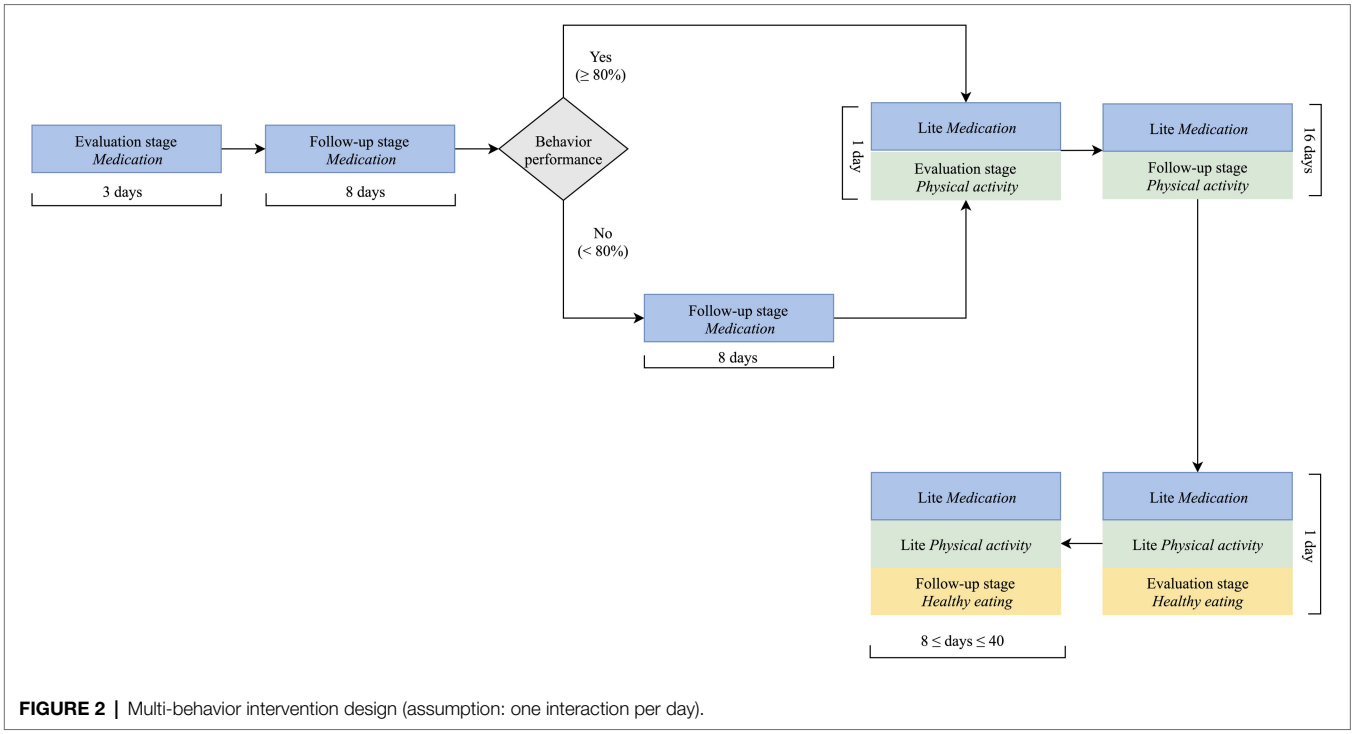

FIGURE 2 | Multi-behavior intervention design (assumption: one interaction per day).

healthy eating behaviors, to enable intervention tailoring in the long term.

Design of the Physical Activity Component as Part of the Multi-Behavior Intervention

For the physical activity component, the VASelfCare intervention focused on ambulatory activity, mostly walking, as it has been endorsed for persons with T2D (Moghetti et al., 2020). This target group is regarded at high risk for exercise-related complications (Burr et al., 2012). Hence, we refrained from including recommendations of moderate to vigorous exercise, as the anthropomorphic conversational agent is unable to assess exercise tolerance and monitor exercise. Walking or walking-related activities are part of daily routine and considered feasible and low risk for older persons with T2D (Dasgupta et al., 2017; Barbosa et al., 2020). Correspondingly, daily step counting was chosen as a primary marker of this lower-level target behavior, focusing on helping users to achieve healthy levels of ambulatory physical activity (Tudor-Locke et al., 2011b).

An increase of 4,000 steps/day on a 5-day average step counts, from baseline, was found to be the threshold to elicit a clinically meaningful reduction on glycated hemoglobin in persons with type 2 diabetes, in a 24-week pedometer-based physical activity intervention (Van Dyck et al., 2013). More recently, a randomized controlled trial, resorting to a simple physician-delivered step count prescription strategy incorporated into routine clinical practice, showed that an average increase of 1,220 steps/day elicited a significant increase in insulin sensitivity and reduction of glycated hemoglobin (Dasgupta et al., 2017). A systematic review of studies in adults from non-clinical populations found that an increase of 1,000 steps/day elicited a reduction in the risk of all-cause mortality and cardiovascular morbidity and mortality (Hall et al., 2020). Data are currently lacking to identify an optimal health enhancing minimum threshold of daily step counts, still, health benefits can be found below 10.000 steps/day (Hall et al., 2020).

A walking cadence of 100 steps/min has been considered to be a reasonable empirical value for adults, indicative of walking at approximately the lower limit of the moderate-intensity spectrum (i.e., ≈ 3 METs; Tudor-Locke et al., 2011b; Tudor-Locke and Rowe, 2012). A target step counts of 7,000 steps/day, considering a step cadence of about 100 steps/min, is equivalent to approximately 70 min of walking per day. However, not all daily steps are expected to be performed at a cadence of 100 steps/min and, therefore, within the spectrum of moderate-intensity physical activity (Tudor-Locke et al., 2011a). Still, the goal of 7,000 steps/day has been shown to be consistent with physical activity guidelines for adults (Tudor-Locke et al., 2011c), particularly with the recommendation of 150 to 300 min/week of moderate–intensity, which has been recently endorsed also for persons with T2D (Kanaley et al., 2022), and has already been used and found beneficial in interventions in older and clinical populations (Gardner et al., 2021; Saad et al., 2021), including in persons with T2D (Rossen et al., 2021).

According to the rationale presented and the selected physical activity primary surrogate, a pedometer (New-Lifestyles NL-2000i Activity Monitor; New-Lifestyles Inc., Euless, TX, United States) was chosen to count daily steps. This device provides a reliable measure of this marker (Crouter et al., 2005; Grant et al., 2008; Tedesco et al., 2019); additionally, self-monitoring *via* a pedometer has been found useful on its own to increase daily step counts (Bravata et al., 2007), and beneficial for persons

with T2D (Idowu et al., 2021). To foster scalability (future use across a range of devices), daily steps are inputted directly by users in the application interface.

A requirement for the content of the intervention was using behavior change techniques (BCTs) from an established taxonomy across the three target behaviors addressed by the intervention. A BCT is "an observable, replicable and irreducible component of an intervention designed to alter or redirect causal processes that regulate behavior (Michie et al., 2013). The Behaviour Change Taxonomy version 1 (BCTTv.1) was selected to specify these active ingredients of the intervention. BCTTv1 is an extensive hierarchically ordered and reliable taxonomy of 93 distinct BCTs that are categorized into 16 groups. For the physical activity component, the literature offered meta-research on effective BCTs (Cradock et al., 2017; Gillison et al., 2019), and therefore selecting BCTs using a systematic and structured process, as described for the medication adherence component (Félix et al., 2019), was deemed unnecessary.

In particular, one of the meta-analysis linked BCTs from the BCTTv.1 with the three basic psychological needs encompassed in the self-determination theory (Gillison et al., 2019).

Self-determination Theory (SDT) is a broad meta-theory of motivation. Central to the theory is the distinction between autonomous (self-determined) and controlled (non-self-determined) forms of motivation, which are further specified in a motivational continuum ranging from the most autonomous form of motivation (intrinsic motivation) to the most controlled form of motivation (external motivation; Ryan and Deci, 2017).

Autonomous motivation refers to a motivation that is based on self-endorsed reasons to choose and pursue a goal or action, when one has a full sense of willingness, volition, and choice, independently of the activity. One can feel autonomously motivated when doing an activity that is intrinsically enjoyable or fun (intrinsic motivation) or because that activity or goal genuinely fits their sense of self and values (integrated motivation). When acting with autonomy, a person is fully functioning, willingly engaged in activity with awareness and congruence, and able to harness vitality in the self-regulation of action (Ryan and Deci, 2017). In contrast, controlled motivation refers to reasons for acting that are not self-endorsed, that are subject to some form of pressure, either external by others or internally by the individual (e.g., feelings of guilt, for an external reward). Research in diverse life domains suggests that more autonomous, relative to controlled, motives are not only associated with, but essential to, a variety of positive outcomes (Ryan and Deci, 2017).

Additionally, the authors argue that all human beings have three basic psychological needs - Autonomy, Relatedness, Competence - that need to be satisfied for one to feel autonomously motivated and, consequently, to achieve optimal performance, psychological health and well-being (Ryan and Deci, 2017; Vansteenkiste et al., 2020). The need for competence reflects the need to feel effectance and mastery over tasks and behavior; the need of autonomy reflects the need to feel a sense of ownership and choice in acting; lastly, the need of unconditional support and connectedness with others is reflected by relatedness. It is posited that when the three basic psychological needs are satisfied, autonomous motivation and mental health are enhanced (Ryan and Deci, 2000).

There is strong evidence on the effectiveness of interventions based on the self-determination theory across a wide range of health domains, including physical activity (Teixeira et al., 2012). Primary research also supports the use of this theory as successful in increasing physical activity in older adults with type 2 diabetes (Koponen et al., 2018). Taken together, this evidence led to choosing the self-determination theory (SDT) to inform the design of the physical activity component. A more recent meta-analysis corroborates this choice; Ntoumanis et al. (2021) showed that SDT-based interventions (n = 73) positively affect health behaviors at the end of the intervention period and at the follow-up, in particular physical activity.

BCTs were extracted and listed from meta-research (Cradock et al., 2017; Gillison et al., 2019). As explained, Gillison et al. (2019) presented BCTs to promote psychological needs, satisfaction and motivation in health interventions based on the self-determination theory; Cradock et al. (2017) identified the BCTs associated with changes in glycated hemoglobin and body weight in persons with T2D.

From the listed BCTs, we selected the most appropriate to be operationalized *via* the conversational agent through multidisciplinary discussion, inspired by the practicality criterion, as defined by Michie et al. (2014) - extent to which the intervention can be delivered as designed through the means intended to the target population. In essence, foci of discussions were whether it was practicable to deliver the listed BCTs through the conversational agent. The team included expertise from the disciplines of sport sciences, psychology, nursing, pharmacy, and informatics.

Vitoria dialogues resort to an artificial intelligence rule-based engine. Rules derived to control the dialogue flow take the form "if some conditions hold then execute some action," where the conditions may include context information regarding the interaction (e.g., user characteristics or the date when interaction takes place) and the action represents the subsequent act to be performed by the conversational agent. These rules were informed by the Basic Psychological in Exercise Scale (Moutão et al., 2012), published evidence (BCTs emanating from meta-research, as explained) and multidisciplinary discussions. The Basic Psychological in Exercise Scale is used to assess psychological needs for exercise underlying Self-Determination Theory (Ryan and Deci, 2017); it comprises a total of 12 items grouped into three factors: autonomy (four items), competence (four items) and relatedness (four items). Responses are provided on a 5-point Likert-type scale ranging from 1 (strongly disagree) to 5 (strongly agree). The maximum score for each construct is 20.

RESULTS

Selection and Operationalization of BCTs in the Physical Activity Component

Thirteen BCTs were selected for implementation in the mobile application prototype *via* the conversational agent. **Table 1** details these BCTs and their operationalization according to the interaction

TABLE 1 | Description of the BCTs and operationalization used by the anthropomorphic conversational agent.

Behavior change techniques and definition (BCTTv.1)	Operationalization	Dialogue step
Goal setting (behavior; **1.1)** *Set or agree on a goal defined in terms of the behavior to be achieved*	Vitoria collaboratively defines with the user the number of daily steps to be achieved	Assign tasks
Problem-solving (1.2) *Analyze, or prompt the person to analyze, factors influencing the behavior and generate or select strategies that include overcoming barriers and/or increasing facilitators*	Vitoria lists the potential barriers to walking as agreed and, based on the selected factors influencing the behavior, offers options to overcome barriers or enhance facilitators	Counseling
Review behavior goal(s) (**1.5)** *Review behavior goal(s) jointly with the person and consider modifying goal(s) or behavior change strategy considering achievement. This may lead to re-setting the same goal, a small change in that goal or setting a new goal instead of (or in addition to) the first, or no change*	When the goal (i.e., number of steps) is not achieved, Vitoria reviews it collaboratively with the user to define a new goal (i.e., number of steps) or keeping the same goal	Assign tasks
Feedback on behavior (2.2) *Monitor and provide informative or evaluative feedback on performance of the behavior (*e.g., *form, frequency, duration, intensity)*	Vitoria provides verbal and visual information on daily step counts, using a helpful-cooperative communication style and *via* a chart	Assess
Self-monitoring of behavior (2.3) *Establish a method for the person to monitor and record their behavior(s) as part of a behavior change strategy*	Vitoria asks the user to input step counts, measured by a pedometer	Review tasks
Social support (unspecified; **3.1)** *Advise on, arrange or provide social support (*e.g., *from friends, relatives, colleagues,' buddies' or staff) or non-contingent praise or reward for performance of the behavior. It includes encouragement and counseling, but only when it is directed at the behavior*	Vitoria advises the user to invite friends or family members to go for a walk	Counseling
Instruction on how to perform the behavior (4.1) *Advise or agree on how to perform the behavior (includes 'Skills training')*	Vitoria advises on how to accommodate physical activity in the daily routine, such as walking the dog, exercise while watching TV and parking further away from the destination	Counseling
Information about health consequences (5.1) *Provide information (*e.g., *written, verbal, visual) about health consequences of performing the behavior*	Vitoria highlights the positive consequences of walking and the negative consequences of sedentarism	Counseling
Information about social and environmental consequences (5.3) *Provide information (*e.g., *written, verbal, visual) about social and environmental consequences of performing the behavior*	Vitoria highlights that walking is considered important to people's health and for the sustainability of the planet	Counseling
Information about emotional consequences (5.6) *Provide information (*e.g., *written, verbal, visual) about emotional consequences of performing the behavior*	Vitoria focuses on the psychological benefits of physical activity (e.g., well-being)	Counseling
Restructuring the physical environment (12.1) *Change, or advise to change the physical environment to facilitate performance of the wanted behavior or create barriers to the unwanted behavior (other than prompts/cues, rewards and punishments)*	Vitoria advises the user to leave the walking shoes or walking aids at sight (e.g., by the entrance door instead of locked in a closet)	Counseling
Restructuring the social environment (12.2) *Change, or advise to change the social environment to facilitate performance of the wanted behavior or create barriers to the unwanted behavior (other than prompts/cues, rewards, and punishments)*	Vitoria advises the user to persuade family or friends to accompany him or her in walks	Counseling
Verbal persuasion about capability (15.1) *Tell the person that they can successfully perform the wanted behavior, arguing against self-doubts, and asserting that they can and will succeed*	Vitoria asserts that the user can increase step counts despite potential difficulties or limitations	Assign tasks

The number between brackets refers to the BCTTv1.

steps in the follow-up stage. In the evaluation stage, BCTs are not applicable as its purpose is not changing behavior.

Rules for Tailoring BCTs in the Physical Activity Component

This section presents rules for tailoring BCTs in the physical activity component. Firstly, the "if-then" rules are summarized in **Table 2**, then rules are put into context in the interaction steps through process flow diagrams, which map how the system functions.

BCTs were operationalized differently on the first day of follow-up and on the subsequent even and odd days. Underlying this approach was the fact that the walking goal defined with Vitoria on any given day (D) pertains to the day after the

TABLE 2 | Decision rules for tailoring BCTs.

Example	Interaction step	Rule	Related BCTs
A	Day 1, Assign tasks (see **Figure 3**)	If competence score ≤ 10	Goal setting behavior (1.1)
		Then, apply BCT 1.1 with 500 steps increments as options for setting the daily walking goal	
		If competence score > 10	Goal setting behavior (1.1)
		Then, apply BCT 1.1 with 1,000 steps increments as options for setting the daily walking goal	
B	Day 2 and subsequent even days, Counseling (see **Figure 4**)	If competence score < (autonomy score AND relatedness score)	Instruction on how to perform a behavior (4.1)
		Then, BCTs 4.1, 12.1 AND 15.1 applied during 8 days	Restructuring the physical environment (12.1)
			Verbal persuasion about capability (15.1)
		If autonomy score < (competence score AND relatedness score)	Information about health consequences (5.1)
		Then, BCTs 5.1, AND 5.3 applied during 5 days	Information about social and environmental consequences (5.3)
		If relatedness score < (competence score AND autonomy score)	Social support (unspecified; 3.1)
		Then, BCT 3.1, applied during 2 days	
C	Day 3 and subsequent odd days, Assess/Counseling (see **Figure 5**)	If behavior goal achieved	See example B
		Then, apply BCTs corresponding to the construct with the lowest score (competence OR autonomy OR relatedness)	
		If behavior goal not achieved	Problem-solving (1.2)
		Then, apply BCT 1.2 AND (BCT 3.1 OR 4.1 OR 5.1 OR 5.3 OR 5.6 OR 12.1 OR 12.2)	Social support (unspecified; 3.1)
			Instruction on how to perform a behavior (4.1)
			Information about health consequences (5.1)
			Information about social and environmental consequences (5.3)
			Information about emotional consequences (5.6)
			Restructuring the physical environment (12.1)
			Restructuring the social environment (12.2)
D	Day 3 and subsequent odd days, Counseling/Assign tasks (see **Figure 5**)	If Δ ≥ ± 2000 steps in relation to the agreed goal	Review behavior goal(s) (1.5)
		Then, apply BCT 1.5 (based on step counts achieved on the previous day OR step counts of the agreed goal two days before) using increments determined by the competence score	
		If Δ < ± 2000 steps in relation to the agreed goal	Review behavior goal(s) (1.5)
		Then, apply BCT 1.5 (based on the step counts observed in the previous day) using increments determined by the competence score	
E	"Lite" version, Assess/Counseling (see **Figure 8**)	If average weekly goal not achieved	Problem-solving (1.2)
		Then, apply BCT 1.2 AND (BCT 3.1 OR 4.1 OR 5.1 OR 5.3 OR 5.6 OR 12.1 OR 12.2)	Social support (unspecified; 3.1)
			Instruction on how to perform a behavior (4.1)
			Information about health consequences (5.1)
			Information about social and environmental consequences (5.3)
			Information about emotional consequences (5.6)
			Restructuring the physical environment (12.1)
			Restructuring the social environment (12.2)
F	"Lite" version, Counseling/Assign tasks (see **Figure 8**)	If Δ ≥ ± 2000 steps in relation to the average weekly goal	Review behavior goal(s) (1.5)
		Then, apply BCT 1.5 (based on average step counts of the last seven days OR step counts of the average weekly goal) using increments determined by the competence score	
		If Δ < ± 2000 steps in relation to the average weekly goal	Review behavior goal(s) (1.5)
		Then, apply BCT 1.5 (based on the average step counts of the last seven days) using increments determined by the competence score	

interaction (D + 1); in other words, the walking goal entails the full steps of D + 1. Since the user can interact with Vitoria at any time on D + 1, goal achievement could be unduly compromised. Therefore, the goal set on day 1 was designed to be assessed on day 3 (Feedback on behavior, 2.2), by reporting the step counts on day 2, corresponding to a full day, and so forth.

Day 1 of Physical Activity Component: Follow-Up Stage

Figure 3 details the dialogue flow on day 1 of the follow-up stage according to the rules described above.

The first and last two steps ("opening" and "social talk" plus "pre-closing" and "closing," respectively) are common in terms of content across the interactions, regardless of the day, as explained in the Materials and Methods section.

On the first day of follow-up, information is collected about the average step counts of the last 7 days, in "review tasks" (self-monitoring of behavior 2.3). At this stage no behavior goal has been set up yet, and therefore the "assess" step, in which feedback would be given, is skipped.

In the "counseling" step, Vitoria gives general information about T2D and complications, such as details on hypoglycemia symptoms and how to manage them, to improve health literacy.

Next, in the "assign tasks" step, Vitoria collaboratively agrees with the user on a goal for step counts for the next day (goal setting behavior 1.1). The three options presented are informed by the competence score, yielded in the evaluation phase, and the average step counts of the last 7 days, as shown in example A of **Table 2**. For example, if the user reports an average of 7,000 steps in the last 7 days and the competence score is >10, Vitoria suggests three goals for the next day: 8000, 7,000 and 6,000 steps.

Day 2 and Subsequent Even Days of the Physical Activity Component: Follow-Up Stage

On the second day and even days of the follow-up stage, Vitoria dialogue follows the steps detailed in **Figure 4**.

In the "review tasks" step, Vitoria asks the user to input the step counts recorded by the pedometer on the previous day (self-monitoring of behavior 2.3). This step is followed by the "assess" step, in which Vitoria reminds the user of the agreed goal (first day and odd days).

Then, information to improve competence, autonomy and relatedness is delivered stepwise throughout the intervention ("counseling" step), starting with the construct with the lowest score. For instance, in a user with a competence, autonomy and relatedness scores of 4, 12, 18, respectively, Vitoria will firstly address competence, encompassing a set of BCTs, as illustrated by example B, **Table 2**. The number of days allocated to each construct varies between two for relatedness and eight for competence, assuming one interaction per day, as already explained in section 2.1. Each construct is targeted in consecutive days, or interspersed with eliciting behavioral barriers, if the walking goal is not met, as assessed on odd days. When competence is addressed, Vitoria explains, for instance, how to use resources to walk, such as a walker, a cane, or a trekking pole (instruction on how to perform the behavior 4.1). Addressing autonomy entails, for example, information about the positive consequences of walking (information about health consequences 5.1). To promote relatedness, Vitoria suggests inviting a friend or a family member to walk or joining group classes (social support unspecified 3.1).

Day 3 and Subsequent Odd Days of the Physical Activity Component: Follow-Up Stage

Figure 5 presents the dialogue flow on the third day and subsequent odd days; the key features in relation to even days is that feedback on behavior is provided, and the walking goal is reviewed. As illustrated in **Figure 5**, the step counts collected in "review tasks" is compared with the behavior goal, through verbal and visual feedback (2.2), *via* Vitoria's speech and a chart ("assess" step). If the agreed goal has not been reached, Vitoria addresses barriers and proposes strategies to overcome them in the "counseling" step (problem-solving 1.2), as already explained in example C (**Table 2**). In **Figure 6**, Vitoria is portrayed implementing problem-solving (1.2). For instance, if the user chooses time constraints as a barrier, Vitoria recommends simple ways to improve step counts by integrating walking in the user's routine, such as parking the car further away from the destination, selecting different routes to walk longer distances or using the stairs.

If the agreed goal is achieved, the intervention turns to the three basic psychological needs (competence, autonomy, and relatedness) in "counseling," according to the ranking set up on day 2 for these constructs, as already explained. BCTs operationalized in this step are detailed in **Table 2** (see example B).

Next, in the "assign tasks" the variation of step counts in relation to the agreed goal determines two paths (example D, **Table 2**). For the sake of illustration, if a user reports a count of 14,000 steps and the agreed goal was 6,000 steps, the variation is greater than 2000 ($\Delta \geq \pm$ 2000 steps). Vitoria asks whether the user wants to review the goal using the reported step counts or the agreed goal as the basis. Assuming the user selects the latter, the goal is reviewed using 6,000 steps as the basis, with increments above and below determined by the competence score (e.g., 5,500, 6,000, 6,500 steps). **Figure 7** depicts another example.

"Lite" Physical Activity Component

The "lite" physical activity component, depicted in **Figure 2**, starts on the first day of the healthy eating component, when both the medication taking, and physical activity have been addressed more thoroughly. In essence, in the "lite" component, Vitoria collects information on step counts in each daily interaction but only assesses and counsels every 8 days; moreover, "assign tasks" set goals for the next week, and not for the next day.

Figure 8 presents only the dialogue steps regarding the "lite" version of the physical activity component. Vitoria starts by asking the user to input the step counts ("review tasks"). Then, the dialogue guides the user to the healthy eating component. This flow is repeated for 7 days. On the eighth day, Vitoria gives feedback on the average step counts of the last 7 days, which corresponds to the "assess" step (feedback on behavior 2.2).

Next, in the "assign tasks" the variation of step counts in relation to the average weekly goal determines two paths

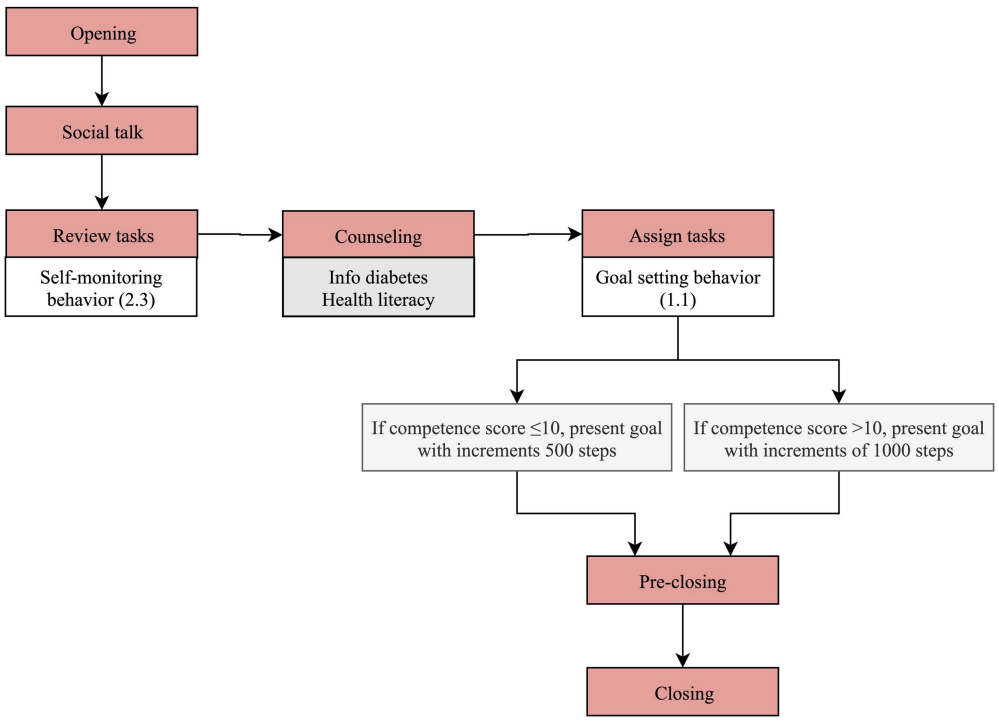

FIGURE 3 | Dialogue flow in day 1 of physical activity component of the follow-up stage.

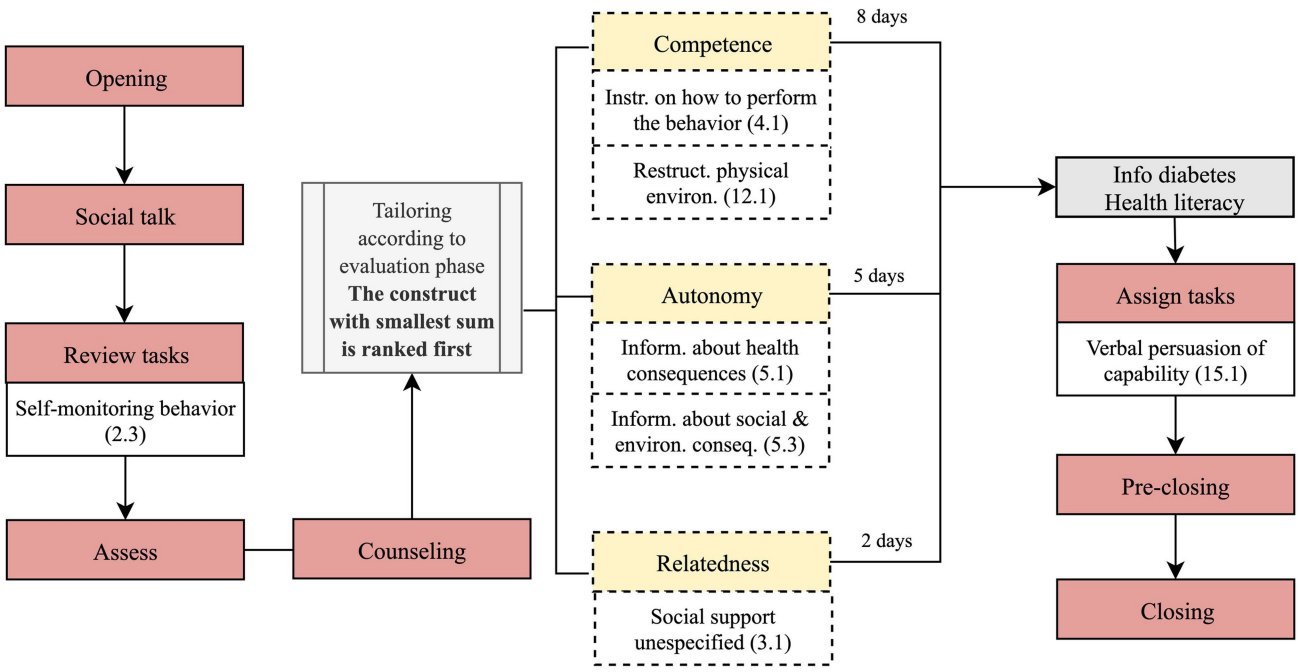

FIGURE 4 | Dialogue flow on day 2 and even days of physical activity component of the follow-up stage.

(example F, **Table 2**). For the sake of illustration, if a user has an average weekly count of 6,600 steps and the agreed goal for the week was 6,000 steps, the variation is smaller than 2000 ($\Delta < \pm$ 2000 steps), the goal is reviewed using 6,600 steps as the basis, with increments above and below determined by the competence score (e.g., 5,600, 6,600, 7,600 steps).

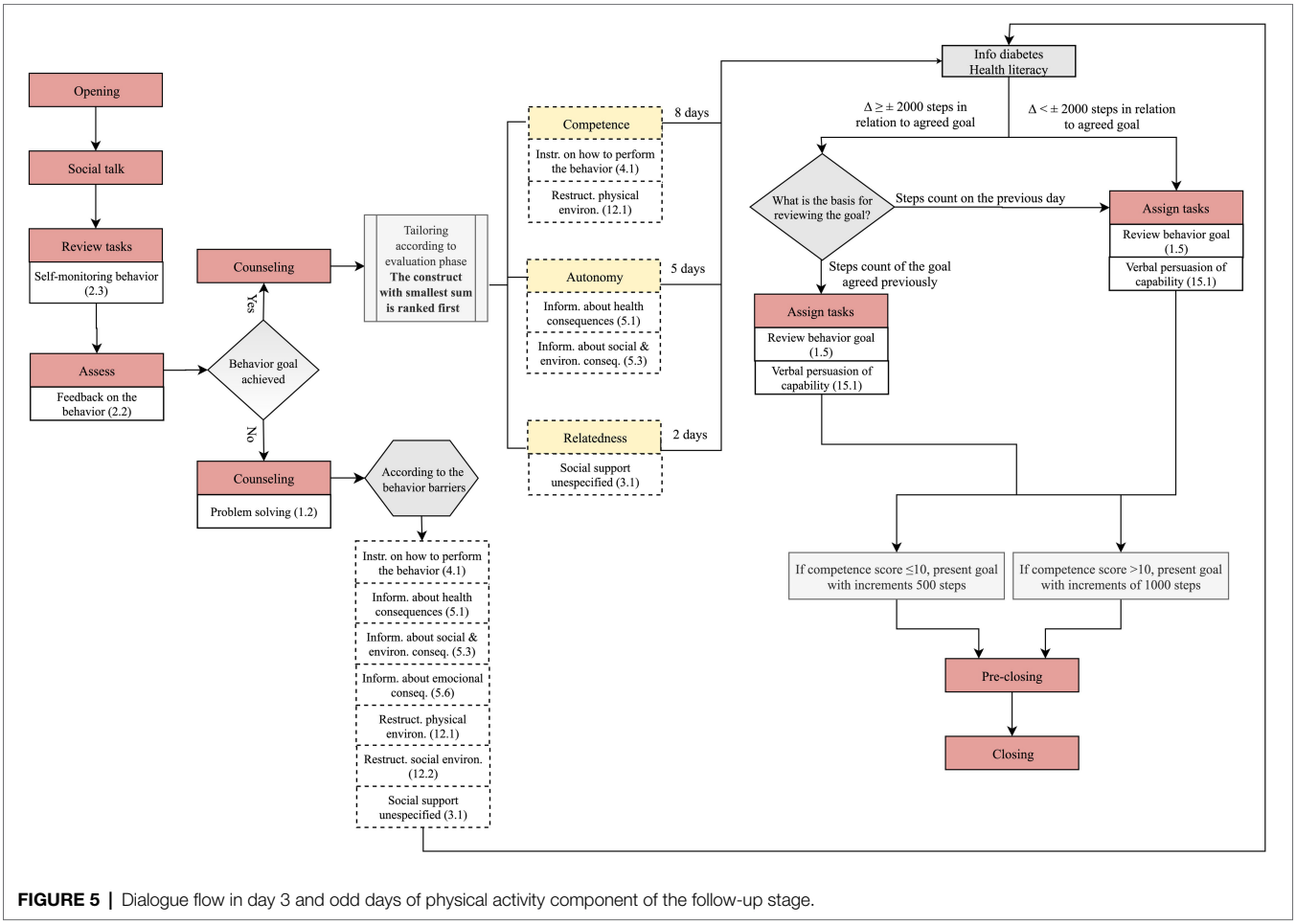

FIGURE 5 | Dialogue flow in day 3 and odd days of physical activity component of the follow-up stage.

DISCUSSION

This article illustrates an evidence and theory-based approach to specify the BCTs and their tailoring of an intervention to improve physical activity in older adults with T2D, subsumed in a multi-behavior intervention, *via* a mobile application with an anthropomorphic conversational agent.

While the design of the physical activity component drew on evidence and theory, there was a strong concern to keep a good fit with daily routine, by resorting to step counts as a measure of physical activity and by drawing on the multidisciplinary experience of the team to list facilitators and barriers.

Thirteen standardized BCTs from the BCTTv1 were chosen, based on meta-research and their practicality to the intervention. These BCTs were tailored in predefined steps of each interaction, using six if-then rules, which determine how the anthropomorphic conversational agent, Vitoria, interacts with users.

A limitation of our work is that users have to choose from a limited set of options when talking to Vitoria; moreover, BCTs are embedded in the dialogues in a rigid way, which limits the possibilities of tailoring. More recently, we attempted to overcome these issues by using an advanced natural language platform (e.g., Google Dialogflow) and an ontology-based knowledge representation, indicating how BCTs can be operationalized (Bastos et al., 2022).

Our work can also be criticized by the fact that the effectiveness of the digital intervention has not yet been evaluated. Usability testing with older adults living with T2D showed encouraging results (Balsa et al., 2020), but ultimately the merit of the intervention will be judged based on its ability to produce positive health outcomes. While a clinically significant decrease in glycated hemoglobin is typically warranted, humanistic health outcomes should not be demeaned. A paper provocatively entitled "If it does not significantly change HbA1c levels why should we waste time on it?," reminds us of the perils of providing care to persons with diabetes contingent only upon achieving clinical outcomes (Jones et al., 2015). The only example that we are aware of a virtual human coach intervention for self-managing chronic disease resulted in statistically significant improvement in health-related quality of life, but not in glycated hemoglobin (Gong et al., 2020). This should be regarded as equally beneficial as improvements in glycated hemoglobin. The mean age of participants in the intervention group ($n = 93$) of this Australian randomized effectiveness-implementation trial was 55.4 years (SD 9.7; Gong et al., 2020), which reinforces the need for trialing our intervention in older

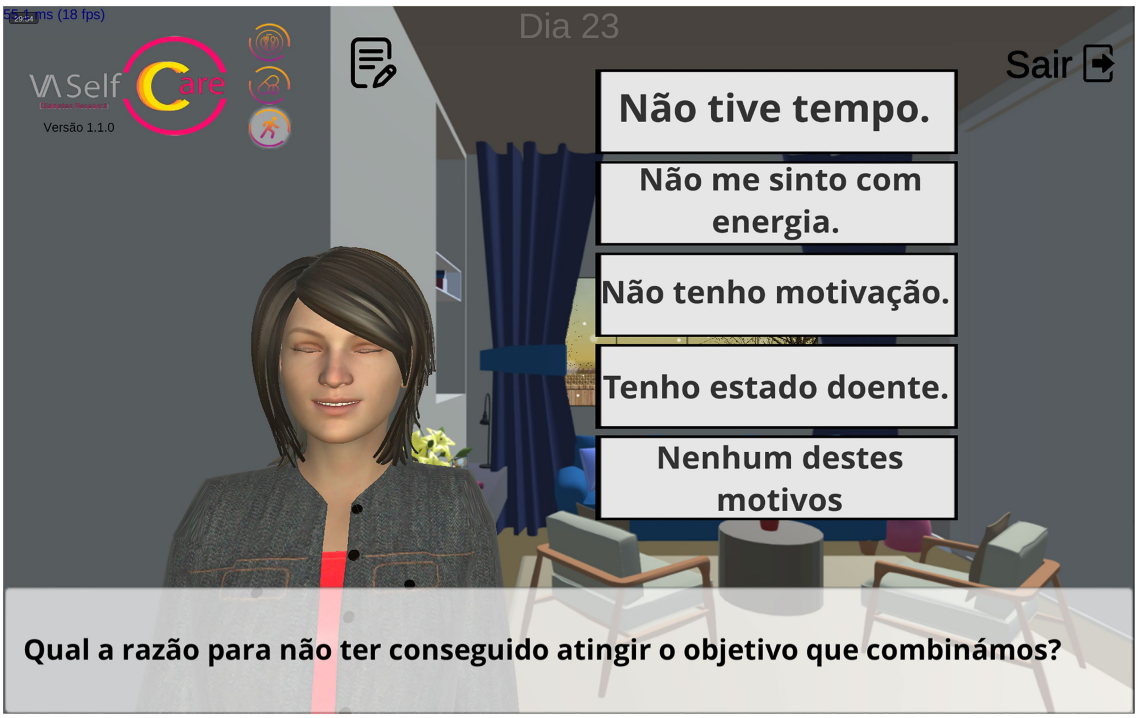

FIGURE 6 | Interface of the mobile application: Vitoria addressing barriers to walking (problem-solving 1.2). Translation to English: What is the reason for not having achieved the goal we agreed upon? (subtitle); (A) I did not have time; (B) I do not feel energetic; (C) I am not motivated; (D) I have been sick and (E) None of these reasons (response options).

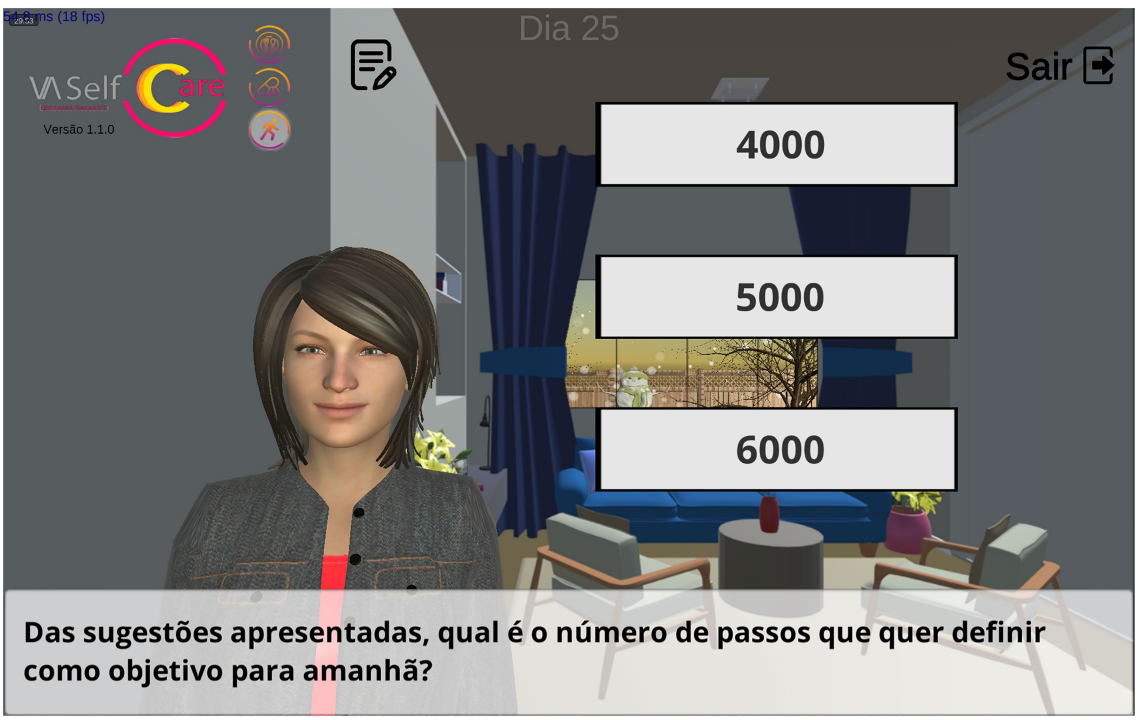

FIGURE 7 | Interface in the mobile application: Vitoria reviewing the number of steps goal (review behavior goal 1.5). Translation to English: Of the suggestions presented, what is the number of steps you want to set as a goal for tomorrow? (subtitle).

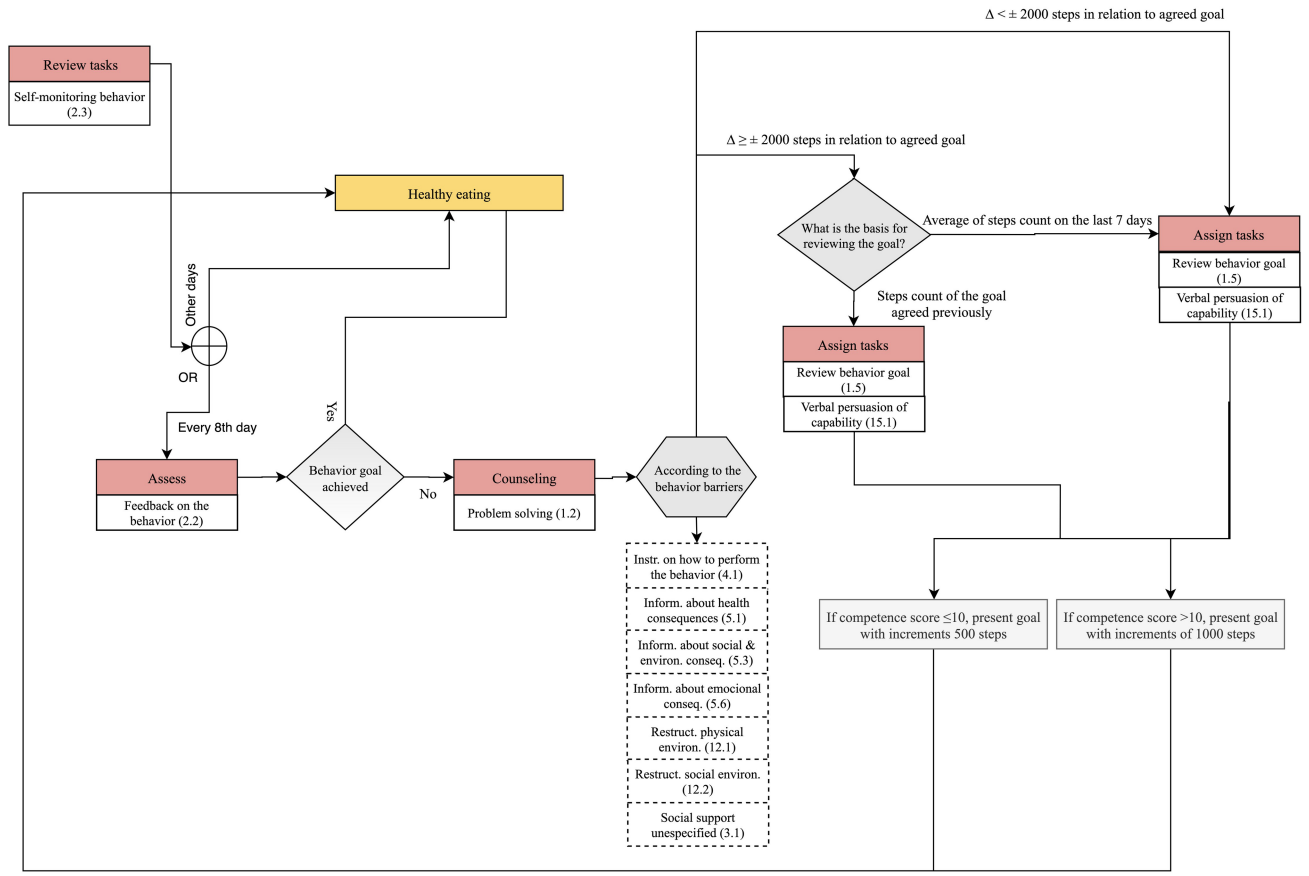

FIGURE 8 | Dialogue flow in "lite" physical activity component.

adults, in a different context, leading to the accumulation of evidence on fully automated virtual human coaches. To determine trends in outcomes of interest, a protocol was drafted for a non-randomized non-controlled 3-month feasibility trial in nursing consultations in primary care. Endpoints, selected according to the International Consortium for Health Outcomes Measurement (ICHOM, 2019), included steps count as part of lifestyle factors, glycated hemoglobin for diabetes control, and psychological well-being as a patient-reported outcome. Self-monitoring of step counts resorting to pedometers is, on its own, beneficial to promote physical activity and related health outcomes (Bravata et al., 2007; Idowu et al., 2021). However, the need to input step counts manually in the mobile application prototype may be burdensome over time and can impact on intervention engagement and intervention fatigue, two important mechanisms influencing the use of mobile applications and retention (Nahum-Shani et al., 2018).

Just-in-time adaptive interventions (JITAIs) provide the right type (or amount) of support, at the right time, while eliminating support that is not beneficial, through continuous monitoring of the person's state and context (Nahum-Shani et al., 2018). In what concerns physical activity, JITAIs are exemplified by prompting users for exercise at a particular time of the day if a certain accumulated steps count collected *via* passive assessment (e.g., *via* a smartphone accelerometer) has not been reached (Nahum-Shani et al., 2018). While self-report of step counts may undermine engagement over time and contribute to intervention fatigue, it has the advantage of improving the scalability of the intervention, by keeping it functional on a range of devices and simple to use. The latter is also important when attempting not to aggravate health inequalities. It has been suggested that the digital divide is shifting from access and connectivity to a knowledge gap on how to use information and communication technology (McAuley, 2014). This is particularly important for older adults, who are our target group. While global data show a consistent upward trend in smartphone penetration in those 65+, this does not necessarily translate in the use of mobile applications (Berenguer et al., 2017). Therefore, currently it appears sensible to keep applications for older adults as simple as possible. Usage data from trials in conjunction with qualitative explorations will shed light on older adults' engagement with the VASelfCare digital intervention and their preferences.

An analysis of 16 mobile applications marketed for the prevention and management of T2D pleaded for more transparency in reporting the app features and employed BCTs (Keller et al., 2022). We believe the same plea should be made to researchers. We found little guidance from the scientific

literature on granular aspects of intervention design and the operationalization of BCTs for digital behavior change interventions in T2D. For instance, the work of Gong et al. (2020), while providing much needed evidence on the effectiveness and implementation of a virtual human coach to support T2D self-management, offers little detail on the BCTs employed, hindering not only replication but also improvements in the intervention design and content.

The way in which the behavior change techniques are delivered is considered an element of behavior change interventions that warrants consideration as it can explain the (in-)efficacy of a given technique (Marques et al., 2020). Vitoria's dialogues were created resorting to a helpful-cooperative communication style (Niess and Diefenbach, 2016), aiming to build rapport and trust. This non-judgmental approach is considered to increase autonomy and relatedness which are core basic psychological needs according to the Self-Determination Theory. Further, this communication style is in line with recommendations on the use of language to communicate with and about persons with diabetes, grouped under the umbrella of the Language Matters Diabetes global movement.[2] These recommendations were developed based on evidence and expert opinion in countries such as Australia, United States and the United Kingdom (Dickinson et al., 2017; Cooper et al., 2018; Speight et al., 2021) and adapted for other countries, for guiding health professionals and other stakeholders (Batata et al., 2022). We believe there is room for applying the preferred language and principles entailed in these recommendations to digital behavior change interventions in T2D, to harness higher rapport and trust, aiming at higher engagement and effectiveness.

A final point meriting discussion is whether the VASelfCare prototype is appropriate to other cultures. Walking is a commonly accepted form of physical activity for both men and women in western societies, but maybe less common in other cultures. For example, research in India suggested that women associate physical activity mostly with household chores and do not contemplate walking as an exercise option, albeit finding it feasible (Mathews et al., 2016). This raises the point of cultural adaptation of digital behavior change interventions.

CONCLUSION

Evidence and theory have been translated into an m-health prototype using an anthropomorphic conversational agent to promote physical activity in older adults with type 2 diabetes, as part of a multi-behavioral intervention. This approach, which includes 13 BCTs and six if-then rules that determine their tailoring and dialogue flow, is expected to maximize effectiveness and to facilitate replication. Ultimately, the present work may leverage the efforts of others in developing self-management interventions targeting lifestyle behaviors.

[2]https://www.languagemattersdiabetes.com

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

IF, NP, and MG conceived the work reported in this paper. IF and NP led the design of the physical activity component, supported by MG, DM, and MM. IF, NP, and MG wrote the first draft of the manuscript. MM performed a first critical review. Subsequent iterations of the manuscript were commented on by all authors. All authors contributed to the article and approved the submitted version.

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Experience of using a smartphone WeChat applet for dental anxiety assessment and preoperative evaluation: A nationwide multicenter study

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Introduction: Dental anxiety is a multivariate phenomenon that regularly occurs during a dental procedure. Although it may lead to patients' safety concerns and adverse events in routine treatment, it is often ignored. The purpose of this research is to develop a novel WeChat Applet for dental anxiety (WADA) with the following features and aims: (1) to help patients with dental anxiety management; (2) provide patient with a physical status self-evaluation; and(3) provide a platform for online assessment and tele-consultancy by dentists. We aimed to test and verify whether such an applet could play a beneficial role before and after a dental procedure and facilitate management of high-risk patients during the COVID-19 pandemic.

Materials and methods: During the 12-month survey period (August 2020 to July 2021), a total of 180 patients aged 3–74 years from eight different cities (n = 180 at the end of treatment, n = 25 for the System Usability Scale (SUS) and follow-up interview) and 20 medical staff from eight different cities (n =20 for follow-up interview) were evaluated by WADA. At the end of the survey period, the results of the interviews were analyzed thematically.

Results: WADA assessment results from 180 patients and follow-up interview results from 45 participants were analyzed. In this study with a male to female ratio of 2:3, 75% were found to be suffering from dental anxiety, 86% were found with postoperative complications, and 11 cases were found to have contraindications to surgery. The total SUS score for WADA is 72.25 above the mean score, proving that WADA is a relevant and useful tool before and after dental treatment. Based on the results of the interviews, the following themes were identified: patient satisfaction; dentists' effectiveness; multi-center data integration; and increase its frequency of usage.

Conclusions: The WADA was developed for dental procedures and is effective for reducing treatment risks, improving patients' satisfaction and dentists' convenience, especially in terms of facilitating management of high-risk patient during the COVID-19 pandemic.

KEYWORDS

intelligent personality assessment, WeChat applet, dental treatment, dental anxiety, comfort therapy

Introduction

Despite the recent innovations and technological advances in modern dentistry, dental anxiety continues to be widespread (1, 2). It occurs globally and is considered a public health problem (3). Dental anxiety disorder is a complex phenomenon related to a variety of factors (4), and according to study with incomplete statistics, 83.1% of Chinese adult patients had moderate to high dental anxiety and 16.2% met the criteria of dental phobia (Modified Dental Anxiety Scale [MDAS] score $\geq$ 19) (5). People suffering from dental anxiety often try to avoid or delay dental treatment, leading to deterioration of oral health and a reduced quality of life. The progression of untreated oral infections, combined with feelings of remorse, humiliation, or worthlessness, contributes to an increase in dental anxiety, and the vicious cycle continues. This has been described by several researchers as a "dynamic vicious cycle"(6). Identifying and preventing dental anxiety in the early stages of oral disease is considered a key approach to improving patients' oral health and dental-visit experience (7).

eHealth (electronic health) is a broad term that describes the use of electronic devices to provide healthcare. Mobile health (mHealth) is a component of eHealth and involves the use of mobile devices to collect data about an individual's health status and provide information to professionals and patients in real-time (8, 9). The market for mHealth applications has exploded in the last decade (10). There is a wide range of medical applications available at home and abroad, such as MedActionPlan Pro (MPP), Kræftværket, and iManage, among others (11–13). The scale of mobile internet continues to expand, with data showing that as of September 30, 2020, the number of global Internet users was nearly 4,929,926,187. More than half (2,555,636,255; 51.8%) of these Internet users are in Asia (14). In 2017, WeChat applets were launched, which were downloaded by 1.09 billion users, and WeChat-based small programs are used by 400 million users every day (15). It is expected that such an applet will be the main form of mobile Internet applications and a promising way to increase the frequency of application use, including that for health management and self-monitoring, which is already popular.

The WeChat Applet for dental anxiety (WADA) was initially developed by the Comfort Dentistry Center of the Stomatology Hospital affiliated with the Chongqing Medical University in 2018. Today, with the continuous progress of artificial intelligence technology, the development of an intelligent preoperative evaluation platform system combined with artificial intelligence can partially solve the problems of high information load and high repetitive labor intensity of anesthesiologists in the evaluation of dental treatment, and this method is less prone to errors and omissions. Therefore, the idea of creating a WeChat-based applet to manage patients more conveniently and efficiently was discussed by the doctors of Comfort Dentistry. It was proposed that a remote and intelligent medical assistance platform system needed to be built with the integration of information previously obtained by the Comfort Dentistry Center.

The purpose of this research was to develop a novel applet, WADA, and to investigate how patients seeking dental treatment evaluate WADA after use. We aimed to test and verify whether such an applet could play a beneficial role before and after a dental procedure and facilitate management of high-risk patients during the COVID-19 pandemic.

Methods and Analysis

Study design

A participatory design was adopted (16). It is a design that aims to actively involve all stakeholders in the design process to help ensure that the results meet their requirements and improve usability. Participatory design is guided by a fundamental ethical stance that end users who may be affected by the design in the future should have a voice in the process (17, 18). Face-to-face participatory design sessions were conducted, which is a way for end users to actively co-design technical solutions together with researchers and product designers, involving patient representatives, anesthesiologists, dentists, and computer scientists. The aim was to make WADA more attractive and effective for all users. Additional face-to-face and online participatory sessions were planned during the study when necessary.

TABLE 1 Demographic data of participants.

City	Number of medical staff(M / F)	Number of patiens (M / F)	Age of patiens	Number of patients with dental anxiety	Number of patients with contraindications	Number of patients with postoperative complications
Chongqing	4(2/2)	36(9/27)	3—74	31	3	32
Beijing	3(1/2)	33(15/18)	5—68	23	2	27
Shanghai	3(2/1)	27(12/15)	4—55	18	1	26
Guangdong	2(0/2)	14(10/4)	6—48	10	1	13
Jiangsu	3(1/2)	22(6/16)	4—52	15	1	17
Henan	2(2/0)	15(8/7)	9—47	14	2	14
Shandong	2(2/0)	23(10/13)	6—53	14	1	18
Neimenggu	1(1/0)	10(6/4)	12—44	9	0	8
Total	20(11/9)	180(76/104)	3—74	134	11	155

Participants and recruitment

Participants for the 12-month WADA survey were recruited by Comfort Dentistry or anesthesia departments in dental offices nationwide. The inclusion criteria were as follows: ability to access the Internet *via* cellular data or Wi-Fi with smartphones either independently or with the help of relatives. Medical staff who were involved in the WADA co-creation development process and patients who were unable to use their smartphones to complete the questionnaire were excluded. Two hundred participants, including 180 patients and 20 medical staff (Table 1), were recruited during the 12-month test period (August 2020 to July 2021) and 180 patients all used WADA before and after treatment. One hundred and eighty patients completed their dental treatment. At the end of the test period, the study team used a stratified random sampling method to select 30 patients for analysis using the System Usability Scale (SUS) and follow-up interview as well as 20 medical staff for the follow-up interview. Of the 30 patients, three were unable to complete the interview for personal reasons, one refused to be interviewed, and one patient passed away due to illness. These patients were excluded, and a total of 45 participants (25 patients and 20 medical staff) were included in the follow-up interviews and randomly mixed in terms of region, sex, and age. The study was conducted during the August 2020 to July 2021 pandemic. First, for protection against COVID-19, the patients were required to present the results of a nucleic acid test within 48 h and a trip code and health code (a way to ensure that you are not in contact with an infected person) before being granted access into Stomatology Hospital affiliated with the Chongqing Medical University. Second, the health care workers took precautions (such as wearing protective clothing, masks, and face masks) and underwent nucleic acid tests once a week to ensure that they were not infected with COVID-19. Finally, the study involved questionnaires and follow-up visits by video call *via* WeChat in July 2021 to minimize the risk of COVID-19 infection (19, 20).

Applet description

The WADA is a smartphone WeChat applet designed and developed by the Comfort Dentistry Center of the Stomatology Hospital affiliated with the Chongqing Medical University and has not been published anywhere. This is the first study on WADA. We incorporated the entire preoperative assessment system, including the Modified Dental Anxiety Scale (MDAS), Children Fear Survey Schedule-Dental Subscale (CFSS-DS), and various body systems assessment scales (Q4) such as allergy history, surgical history and various underlying diseases into the cloud database and WeChat applet through programming to establish logical relationships and perform intelligent assessments to assist anesthesiologists in decision-making. (Q1) Both MDAS and CFSS-DS are in Chinese and have been proven to be valid and reliable (21, 22). The applet realizes intelligent formulation of multi-level and multi-selective information fusion analysis to achieve personalized patient management. In turn, the collected big data can be used to perform intelligent assessment before treatment and help doctors to select different comfort treatment plans in a hierarchical manner through deep computer learning, finally realizing the closed-loop operation of the whole system and promoting the transformation of large-scale clinical data into medical knowledge. Using the internet, Internet of Things, cloud computing, and artificial intelligence technologies, we can realize smarter, safer, and more convenient medical services for both doctors and patients. As such, the WeChat-based applet needed three interfaces for the three relevant people: dentists, anesthesiologists, and patients, to improve

the current dental medical consultation experience. The idea behind WADA is to allow patients suffering from dental anxiety to eliminate or alleviate their nervousness about dental visits by providing them general knowledge of dentistry and adequate pre-treatment assessment while minimizing the medical risks in dental treatment and reducing the repetitive and labor-intensive tasks of some dentists and anesthesiologists.

(Q5) WADA is a WeChat applet that anyone can start and use in WeChat at any time, without the need to download additional applications (Figure 1). There are many functional modules on the patient version of the WADA homepage (Figure 2), including personal center, pre-treatment assessment, pre-operative instructions, and dental knowledge. Users can access these modules after registration and login. In the Personal Center module, patients can fill in their basic information (name, sex and age) and upload the relevant examination results (Figure 3). At the same time, they can review the past visits in the visit record and give feedback on the last visit after treatment. (Q2) Through the pre-treatment assessment

FIGURE 1
Applet opening interface. Patients can search for the WADA and use it by scrolling down on the main screen of WeChat without the need to download additional applications. It takes up little memory and is very convenient.

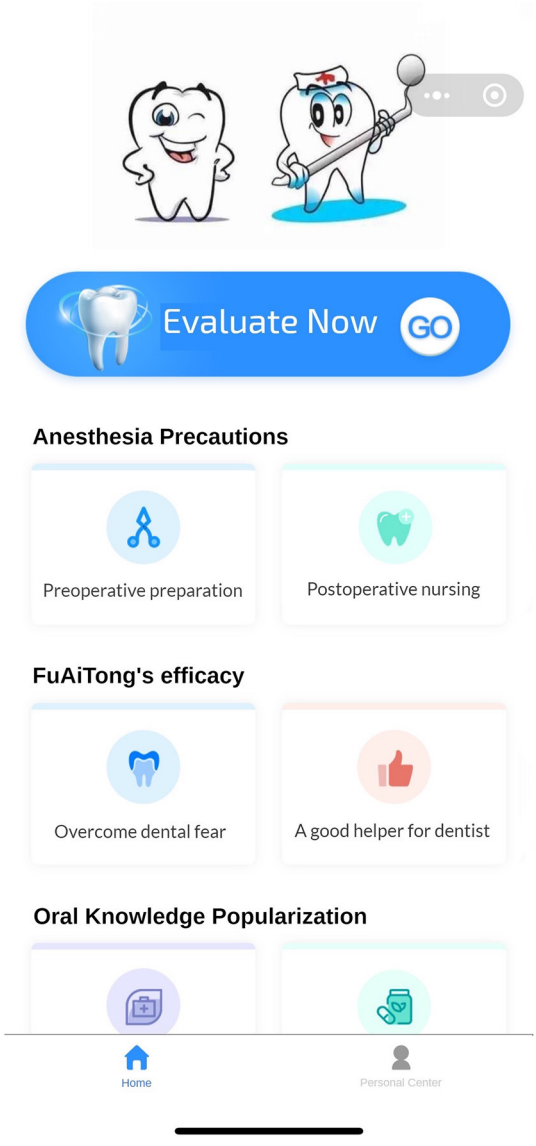

FIGURE 2
The main interface. It includes sections for immediate pre-treatment assessment, anesthesia instructions, dental knowledge, and personal center. Users can choose according to their needs.

module, patients can make an CFSS-DS or MDAS and other intelligent assessment according to the age they filling in before treatment (Figures 4, 5), and then the system will automatically generate primary assessment results and provide medical advice to doctors. The preoperative information and dental science sections allow patients to browse preoperative preparation and postoperative care precautions, as well as to obtain oral health care knowledge. The doctors can use WADA to promptly see the patient's assessment results, as well as the treatment recommendations and risks based on the patient's pre-treatment assessment (Figure 6). When patients upload their questions or test results through the patient version of the app, the doctor is notified, and the patient is given instructions and medical advice through the doctor-facing homepage.

The purpose of the application is:

1. Eliminate dental anxiety (through a patient-facing intelligent pre-treatment assessment platform system [Figures 4, 5] and general dental knowledge [Figure 2]).

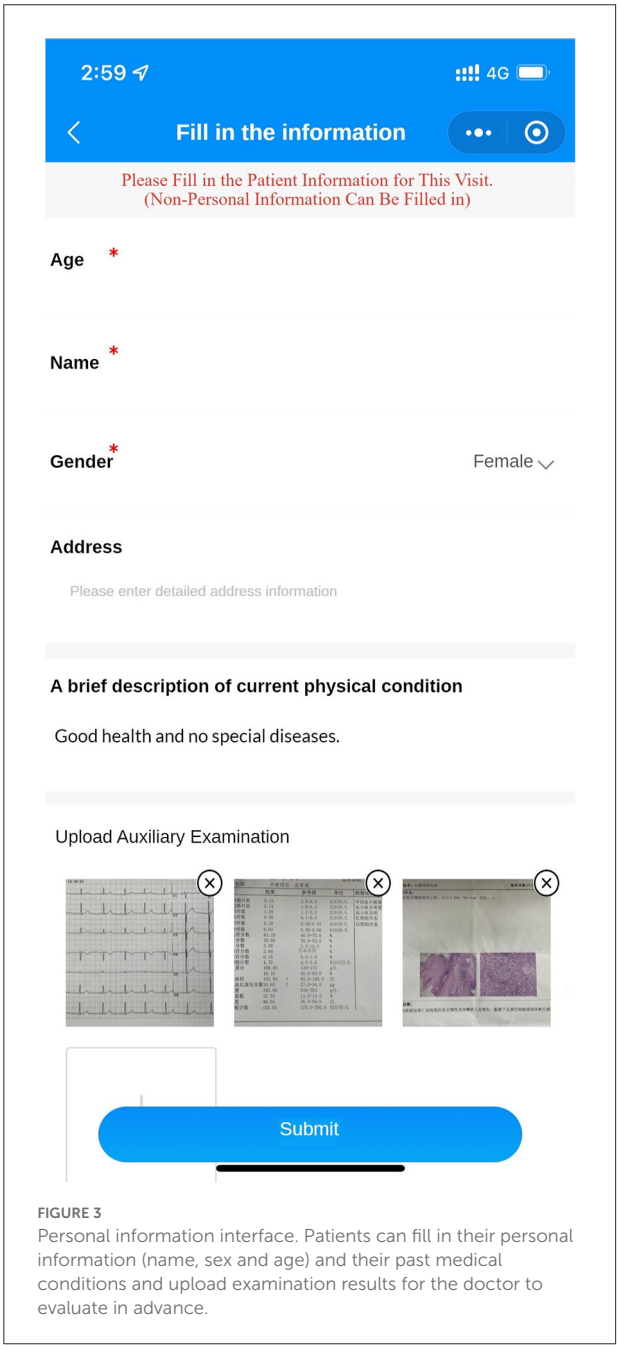

FIGURE 3
Personal information interface. Patients can fill in their personal information (name, sex and age) and their past medical conditions and upload examination results for the doctor to evaluate in advance.

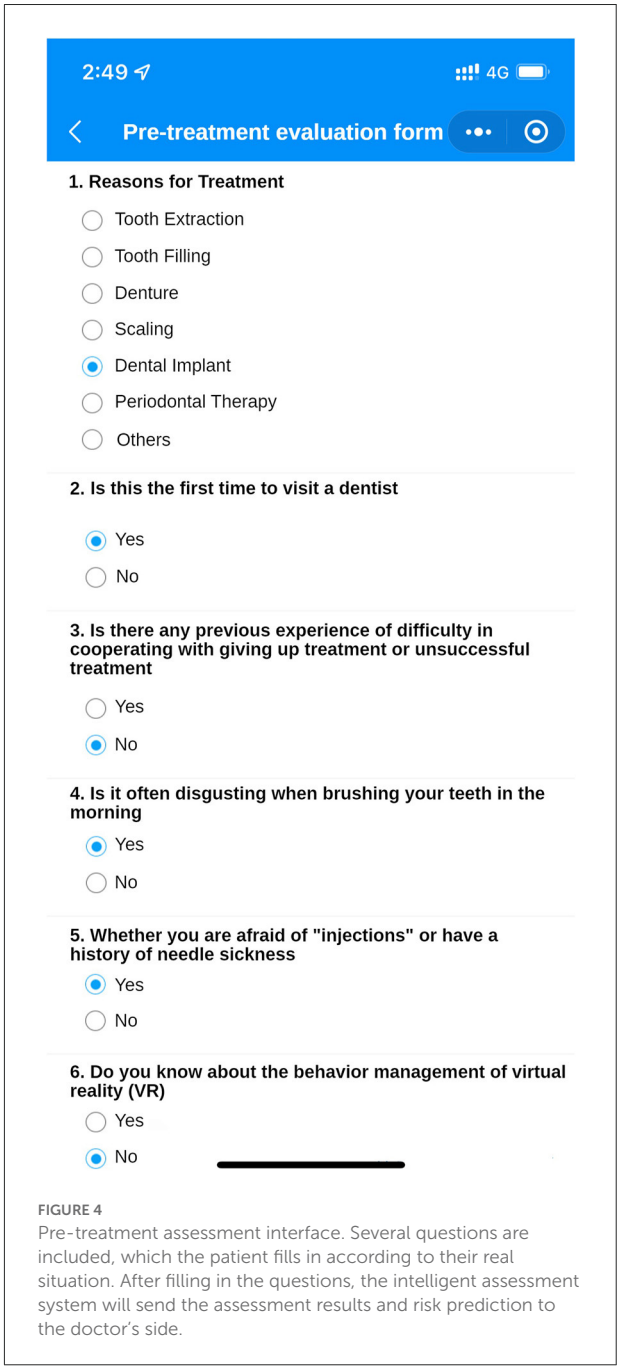

FIGURE 4
Pre-treatment assessment interface. Several questions are included, which the patient fills in according to their real situation. After filling in the questions, the intelligent assessment system will send the assessment results and risk prediction to the doctor's side.

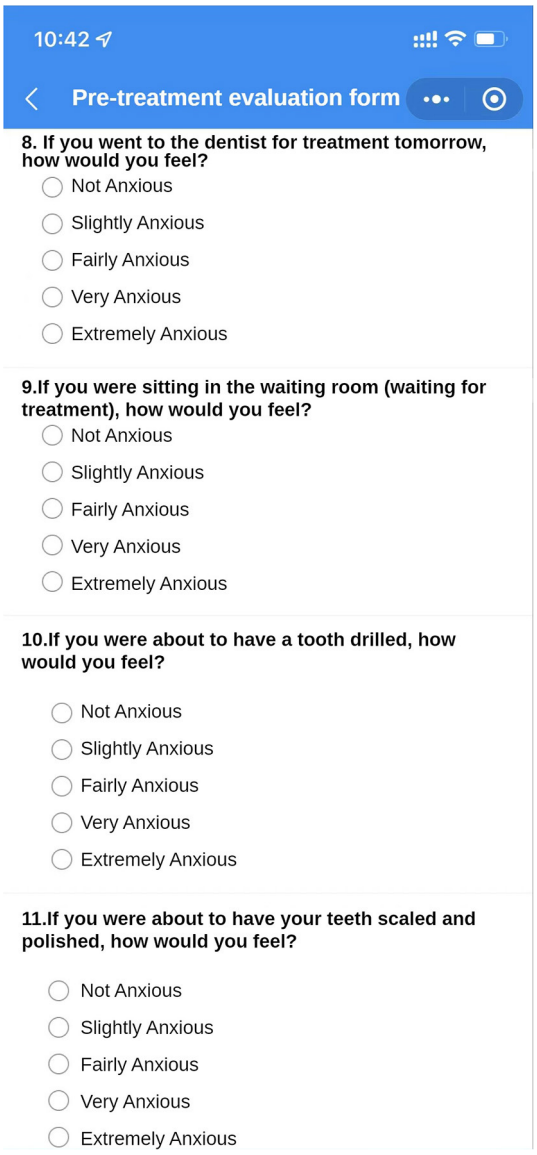

FIGURE 5
Pre-treatment assessment interface. Part of the Modified Dental Anxiety Scale (MDAS). After filling in the questions, the intelligent assessment system will send the assessment results and risk prediction to the doctor's side.

2. Predict treatment risks and complications in advance (through a doctor-facing intelligent pre-treatment assessment results [Figure 6]).
3. Improve patient satisfaction (through post-treatment feedback system [Figures 3, 7]).
4. Reduce the work intensity of some anesthesiologists and reduce the risk of errors (through the intelligent pre-treatment assessment platform system on the doctor's side).
5. Collect data and knowledge for medical research.

Data collection

During the 12-month survey period (August 2020 to July 2021), 200 participants had access to WADA at any time. They were instructed to use WADA before or after their dentist visit depending on their own needs but were not given any specific instructions on the frequency of usage. At the end of the survey period, 25 patients were asked to complete the SUS (Table 2) and undergo a usage experience interview (Table 3). The SUS is a simple, 5-point Likert scale that was developed as a fast and efficient method to collect an overview of the usability of a system (23, 24). SUS provides an overall usability assessment metric consisting of 10 questions, with odd-numbered questions being positive statements and even-numbered questions being negative statements. At the same time, 20 medical staff were interviewed about their usage experience (Table 3).

The return experience was guided by a semi-structured interview guide. The interview guide was driven by existing knowledge in the field and contained topics related to patient satisfaction, physician effectiveness, and multicenter experience (Table 4). The interviews involved open-ended and broad initial questions, which included the participants' direct impressions of WADA and considered new and unforeseen observations of the experience with opening questions followed by targeted follow-up questions.

All interviews were conducted by video call *via* WeChat in July 2021. Interviews were conducted between one participant and one researcher. The first author (XLH) studied the relevant training and guidelines on the internet before conducting the interviews in Chinese. The interviews lasted for 45 min on average and were audio recorded and transcribed verbatim. Quotations were subsequently translated into English by a professional translator.

Data analysis

The SUS scores were analyzed using the SPSS statistical software (version 17, SPSS, Inc., Chicago, IL, USA). Quantitative Likert scale data are presented as the mean ± standard deviation. According to Bangor and colleagues' thorough evaluation of the SUS, a system needs to score above 70 to be considered at least passable. Better systems score in the high 70s to high 80s, and scores over 90 indicate a truly superior system (25).

The interviews were recorded and transcribed verbatim. The Ritchie and Spencer qualitative Framework approach was used as the analytical framework. This involves: (1) familiarization with the data; (2) identification of a thematic framework; (3) indexation of the themes; (4) charting those themes into a hierarchical framework; and (5) mapping and interpretation of those themes (26). Using this analysis strategy, it was possible to mix theoretical and empirical perspectives, which made it

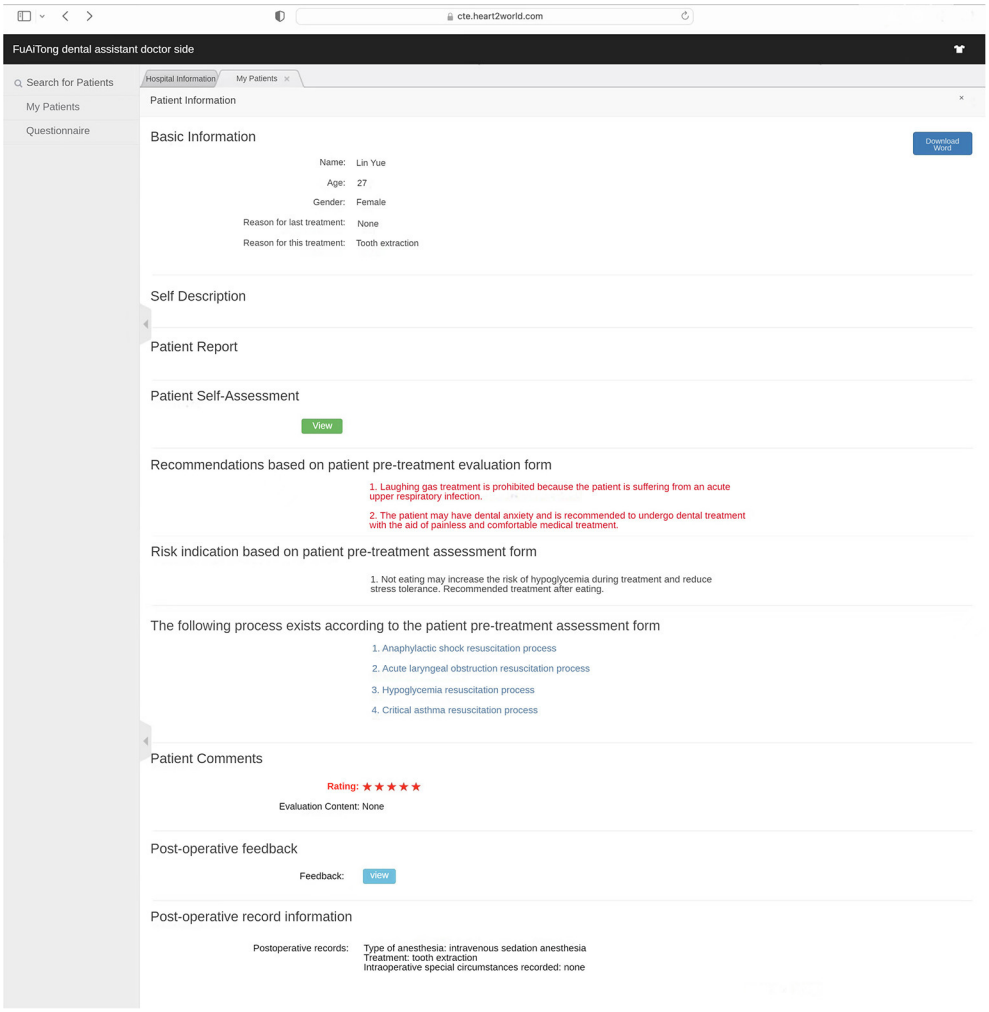

FIGURE 6
Doctor-side assessment result interface. Doctors can view patient assessment results, recommended anesthesia, risk warnings, post-operative records, etc. The symbol * means that the patient rated this treatment experience with a maximum of 5* and a minimum of 1*.

applicable to both pre-existing knowledge and new unforeseen topics related to the participants' immediate experiences of using the applet.

To ensure consistency in the coding process, the authors independently performed steps 1 and 2, which involved familiarizing themselves with the richness and diversity of the data and making notes to develop ideas about the concepts and initial themes (identifying a thematic framework). After step 2, the authors met to discuss all concepts and initial themes that emerged from the transcripts to reach consensus on a set of related themes. The first author, XHu, then performed steps 3–5 to reorganize and annotate the data according to the thematic framework and to organize citations according to themes, which were found in the syndication process (indexing the themes). XHu then arranged all themes into a coded tree with related subthemes (charting themes into a hierarchical framework). Finally, XHu mapped and interpreted the dataset as a whole through a systematic process (mapping and interpretation) that culminated in a discussion among all authors to identify any overlooked insights.

Rigor was established to ensure dependability and credibility by properly transcribing data, individual analysis of data, discussing concepts and themes, and by validating the design through a theory-driven interview guide ensuring that all participants were asked the same range of questions.

Results

During the survey period, 180 patients from eight different cities in China completed the survey. Of all respondents, 57.8% (104/180) identified as women and 42.2% (76/180) as men. The

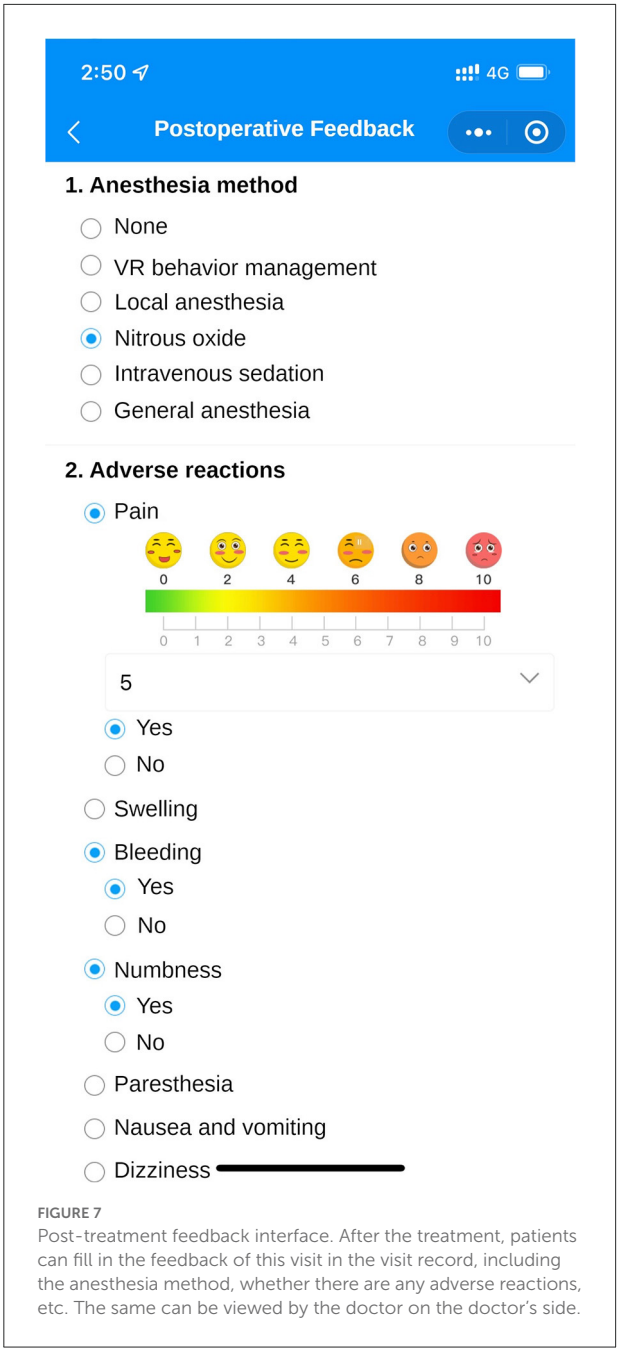

FIGURE 7
Post-treatment feedback interface. After the treatment, patients can fill in the feedback of this visit in the visit record, including the anesthesia method, whether there are any adverse reactions, etc. The same can be viewed by the doctor on the doctor's side.

total SUS score of this WeChat applet was 72.25, which indicated good usability, learnability, and satisfaction.

The analysis of the participant interviews yielded a series of themes and sub-themes (Table 5).

Patient satisfaction

Eliminate tension and anxiety

Among the 180 patients who participated in the test, 134 were found to suffer from dental anxiety. WADA contains a library of popular science articles, including general knowledge about dentistry and oral health care from authoritative hospital-based dentists. Many participants knew the authors of these popular articles, which created a sense of authority and trustworthiness. Eighty-eight percent of the patients who participated in the interviews mentioned that the general knowledge and pre-treatment assessment before the visit made them feel more at ease.

> *"WADA can help acquaint me with some oral-science information and provide treatment-related precautions, which can calm me and reduce my anxiety when facing the doctor and oral treatment."* (18-year-old male participant from Beijing, China, who underwent tooth extraction).

Increase doctor-patient communication and interaction

Eighty-four percent of the patients who participated in an interview said that WADA has increased the interaction between them and their doctor and made their visit a more complete experience. They felt they could write their true feelings about the visit and upload the current examination results for the doctor to view in the post-treatment feedback.

Upload laboratory examination results

Fifty-six percent of the participants chose to take photos of their examination results and upload them before or after the treatment.

> *"This way I can check the examination and treatment results after each visit and at any time without worrying about losing the data."* (22-year-old female participant from Guangdong, China, who received a dental caries restoration)

In addition, the applet also helped saved time during the next visit.

> *"When I visit a new hospital, I can access the results of previous examinations, which are readily available on WADA. This can help me save time and money needed to undergo the examinations again."* (38-year-old female participant from Chongqing, China, who underwent dental implant placement).

Give prompt feedback

Seventy-four percent of participants filled out a postoperative feedback form promptly after the treatment, which included questions regarding the type of anesthesia, adverse reactions, and any complications.

TABLE 2 The system usability scale.

	Strongly disagree.				Strongly agree
	1	2	3	4	5
1. I think that I would like to use this system frequently					
2. I found the system unnecessarily complex					
3. I thought the system was easy to use					
4. I think that I would need the support of a technical person to be able to use this system					
5. I found the various functions in this system were well integrated					
6. I thought there was too much inconsistency in this system					
7. I would imagine that most people would learn to use this system very quickly					
8. I found the system very cumbersome to use					
9. I felt very confident using the system					
10. I needed to learn a lot of things before I could get going with this system					

There are ten questions on the SUS.

For problems with odd serial number, subtract 1 from their score.

For problems with even serial numbers, the score is subtracted by 5.

Add the final scores of all questions together and multiply by 2.5 and the calculated result is the SUS score of the applet.

The range of score for each question is recorded as 0∼4, the maximum score is 40, and the range of SUS score is 0∼100.

Tips:

1. Should not be summarized or discussed prior to completion.

2. Participants should be asked to complete each question quickly and without too much thought.

3.The second and sixth questions may be difficult for participants to understand and need to be explained clearly.

4. If the participant is unable to complete one of the questions for some reason, the participant is considered to have chosen the middle score for that question.

TABLE 3 Examples from the semi-structured interview guide ($N = 45$).

Sample questions of patient satisfaction	Sample questions of doctor effectiveness
What is your immediate impression of this WeChat applet? Is it aesthetically pleasing?	What is your immediate impression of this WeChat applet? Is it aesthetically pleasing?
Which features do you use? And why?	Is this WeChat applet convenient and easy to use?
How would you rate the Intelligent Assessment System (is it relevant, easy to use and adequate)?	How would you rate the Intelligent Assessment System (is it relevant and accurate)?
How would you evaluate the dental knowledge section (is the information relevant and sufficient)?	Can this WeChat applet reduce the amount of repetitive work you have to do?
How do you assess the post-operative feedback function (is it relevant and how do you use it)?	Can this WeChat applet reduce the risk of dental treatment?
Is it possible to integrate this WeChat applet into your daily life? And how?	Is the anesthesia method recommended by the intelligent assessment system accurate?
What needs does the WeChat applet meet and what needs does it not meet?	What needs does the WeChat applet meet and what needs does it not meet?
What are the advantages and disadvantages of this WeChat applet?	What are the advantages and disadvantages of this WeChat applet?
Were you able to find the answers to the questions you were looking for?	

> *"This allowed me to note how I felt in real time, for example, with regard to pain or other discomforts, and to communicate this with the doctor to avoid this experience during subsequent treatment."* (36-year-old male participant from Chongqing, China, who underwent dental implant placement).

TABLE 4 The usability assessment of the mobile system ($N = 25$).

	Mean score	SD
1. I think that I would like to use this system frequently	3.0	0.78
2. I found the system unnecessarily complex	2.90	0.70
3. I thought the system was easy to use	2.80	0.75
4. I think that I would need the support of a technical person to be able to use this system	2.90	0.83
5. I found the various functions in this system were well-integrated	2.70	0.90
6. I thought there was too much inconsistency in this system	3.20	0.75
7. I would imagine that most people would learn to use this system very quickly	2.70	0.90
8. I found the system very cumbersome to use	2.80	0.75
9. I felt very confident using the system	3.0	0.78
10. I needed to learn a lot of things before I could get going with this system	2.90	0.70
The overall value of SUS	72.25	

TABLE 5 Themes and sub-themes.

Patient satisfaction	Doctor effectiveness	Multi-center data integration	Increase the frequency of usage
Eliminate tension and anxiety	Reduce repetitive work, effort, and risk	More comprehensive	
Increase doctor-patient communication and interaction	Remote diagnosis, advanced preparation, and detection of special cases		
Upload laboratory examination results	Optimize and improve treatment with previous visit results		
Give prompt feedback			

Doctor effectiveness

Reduce repetitive work, effort, and risk

In today's aging and pediatric population, children with dental anxiety and elderly patients with multiple systemic complications are very challenging for dentists in their offices.

> *"The applet helps reduce unnecessary repetition of steps and avoid errors in judgment due to excessive duplication of work, especially among the elderly people with many complications."* (32-year-old anesthesiologist from Chongqing, China).

Remote diagnosis, advanced preparation, and detection of special cases

Four out of seven anesthesiologists mentioned that they could make an initial diagnosis remotely based on the pre-treatment assessment submitted by the patient and prepare medications and emergency measures in advance for possible complications.

> *"For example, for patients with a history of a cardiac disease in the last 6 months, we can prepare emergency measures in advance. Patients with a history of hypertension can be instructed to take medication to lower their blood pressure and visit when the blood pressure normalizes, helping to save the time of both doctor and patient."* (35-year-old anesthesiologist from Shangdong, China)

During the 12-month survey period, the WADA Smart Assessment System screened a total of 11 individuals with combined contraindications, 9 of whom were contraindicated for nitrous oxide anesthesia.

> *"Patients are reminded that nitrous oxide therapy is prohibited when they have a history of intestinal obstruction, pneumothorax, or pulmonary fibrosis, which is very smart and reduces our duplication of workload"* (32-year-old anesthesiologist from Chongqing, China).

Optimize and improve treatment with previous visit results

Through the information that patients fill out in the postoperative feedback system at the end of the treatment, 86% of the patients had different degrees of complications such as pain, dizziness, and numbness. All anesthesiologists believe that the postoperative feedback function of WADA allowed them to reflect upon the treatment process.

> *"We advise patients to complete the WADA post-operative feedback form following the treatment do that their feedback can be used for continuous adjustments and improvements to optimize the patient experience."* (33-year-old anesthesiologist from Shanghai, China)

Three out of 7 dentists also mentioned the convenience of having patients' test results uploaded through WADA.

> *"I habitually check the patients' previously uploaded test results when they come to the clinic, which saves time for both sides"* (36-year-old dentist from Henan, China).

Multi-center data integration

More comprehensive data

WADA was utilized in multiple dental clinics of nine cities nationwide and was well accepted by dental professionals. This multi-center application allows easier dissemination of the results to a wider audience irrespective of regional differences and allows for continuous optimization of the intelligent assessment system and treatment modalities by analyzing patient data from each city.

Increase the frequency of usage

As a WeChat applet, WADA uses simplified steps, and they can be opened directly without downloading the application package. When patients want to undergo self-assessment or receive a dental consultation at anytime and anywhere, they can open the relevant pages directly from the main WeChat interface, which makes the process convenient and can help increase the frequency of usage.

Discussion

The traditional face-to-face medical consult model is no longer sufficient to meet the demand for medical services. Therefore, more and more medical institutions and computer scientists are using technologies to provide more effective and convenient medical services to patients. There are more than 318,000 medical apps available to help diagnose and manage diseases (27), for example, there apps for blood pressure monitoring (28) and electrocardiogram measurements (29).

Our PubMed search identified many articles on medical apps. These apps can be broadly classified into three categories according to the target user: patient-facing behavioral and health management apps (12, 30, 31), physician-facing apps to aid diagnosis (32–34), and apps to aid learning for medical students (35, 36). Regarding patient-facing apps, the most common categories are mobile health apps intended for monitoring and management of blood glucose levels (37–39) (e.g. SuCare, Sanofi-Aventis US LLC), blood pressure levels (39, 40), and cholesterol (41), with other apps for medical conditions (e.g., Vitadoc+, Medisana GmbH). Certain apps can alert patients when they need further professional help and others help to diagnose specific pathologies. In the dental field, in 2016, Francesca et al. found that oral hygiene compliance and reduced incidence of white spot lesions could be improved *via* the use of apps (42). In the same year, Janneke et al. launched an app called WhiteTeeth to improve oral hygiene in adolescents and determined its usability to be good using SUS (43). In 2020, Kim et al. identified the location and distribution of users' dental plaque *via* the hand-held LIF device or mobile app (44). Tobias et al. designed a mobile health app called iGAM, which uses selfies to monitor gingivitis (45), thereby facilitating the flow of information between the dentist and patient during the examination.

To our knowledge, there is no intelligent personalized assessment system for pre-treatment of common oral diseases in China or abroad. Therefore, we have designed and developed an intelligent preoperative evaluation platform system combined with artificial intelligence, moving the entire preoperative evaluation system to the cloud database and embedding it into a WeChat applet to establish logical relationships through programming to produce intelligent evaluation results to assist anesthesiologists in making decisions. In this study, we explored how participants evaluated the applet and its convenience, and the statistical results demonstrated the usefulness of WADA in reducing patient dental anxiety and increasing patient satisfaction.

On reviewing these existing dental applications (42–48), it was found that most of them monitor the patient's lifestyle and oral health status. None of them played a complete role in the whole process of patient treatment like WADA, including pre-treatment assessment, during-treatment advice, and post-treatment feedback.

The convenience provided by WADA points to four main areas: patient satisfaction, physician convenience, multi-center data integration, and warning of systemic risk in dental treatment. Systematic risk assessment becomes easier to perform along with dental treatment, and treatment complications can be predicted in advance and prevented, thereby improving the satisfaction and convenience experienced by both patients and doctor, enabling effective communication between patients and doctors, and allowing acquisition of oral health care knowledge. Overall, our survey showed that WADA is an intelligent and convenient medical application for dental treatment that contributes to the safety and efficiency of dental treatment. Patients also provided some key suggestions that will be considered in the subsequent development of the WADA upgrade.

Some references mention that filling a dental fear questionnaire before treatment may give false results as the child may experience anticipatory anxiety prior to treatment, which would be expressed through the questionnaire instead of the fear relating to the dental procedure in the moment. On

the other hand, applying measures immediately after treatment might capture the child's dental fear, and children who have recovered after treatment may rate the treatment procedure more positively than their actual experience (2). Also, the duration of dental treatment was a factor in children's anxiety, which may be reflected in the study results (49). Therefore, future studies should attempt to standardize the assessment periods over the course of the treatment and follow-up (2).

Limitations

Some limitations of this study should be considered. Patients who may have had an underlying anxiety disorder or a condition that may have affected their anxiety were not excluded. We also did not screen and exclude some factors that might influence the assessment of patients' dental anxiety disorders (e.g., self-concept, behavioral management, attention-deficit hyperactivity disorder, and oppositional defiant disorder) (50–53), which may have impacted the results.

According to the feedback provide by some, there is no way to provide real-time notifications for WADA due to the specificity of WeChat applets. Notifications would be a great help for people with busy lives. Another possible limitation is that the uneven distribution of males and females participating in this study created a response imbalance. In addition, the number of participants was uneven across age groups. Therefore, the results and feedback may have been different if the sex and age distributions were more equal.

It should also be noted that although this study covered multiple dental hospitals in multiple cities, it did not have full coverage across China. Future studies will be based on the final version of WADA and will be tested more comprehensively through efforts by all parties to recruit national beta users from all cities of China.

Conclusion

In this study, we developed a pre-treatment intelligent personalized assessment system, which includes pre-treatment assessment, preoperative instructions, dental knowledge, post-treatment feedback on the patient side, and anesthesia modality recommendation and risk assessment by the doctor.

Overall, most participants were satisfied with the feedback on WADA. Patients and their caregivers were able to access more useful services through WADA. For some of the participants who were physicians, WADA provided a lot of convenience in providing treatment, especially through the post-treatment feedback and uploading of the test results. On the other hand, WADA also enhanced the convenience of doctors, saving time and reducing treatment risks, especially for high-risk patients during the COVID-19 pandemic.

Data availability statement

The original contributions presented in the study are included in the article/supplementary files, further inquiries can be directed to the corresponding author/s.

Ethics statement

The study was performed according to the World Medical Association's Declaration of Helsinki and the procedures were approved by the Ethics Committees of the Stomatological Hospital of the Chongqing Medical University (2020-023). All participants signed an informed consent form prior to participation. Use of anonymized data from the app for academic research purposes is allowed under the app's terms of service.

Author contributions

CY, JZ, and XMH participated in the study concept and design. XLH collected the data and drafted the manuscript. XLH, JZ, NZ, and DJR participated in the analysis and interpretation of the data. JZ, CY, and LF critically revised the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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mHealth Applications to Monitor Lifestyle Behaviors and Circadian Rhythm in Clinical Settings: Current Perspective and Future Directions

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Metabolic diseases are a global rising health burden, mainly due to the deleterious interaction of current lifestyles with the underlying biology of these diseases. Daily habits and behaviors, such as diet, sleep, and physical exercise impact the whole-body circadian system through the synchronization of the peripheral body clocks that contribute to metabolic homeostasis. The disruption of this system may promote the development of metabolic diseases, including obesity and diabetes, emphasizing the importance of assessing and monitoring variables that affect circadian rhythms. Advances in technology are generating innovative resources and tools for health care management and patient monitoring, particularly important for chronic conditions. The use of mobile health technologies, known as mHealth, is increasing and these approaches are contributing to aiding both patients and healthcare professionals in disease management and education. The mHealth solutions allow continuous monitoring of patients, sharing relevant information and data with physicians and other healthcare professionals and accessing education resources to support informed decisions. Thus, if properly used, these tools empower patients and help them to adopt healthier lifestyles. This article aims to give an overview of the influence of circadian rhythms disruption and lifestyle habits in the progression of metabolic diseases while also reviewing some of the mobile applications available to monitor lifestyle behaviors and individual chronobiology. Herein is also described the design and development of the NutriClock system, an mHealth solution developed by our team to monitor these variables.

Keywords: mHealth, chronic care management, metabolic diseases, circadian rhythms, nutrition, sleep, physical exercise, usability

INTRODUCTION

The prevalence of metabolic diseases, particularly obesity and type 2 diabetes mellitus (T2DM), continues to rise globally. Obesity has grown to epidemic proportions, with over 4 million annual deaths attributed to overweight in 2017 (1). This condition is also an established risk factor for T2DM, with around 80% of people with T2DM being obese. In the next 25 years, it is expected

that more than 600 million people will be diagnosed with T2DM, and around the same number of people will develop impaired glucose tolerance, a state that frequently precedes T2DM (2).

These statistical predictions, in combination with the global epidemic of the novel coronavirus (COVID-19), heightened an additional need for valid and reliable technology in health care. This includes the development and improvement of digital platforms dedicated to assisting professionals in providing health care to patients whenever face-to-face interactions are not viable (3). The proliferation of mobile health apps (mHealth) has fostered their use in delivering health-related behavior change interventions (4). These apps are now commonly used to self-monitor lifestyle behaviors and some even allow sharing of information with healthcare professionals (3).

Several mHealth apps have been developed to assist patients in managing chronic diseases, such as metabolic diseases. Through education, diet, activity tracking, and personalized health advice, these apps have the potential to guide behavior change. Dietary changes combined with healthy lifestyle adjustments should be the first approach since they have been identified as one of the most effective interventions for preventing, managing, and reversing chronic conditions. mHealth apps designed to support these actions may have a central role in health promotion and care (4).

The relevance of circadian rhythms in the regulation of energy metabolism, as well as the role of circadian disruption in poor health outcomes, is well-documented in the literature, both in clinical and non-clinical experimental settings (5). These rhythms are driven by an endogenous mechanism and enable our body to achieve optimal functional performance. Circadian rhythm disruption is associated with an increased risk of developing metabolic diseases (6, 7). Patients and healthcare professionals would benefit from access to standardized and clinically validated technology to monitor disrupted circadian rhythms and implement personalized nutritional approaches. Due to the widespread use of smartphone devices across the world, mHealth applications already represent a useful resource in clinical settings.

The present article aims to provide an overview of the current clinical evidence regarding the impact of circadian rhythms on the development of metabolic diseases and summarize the mobile applications available to monitor lifestyle behaviors and individual chronobiology, highlighting the innovative aspects brought by the NutriClock mHealth solution.

CIRCADIAN RHYTHM, METABOLIC HOMEOSTASIS, AND LIFESTYLE BEHAVIORS

Metabolic homeostasis is a critical component that regulates energy metabolism. In recent years, several studies enlightened the relationship between human physiology, the circadian rhythm and a cluster of metabolic diseases, including T2DM and obesity (8, 9).

The circadian rhythm, also known as the biological clock, refers to the physiological, molecular and behavioral changes that occur during a cycle of approximately 24 h. In humans, these rhythms are synchronized by a hierarchical system: the central clock in the suprachiasmatic nucleus (SCN) of the hypothalamus and the peripheral clocks, located in several organs and tissues throughout the body (10). While the SCN is mainly synchronized by the light/dark cycles, the peripheral clocks react to other stimuli, including the feeding/fasting state, nutrients, sleep-wake cycles, and physical activity (11, 12).

Daily eating patterns are affected by several factors, including, hunger and satiety, social habits and food availability. Nonetheless, when eating occurs at a consistent and expected schedule, the circadian clock system initiates nutrient-sensing pathways to uphold nutrient homeostasis (13). When eating schedules are altered to occur at random times, these same nutrient-responsive pathways give feedback to the circadian clocks to adjust their phase shift. This disruption acutely impacts glycemic control and insulin sensitivity, increasing the risk of developing T2DM (14). Besides insulin sensitivity, the effects of the circadian system are seen in numerous metabolic and hormonal rhythms, including cortisol and melatonin. These two anti-phasic hormones are involved in the signaling between the master clock and the other peripheral oscillators (15, 16) and can be used to evaluate circadian rhythms, though their measurement can be affected by external factors (17). However, presently, the most straightforward method to study and analyse circadian-derived behavior in humans consists of measuring physical activity.

These findings highlight the importance of measuring variables related to circadian behavior, such as eating schedules, physical activity and circadian biomarkers, to potentiate the effects of current nutritional and medical approaches in the management and prevention of chronic metabolic diseases.

MOBILE SOLUTIONS TO MONITOR OUTPATIENTS' CIRCADIAN RHYTHMS AND HEALTH

The *my Circadian Clock* (mCC) application was developed as part of a chrononutrition-related study to assess the influence that the timing of caloric intake has on metabolic homeostasis and subsequent prognosis of pathology. The 156 participants were asked to record all the meals they ingested. They received app notifications once or twice a day, at random times, to check if they had eaten in the last 30 min and forgotten to record the event. The false-negative rate was estimated to be 10.34%. The results showed that more than half of the participants had an erratic eating pattern. According to the data inserted in the mCC application, the participants spent most of the day consuming calories, with only a brief period of fasting. Furthermore, a higher caloric intake was observed in the afternoon and evening, which could have several consequences, including a negative impact on sleep quality (18).

More recently, Wilkinson and colleagues (19) also used the mCC app in their study to assess the impact of 10-h time-restricted eating (TRE) on 19 patients with Metabolic Syndrome (MetS). The mCC app was used during baseline and the

intervention to register food/beverage intake and sleep. The adherence to logging information in the app was 94.30 ± 7.25% during the 2-week baseline, and 85.61 ± 12.39% during the 12-week intervention (19). Caloric intake was estimated based on photos and/or annotations since the mCC app is not designed to enter the exact food portions. The results of this study showed a general reduction in body weight, waist circumference, blood pressure, glycated hemoglobin and an improvement in lipid profile and sleep.

Sakane and colleagues (20) assessed the impact of a chrononutrition-based mobile application on weight changes. The study included 1 835 participants that used the app "Reborn Magic" for 4 weeks to behavior self-monitoring. Aside from weight changes, other outcomes assessed included waking time, breakfast, lunch, and dinner timing, weekend and holiday bedtime, and physical condition score. According to the findings, age was negatively correlated with waking time and dinner timing. Inappropriate meal timing was found in 32.9% of dinners, 34.2% of lunches and 61% of breakfasts. After the intervention, the physical condition scores increased significantly from 6.6 to 8.2 points out of 10. Significant weight loss in participants with overweight and obesity was observed, while significant weight gain was observed in lean participants. Normal-weight participants experienced no weight changes. The authors concluded that chrononutrition-based apps may be effective for weight loss. However, additional research, including randomized controlled trials (RCT), is needed (20), particularly to clarify the individual effects of TRE on metabolic diseases independent of caloric restriction.

Tahara and colleagues (21) conducted a study on Japanese people to assess if changes in chronotype, due to the recent pandemic confinement, were associated with body weight changes. They analyzed data collected from 30,275 Asken mobile app users via an online survey. The results revealed an association between changes in sleep stages and body weight. During a mild lockdown, participants who reported advanced sleep phases on both work and non-workdays lost weight and those who slept later gained weight. Despite these findings, the authors highlighted that the study has methodological limitations, so more research is needed to validate these findings.

Swiatkiewicz and colleagues (22) coordinated the TREMNIOS study, a pilot clinical trial conducted in Polish adults with MetS and an eating period >14 h per day. The study also uses the mCC app to assess if TRE could help patients regain rhythmic daily behavior and improve cardiometabolic outcomes. Participants are expected to complete a 10-h TRE intervention for 24 weeks, and changes in the eating window, body weight, and biomarkers will be assessed. Metabolic, neuroendocrine, inflammatory and antioxidant biomarkers, body weight and composition, blood pressure, heart rate, sleep and activity, personal sense of wellness and dietary timing will be evaluated at the baseline and after intervention with compliance with TRE assessed using the app. The study is estimated to be complete in January 2023 and it is expected that these results can set the foundation for a large-scale RCT to determine the efficacy and sustainability of TRE in reducing long-term cardiometabolic risk in patients with MetS.

NUTRICLOCK: DEVELOPMENT OF A NEW APP AND WEB PLATFORM TO MONITOR CIRCADIAN BEHAVIORS

The NutriClock (National Trademark Registration no. 664951) mHealth platform is a deliverable of the NutriClock study, whose primary goal is to serve as a data collection, monitoring, and analysis support tool. The NutriClock app collects data related to lifestyle behaviors including sleep, physical activity, dietary patterns, and circadian rhythm biomarkers. The multidisciplinary team behind the design and development of this platform included computer engineers, nutritionists, physiologists, and psychologists.

The platform was built using agile methodologies, which enable iterative, incremental, and adaptable system implementation in response to changing requirements, as well as continuous feedback on potential improvements.

Figure 1 depicts the NutriClock system's high-level architecture diagram using Level 2 of the C4 model (23). The C4 model is a set of diagrams used to represent software architecture at four different levels of abstraction: Context (Level 1), Container (Level 2), Component (Level 3), and Code (Level 4) diagrams. Level 2 depicts the high-level shape of the software architecture, the major technology choices, and how the containers communicate with one another. **Figure 1** shows that the platform is divided into four modules: the backend, which is the system's foundation; the backoffice, used by administrators, healthcare professionals, and researchers; the mobile application, used by study participants; and a WebSocket service that allows real-time communication via chat. Each module serves a specific purpose but for the system to work, modules must communicate with one another and with external services for sending notifications, emails, and storing images. Screenshots of the mobile app and backoffice are available in the **Supplementary Material**.

The backend module is a REST API that writes and reads data from the database to provide the information requested by client applications. The available resources are documented at http://nutriclock.herokuapp.com/api/documentation, and are protected by authentication mechanisms. Furthermore, middlewares are used to parse and filter client requests to increase security. To store images, send emails, and manage user notifications, the backend communicates with external services.

The NutriClock Backoffice

The backoffice is a single-page web application designed to provide a platform for administrators, healthcare professionals, and researchers to manage and analyse data from participants. To protect and limit access to participants' data, each user role has different management and access permissions. As an example, healthcare professionals can only access the data of the participants registered in their healthcare institution.

The following are some of the main features available in the backoffice:

1 Authentication and user profile management;

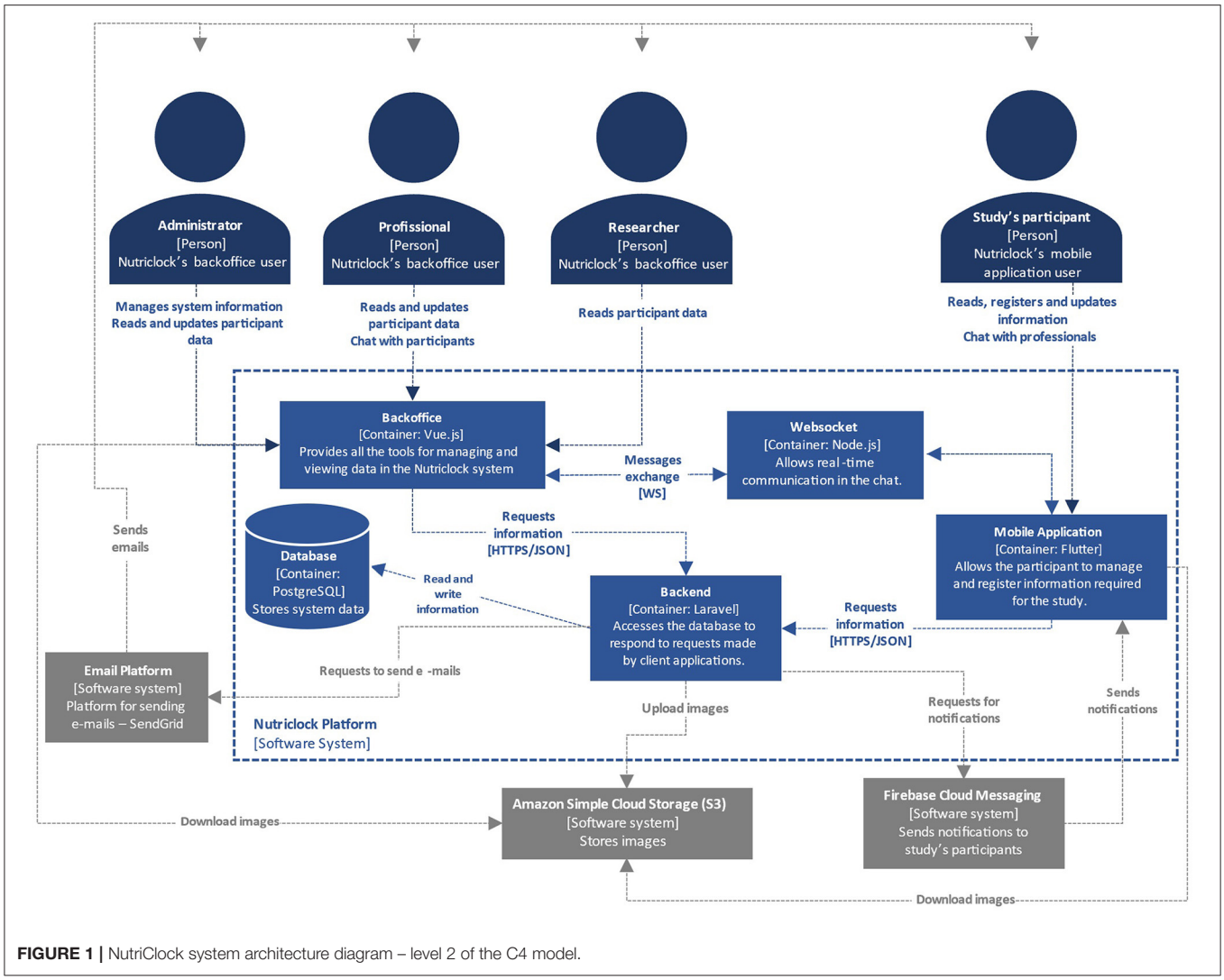

FIGURE 1 | NutriClock system architecture diagram – level 2 of the C4 model.

2 Management of the participants' data (available for all users with differentiated privileges), including:
3 Create and manage personalized meal plans by a registered nutritionist/dietitian;
4 Monitor and analyse the data from the sleep, food, and physical activity diaries;
5 Manage the list of participants (block, unblock, or remove participants);
6 Communicate with the participants via chat (bidirectional exchange). This can be a motivational feature for the participants;
7 Select the participant to the control or experimental arm of the study (for example, it automatically opens the meal plan option);
8 Check if the participant has entered the information necessary for the study through a color system (green, yellow and red). The system will automatically send reminders if there is information missing;
9 Create, update, or delete information, including the professional categories, institutions, pathologies, food database, physical activity database, biomarkers, and terms of acceptance (available for the administrators only). These features were included to help the administrators manage the information available in the app and will be used strictly following the Good Clinical Practice.
10 View the NutriClock mobile app ratings (available for the administrators only).

The NutriClock Mobile Application

The mobile application provides an interface for participants to enter the data and communicate with healthcare professionals via NutriClock's chat. Besides, the application will notify them when data is missing in their meal, sleep, or physical activity diaries, and when saliva and urine samples should be collected. The following are some of the features available:

1 Create a new account and authentication related functionalities;
2 Sleep diary to assess quantity and quality of sleep;
3 Physical activity diary (there is an option to select physical activity or physical exercise);
4 Food diary (enter the food item or meal, quantity, nutritional information and pictures);
5 Chat where the participant can message the healthcare professional;
6 Access to contacts, meal plans, reports and biomarker information (schedule of biological samples collections to determine cortisol and melatonin);
7 Manage the notifications settings (turn on/off);
8 Option to delete the account and data according to the right to be forgotten;
9 Rating of the NutriClock application using a 5-points Likert scale.

PRELIMINARY USABILITY TESTS OF THE NUTRICLOCK SYSTEM

The design and development of mobile applications with an easy-to-use interface is a crucial step for their successful adoption in long term (24). Usability tests represent an assessment method to measure how well-users can interact with the system and how easy and intuitive it is to execute the functions of the mobile application (25). Conducting usability tests is critical and preferably these should cover all or the majority of possible situations, however, this represents a major challenge. So, usability tests may focus only on some features of the mobile application (26). According to Zhang and Adipat (26), usability testing can be performed with laboratory experiments in which participants are required to complete specific tasks using the mobile application in a controlled setting.

Testing the usability of mobile applications is constrained by several factors, including small screen size and limited technological performance compared to other devices. Apps' ease of use and acceptance is linked with users' perception of time consumed when performing tasks, easy-to-learn functions, and user-friendly features (27), characteristics that were assessed in the NutriClock pilot-usability testing. It is also reported in the literature that mHealth apps may be more effective in creating meaningful behavior change interventions when designed to support end-user values and needs, assessed by persuasive system design principles (28). These tools were not used in the NutriClock system development.

In the case of the backoffice application, the development process focused mainly on functionality. However, usability tests conducted on this web application are also important to identify usability related issues that were improved, for example, providing feedback regarding actions taken by users (29, 30).

The NutriClock system was tested using manual, automated, and usability tests. Manual tests were primarily used to validate features and identify changes and improvements to be made to meet the platform requirements. Automated tests helped in the discovery of bugs that were missed during manual testing. Usability tests were useful to improve the user interface and to solve usability problems identified by test users, for example, knowing how to access some sections of the mobile application.

Usability Tests Methods

To participate in the usability tests, people had to be over 18 years old, provide their informed consent and not have any prior contact with the NutriClock system (to allow the assessment of the system's usability and intuitiveness by observing the users' behavior during the initial interactions). No exclusion criteria were applied.

To conduct the usability tests, the researchers created three scripts which included two scripts to test the mobile application with a patient account covering different sets of features of the NutriClock app (seven tasks in each script) and one script with 6 tasks to test the backoffice using administrator and healthcare professional accounts. The three scripts with the complete tasks are detailed in the **Supplementary Material**. To perform the backoffice test, a computer with internet access and an installed browser application were used. The mobile application was tested using either a Huawei tablet, model MediaPad M5 Lite or a Xiaomi Pocophone smartphone, model F1.

Statistical analysis was performed using SPSS 27.0 to assess the differences in execution time between participants with equal or $<$30 years (subgroup A) and participants with more than 30 years (subgroup B) for the seven tasks of test no. 1, 7 tasks of test no. 2 and 6 tasks of test no. 3. The age cut-off point for the subgroups was selected according to the distribution of age ranges of the total sample. Statistical significance was set at p-value < 0.05.

Preliminary Results

Following the Zhang and Adipat (26) methodology, 13 participants (nine women and four men) with a mean age of 35.62 $\pm$ 12.16 years (age range: 21–58 years) performed the usability tests. The tests had to be conducted in person, however, due to COVID-19 restrictions at the time, it was not possible to recruit a larger sample. Nine (69.2%) participants completed all three tests, two (15.4%) completed two tests and two (15.4%) only performed one, the criteria being their time availability.

Usability Test No.1 – Test NutriClock App as Patient

Script no.1 for the NutriClock app, was conducted on 11 people and took, on average, 6 min per participant to complete the seven tasks. Participants took longer to complete tasks 1 and 3 (**Figure 2A**), which were creating a new account and inserting an entry in the food diary, respectively. These were indeed the most time-consuming tasks and since 90.9% (task 1) and 100% (task 3) of the participants followed the expected path (defined as the quickest and most direct way to perform the function) (**Figure 2D**) and only 9.1% needed help from the researchers to perform task 3 (**Figure 2G**) it was considered that these features were simple to understand. However, in task 6, in which the participants were asked to view the biomarkers section, 72.7% of them did not follow the expected path (**Figure 2D**) because they needed to explore the app to find this section since this is more specific for this app and not a general feature. Interestingly, in this

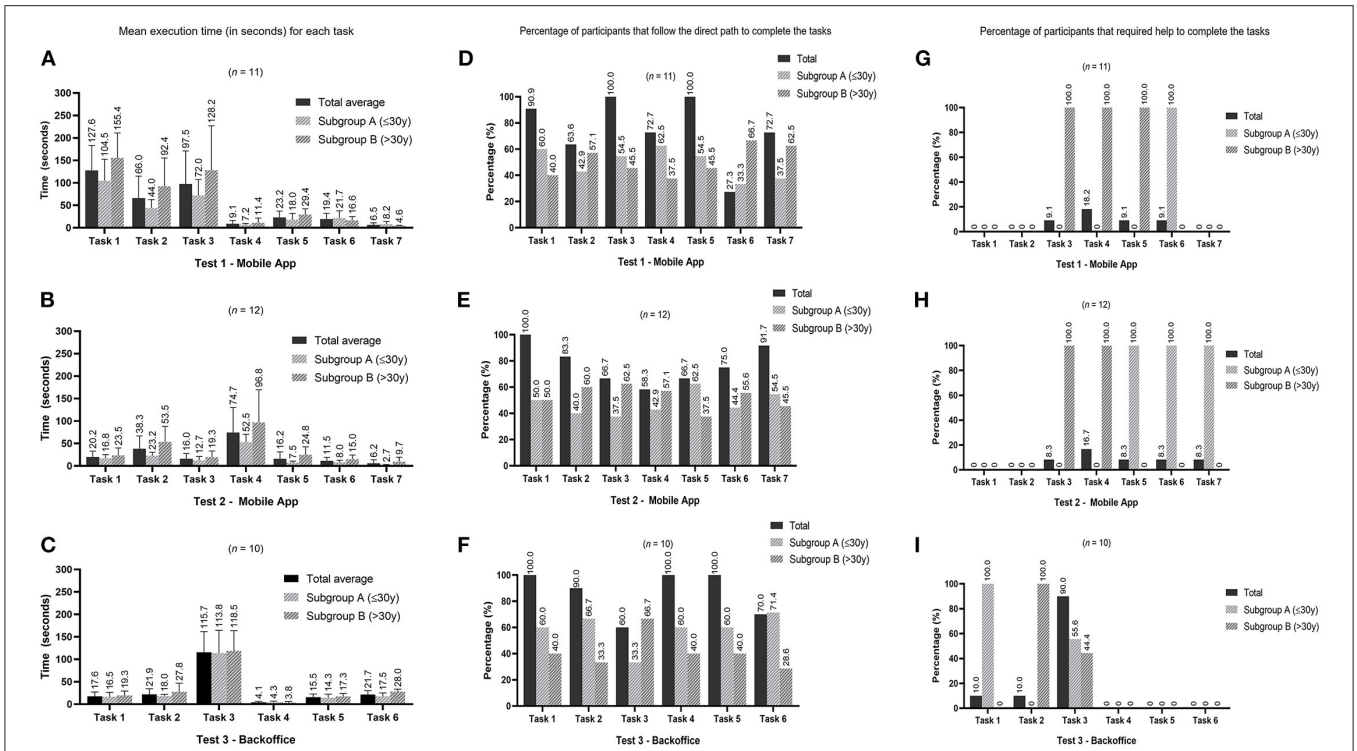

FIGURE 2 | Graphics display the results of the three different usability tests by tasks. Graphics **(A–C)** show the mean execution time (values placed above the standard deviation bar). Graphics **(D–F)** represent the percentage of participants that immediately follow the direct path to complete the tasks defined in the three tests. The percentages of subgroups **(A,B)** are relative to the number of participants who followed the expected path. Graphics **(G–I)** represent the percentage of participants that required assistance from the researcher to complete the tasks in the three tests. The percentages for subgroups **(A,B)** are relative to the number of participants who needed help.

task subgroup A had the worst performance in all three indicators compared to subgroup B which seems to indicate that they had to explore more the application to find this menu. Regarding task 7, there were two paths to logout of the application, and a smaller percentage of participants in subgroup A seems to have chosen the direct path, which led them to take, on average, longer to complete this task compared to subgroup B. Overall, in this test, the expected path for executing the tasks was followed by 75% of the participants and only 7% needed assistance to complete a task.

In this test, there was only a statistical difference in median execution time for task 2 (add an entry in the sleep diary) for subgroups A (38 s) and B (80 s) (Mann-Whitney $U = 4.0$, $n_A = 6$, $n_B = 5$, $p = 0.045$ two-tailed). Although execution time might be an indicator of the difficulties the participants experienced, in this task, participants could take longer because they had to add more information. For example, a participant who answered that they woke up during the night had to fill in more information than a participant who answered no to this first question.

Usability Test No.2 – Test NutriClock App as Administrator

This test was performed by 12 people and took, on average, 3 min per participant to complete the seven tasks. Participants took longer to add a new entry in the physical activity diary (task 4) (**Figure 2B**). This was also the task with the lower percentage of participants (58.3%) following the expected path (**Figure 2E**) and the higher percentage of participants (16.7%) requiring help to execute it (**Figure 2H**) which can indicate that the usability of this feature may be improved. In general, the expected path was followed, on average, by 77% of participants, with 7% of participants needing help to complete a task. In this test, subgroup A had a lower percentage of participants following the expected path in tasks 2, 3, 4, and 6, even though they took less time to complete. This can be an indicator that the mobile application is quick to explore but not always intuitive to some users.

A statistically significant difference was found in the median execution times for task 2 (edit information entered in the food diary): subgroup A = 24 s and subgroup B = 48 s (Mann-Whitney $U = 5.0$, $n_A = 6$, $n_B = 6$, $p = 0.037$ two-tailed). This difference was due to a participant from subgroup B that took 120 s to complete this task, while all the other participants took <55 s. There were also significant differences in median execution times for task 5 (consult notifications settings): subgroup A = 6 s and subgroup B = 22.5 s (Mann-Whitney $U = 4.0$, $n_A = 6$, $n_B = 6$, $p = 0.024$ two-tailed). In this task, the participants that took more than 15 s to complete it were from subgroup B which may explain the difference found in the median execution times. The last statically significant difference was found on median execution times for task 7

(logout application): subgroup A = 2.5 s and subgroup B = 6 s (Mann-Whitney U = 0.5, $n_A = 6$, $n_B = 6$, $p = 0.004$ two-tailed). All of the participants took <10 s to complete this task, except one participant in subgroup B that took 30 s.

Usability Test No.3 – Testing the Backoffice Using Administrator and Healthcare Professional Accounts

Regarding the backoffice test, 10 participants completed this script, taking, on average 3 min to complete the six tasks. Task 3 (adding a food item to a meal plan) was the one that participants had more difficulty completing. This was the one with a longer execution time (**Figure 2C**), a lower percentage of participants (60.0%) following the expected path (**Figure 2F**) and a higher percentage of participants (90.0%) that needed help to complete it (**Figure 2I**). The results of this test highlighted the need to improve this function and make it more user-friendly.

In general, the expected path for executing a task was followed, on average, by 87 and 18% of participants needed assistance.

No significant differences were found in the execution time between subgroups A and B.

Study Limitations

Some limitations were identified that should be considered in future studies, the main one being the small sample size. Also, the usability testing in this controlled setting may not represent how the end-user will interact with the mobile application in their daily routines. The participants were not all representative of the real end-users (patients with metabolic diseases) and the age range of the participants included should have been broader to represent all the potential end-users of the NutriClock application. This will be taken into consideration in the next phase of usability tests as well as in the tests to evaluate the perceived quality of the system. In future work, and after improving the issues identified, the app usability will be re-tested based on a validated model and in real-end users. Also, future tests will be performed in the field to assess how people use the app in a real and not controlled environment.

FUTURE PERSPECTIVES OF MHEALTH SOLUTIONS TO ASSIST LIFESTYLE INTERVENTIONS

The potential of mHealth applications to improve access to healthcare resources and real-time monitoring is already recognized (31–33). Medical health practice supported by mobile devices continues to scale up, and current literature suggests that higher levels of engagement of both patients and healthcare providers are often associated with better health outcomes (34–36). Also, these tools could help healthcare professionals motivate patients in remote settings to adopt healthier lifestyles, manage chronic diseases and reduce complications (37–39).

However, these solutions may also present some issues, particularly concerning data privacy and the protection of sensitive information shared by patients (40). Another challenge faced is the digital gap experienced by some patients and the intellectual capabilities of users which could lead to high attrition rates (41).

To circumvent some of these challenges, when designing a mobile application to address behavior change, it is important to have a comprehensive concept, essential to achieve an ongoing impact (42, 43). McClung and colleagues proposed an approach based on a health-centered design as a solution that would benefit the future of mHealth tools (3). This highlights the importance of starting the development process with a context analysis to identify the primary functions required for the solution, which must meet the needs of all stakeholders involved. Furthermore, a user-centered design is required to create an engaging application (3). The personalization based on user preferences is also relevant for the success of mHealth solutions. This can encompass personalization considering the information on medical factors and personal preferences; disease-specific education tips; the ability to track progress, which includes viewing previous logs and uploading photos; reminders and reinforcement based on user feedback with motivational messages, are some of the characteristics of a successful and engaging mHealth app, according to Joshi and colleagues (4). Also, Salari and colleagues (44) revealed that among 23 minimum set of features for diabetes mobiles apps, mealtime tagging, food database, diet management, educational materials, healthy coping, reminders, target range setting, trend chart view, and numerical indicators view are among the features deemed important by experts. To fulfill all these requirements, interdisciplinary and collaborative work (42) between healthcare professionals, patients, and software development teams is essential throughout the product development process (3).

In the future, evidence-based mHealth solutions may be integrated into traditional clinical treatment approaches to improve health results and access to primary care prevention. This could be particularly important in the context of chronic diseases, such as metabolic diseases since they frequently need to be managed from their onset with few options for a full recovery and these solutions could help patients achieve better results (45, 46). Patients can benefit from mHealth solutions that allow them to self-monitor, stay in control, and be better informed about their health by recording and analyzing information.

This perspective is aligned with the future of the NutriClock app and backoffice, as it is expected that this system can be implemented in clinical settings to help healthcare professionals monitor lifestyle behaviors and individual circadian rhythms and empower patients by giving them an active role in their healthcare monitoring and management process. Besides, this system will also help researchers in the field design clinical studies on chrononutrition and chronobiology, with larger samples since participants can be monitored remotely.

The evidence arising from the use of mHealth solutions appears promising. However, the current published evidence of improvements in patients' health outcomes using these tools is still restricted to a limited number of clinical situations (47). More research should be conducted to investigate the feasibility of these solutions, particularly in the treatment of metabolic diseases, so that the use of these tools can become part of the therapeutic approaches used in clinical settings.

The results of chrononutrition studies are encouraging but more clinical studies with larger samples and longer periods of intervention are necessary before translating the current knowledge to clinical practice. So tools that support these interventions and studies, such as the NutriClock system, are relevant. Currently, there are still improvements to implement in the NutriClock system, including adding reference pictures for the portions, according to the meal or food item entered by the user in the food diary. Another feature that could be important to add would be a time setter and reminders to show the optimum eating window according to the individual chronotype to attempt to control erratic eating patterns. To circumvent the shortcomings of the currently available mHealth applications, especially, the lower engagement of patients, we added the chat function to have a fast direct contact point with the healthcare professionals. Motivational strategies to integrate into the NutriClock app, to lower the dropout rates and increase patients' engagement with this technology, are also being studied. The next steps will include a usability test to assess these new features, followed by a feasibility and acceptability study before starting the clinical validation of the NutriClock system.

CONCLUSION

Lifestyle interventions to treat and prevent chronic metabolic diseases need to consider the daily circadian rhythms since aligning those behaviors with the individual biological rhythm potentiates the health benefits. The use of mHealth is increasing and these solutions represent an interesting opportunity to monitor and measure health variables and lifestyle habits in normal living conditions, helping patients and healthcare professionals in disease management. The NutriClock mHealth system collects data related to lifestyle behaviors and will serve as a basis to elaborate meal plans tailored to the individual circadian characteristics, making this an innovative and differentiating solution. In the future, it is expected that this platform becomes a clinically validated therapeutic tool used to integrate individual biological rhythms in the treatment and prevention of metabolic diseases supporting interventions directed to lifestyle changes.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

ML, MG, and RB led the design of the study with the contributions of IR and CG. ML and IR drafted the manuscript, with the contributions of MG and CG. All authors contributed to the manuscript, revised it critically for intellectual content and approved the final manuscript submitted.

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SUPPLEMENTARY MATERIAL

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Beyond effectiveness evaluation: Contributing to the discussion on complexity of digital health interventions with examples from cancer care

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Digital health interventions (DHIs) have become essential complementary solutions in health care to enhance support and communication at a distance, with evidence of improving patient outcomes. Improving clinical outcomes is a major determinant of success in any health intervention, influencing its funding, development, adoption and implementation in real-world practice. In this article we explore our experiences of developing and testing DHIs to identify and discuss complexity challenges along their intervention research lifecycle. Informed by the case study research approach, we selected three individual DHIs aimed at satisfying the supportive and educational needs of people living with cancer. The Care Expert, the Digi-Do and the Gatapp were underpinned on different complexity frameworks i.e., the Medical Research Council framework and the Non-adoption, Abandonment, Scale-up, Spread and Sustainability framework. This variance on the methodological underpinning was expected to prompt a multifaceted discussion on the complexity dimensions endorsed by each of the frameworks. Our discussion endorses the adoption of mixed-methods research designs, to gather the perspectives of stakeholders and end-users, as well as pragmatic evaluation approaches that value effectiveness outcomes as much as process outcomes. Furthermore, the dissemination and sustainability agenda of DHIs needs to be considered from early-stage development with the inclusion of a business model. This business plan should be worked in partnership with healthcare services, regulatory bodies and industry, aiming to assure the management of the DHI throughout time.

KEYWORDS

interactive health communication technologies, hybrid designs, complex interventions, cancer care, telehealth

Introduction

Digital health interventions (DHIs) are rapidly gaining clinical importance as essential complementary solutions to enhance support and communication at a distance in healthcare (1). The World Health Organization (2016), defines digital health as the use of digital, mobile and wireless technologies to support the achievement of health outcomes (2).

DHIs are useful across many clinical domains. In cancer care, DHIs allow the provision of self-management support, telemonitoring and health education, in a self-paced process and on-demand. As complementary care resources, DHIs have shown evidence of improving person-relevant outcomes, such as self-efficacy, health competence, and healthcare participation, as well as patient-reported outcomes, such as depression, anxiety, pain, fatigue and wellbeing (3).

It has also been established that very few interventions are truly simple, with scholars arguing for a continuum of simplicity-complexity depending on each complexity dimension (4). A complex health intervention might be defined as dynamic activities containing multiple components, with the potential for interaction among them, and that, when delivered to the intended target audience in a specific context, might lead to a range of possible and variable outcomes (5). Considering the emerging evidence on the processes and mechanisms of action, DHIs will more likely be placed toward the complexity-end of the continuum, posing many challenges, particularly with regards to effectiveness assessment and implementation in the real-world (6).

The potential to improve clinically relevant outcomes is a major determinant of success in any health intervention, influencing possibilities for its funding, development, adoption and implementation in real-world practice. In this article, we explore our experiences of developing and testing DHIs to identify and discuss complexity challenges along their intervention research lifecycle. Informed by the case study research approach, we selected three individual DHIs aimed at satisfying the supportive and educational needs of people living with cancer (7). The Care Expert, the Digi-Do and the Gatapp were conveniently chosen, because they were underpinned by different complexity frameworks yet shared similar intervention goals and target samples. We expected that these similarities would allow our analysis to focus on the complexity dimensions and approaches endorsed by these different frameworks, thus we were guided by the Medical Research Council framework (MRCf) (8) and the Non-adoption, Abandonment, Scale-up, Spread and Sustainability framework (NASSSf) (6).

Complexity theory applied to the development and evaluation of digital health interventions

The MRCf for developing and evaluating complex interventions in health pioneered the eliciting of complexity elements in health interventions and advocated for rigorous methodological approaches to manage identified uncertainties. The original framework was revised in 2008, depicting a circular process to the intervention research lifecycle, comprising specific stages of development, piloting and feasibility, effectiveness and implementation with feedback loops in between (4). The circularity of the research process was relevant for promoting an equal focus to the different stages of the intervention research, beyond the effectiveness evaluation, which was previously the main focus in the linear version. In 2021, a new update highlighted the relationship between the intervention and its context and emphasized the adoption of diverse research perspectives in intervention research (i.e., efficacy, effectiveness, theory-based and systems). At each stage, the new guidance identifies the importance of accounting for 6 core elements: contextual relevance, adequacy of program theory, engagement of stakeholders, key uncertainties, intervention refinement, and economic adequacy (8).

The NASSSf complements the MRC by considering complexity dimensions specific to health and care technologies as health interventions, particularly concerning their non-adoption, abandonment, scale-up, spread and sustainability. More concretely, the NASSSf supports researchers to predict and evaluate the success of technology-mediated health or social care programs by posing questions within several domains and the interaction and mutual adoption between these domains over time, while highlighting the challenges pertaining to each of the domains. The more complex the domains are considered to be, the harder it is for an intervention to become mainstream in clinical practice (6). As such, the framework aims to support researchers to work with the various stakeholders to identify the key questions about complex interventions, and to design and conduct research with diverse perspectives and an appropriate combination of methods.

Reflections from intervention research on digital health interventions

Here we present each case in more detail and reflect on the identified complexity elements that, from our perspective, might challenge the traditional effectiveness evaluation designs and the sustainability of DHIs.

TABLE 1 Main features of the individual DHIs projects.

	Care expert	Digi-Do	Gatapp
Target population	Women undergoing treatment for early-stage breast cancer	Women before radiotherapy for breast cancer	Women before radiotherapy for left sided breast cancer
Theory	Person-centered care (9) and Social Support (10)	Person-centered care (9) Health literacy (11)	Person-centered care (9) Health literacy (11)
Complexity framework	MRCf	NASSSf	NASSSf
Delivery medium	Mobile applications	Mobile applications	Mobile application
Intervention lifecycle phase	Usability testing	RCT completed, analysis phase	Pre-studies, prototyping

Aiming to satisfy specific needs of people living with cancer, we developed three prototypes of DHIs, which we summarize in Table 1. The Care Expert, the Digi-Do and the Gatapp each target women undergoing treatment for breast cancer and have many similarities in the founding theory and delivery medium. The distinguishing feature of each DHI is the complexity framework guiding its development, piloting, effectiveness evaluation and implementation.

The Care Expert is an e-supportive system aiming to mediate person-centered care in the context of outpatient oncology. It was developed following the MRCf principles to strengthen women's agency within the care partnership (12). In its current version, The Care Expert app is composed of three individual supportive components, revealing high acceptability in a preliminary usability test (13).

The Digi-Do is a digital information tool to help patients with breast cancer to be involved and prepared before, during and after the start of radiotherapy treatment. It contains a virtual visit to the radiotherapy department using 360 images, maneuvered with Virtual Reality glasses or with a smartphone. Further, it is complemented with information in the form of Q&As, films and weblinks. Its development was conducted in co-design, using participatory design methodology, and the tool is currently in the final stages of evaluation (14, 15). Simultaneously, the development process is being retrospectively assessed using the NASSS-CAT long version.

Departing from our experiences of developing the Digi-Do, we used the NASSSf, complemented with the Quadruple Helix from early-stage design (16). The combination of both frameworks in a participatory design logic was believed to prompt implementation and sustainability in clinical practice. The Gatapp is in the development phase and aims to prepare patients to perform the correct breathing technique during radiotherapy (Deep Inspiration Breath Hold Radiotherapy, DIBH) by using a sensor connected to a mobile application that enables patients to practice at home while awaiting DIBH treatment.

While conducting research at each of the intervention phases, we discovered complexity elements resulting from the interplay between the person, the intervention and the context, regardless of the complexity framework.

The research process leading to The Care Expert was particularly important in eliciting the challenges concerning the effectiveness evaluation of DHIs (17). In the Care Expert project, the time elapsed from the intervention design to the intervention effectiveness evaluation corresponded with the expansion of the Internet as a delivery medium, making the use of CD-ROM obsolete. This concern has been highlighted by other researchers. Specifically, the time for conducting a traditional randomized controlled trial involving technology-mediated interventions is not compatible with the fast pace of today's technological development (18). Moreover, according to the paradata captured from participants' interactions with the application, the patterns of usage were very heterogeneous, leading to uncertainties in determining the optimum intervention dosage.

From our perspective, each person using an intervention will have different motivations, health beliefs, preferences and abilities, which will naturally result in particular ways of participating in the intervention. Accordingly, the exposure to the intervention will vary at the individual level, challenging the establishment of a predefined intervention dosage, upon which the effect of that intervention is determined. Additionally, tailoring mechanisms, aimed at personalized recommendations, are likely to lead to distinct interventions, perhaps with the strength of doses of supportive content varying upon each person's characteristics. Hence, the pathway by which the intervention components contribute to each of the targeted outcomes at the individual level is difficult to pinpoint and therefore to monitor and evaluate.

For intervention delivery medium, the use of the Internet and mobile applications enable great variability in access settings. Because the choice of access settings completely depends on the participant's preferences, heterogeneity will occur naturally. Moreover, accessing the DHI through the

Internet might allow participants to be additionally exposed to other sources of knowledge and support than the DHI, which are not active components of the intervention. The accumulated heterogeneity has great potential to influence the intervention delivery per protocol. If adopting a traditional research design, such elements are likely to constitute pitfalls in the effectiveness evaluation of DHIs.

The Digi-Do project involved end-users and stakeholders from the early stages of intervention design. NASSSf was a useful strategy, along with the Quadruple Helix model (16), to engage multi-level stakeholders and map complexity elements across different domains. The empirical work carried out to identify the requirements, needs and preferences of end-users and stakeholders highlighted the ownership and management of the DHI as a complexity element. From our perspective, the ownership and management of DHIs has significant potential to hinder their sustainability beyond the project's lifetime.

This project further led us to reflect on the adequacy of the measurement instruments used to evaluate effectiveness. Our challenge concerned the selection of outcome measures that were sensitive to the intervention and comprehensively captured the multidimensional phenomena (e.g., quality of life, wellbeing). Such endpoints are increasingly being considered equally important to other biometrically oriented outcomes, as they reflect the relevance and adequacy of health interventions to support persons living with a disease (i.e., long-term illness) (19). One possible strategy to capture multidimensional phenomena might entail the use of multiple measurement instruments to assess specific dimensions of the phenomenon. However, such a strategy might raise the response burden to the extent where adherence to the intervention, attrition and person-relevance might be at risk, consequently jeopardizing the effectiveness evaluation.

We also believe that the adequacy of matching the measurement instruments' content to the phenomena in current society might be a concern. The measurement instruments regularly used to evaluate effectiveness in clinical trials have been developed and tested for many years. Although revealing good reliability and fit, the conceptual equivalence of the phenomenon of attention in current society should be considered and explored alongside each measurement. Quality of life might be an example of such a phenomenon, with different interpretations over time and cultures, particularly considering advancements in medicine and technology.

Working sustainability from early-stage development

From our reflections on these challenges, along with the research on the selected DIHs, we elicited several cornerstones that we believe are crucial to a DHIs' sustainability beyond a project's lifetime.

Engaging end-users and stakeholders

Involving end-users and stakeholders throughout the different stages of research across clinical domains is recognized as a gold-standard and an ethical duty (20). Taking oncology as an example, the European Council has developed principles of successful patient involvement in cancer research (21). These acknowledge the importance of strong patient involvement and accountability for patient experience throughout cancer research processes. Five further considerations for the successful involvement of people living with cancer in research are also recommended: (i) strategy, level and timing, (ii) communication, understanding and relationships, (iii) resources, knowledge and skills, (iv) methods and approaches, and (v) ethical and legal aspects (21).

Involving patients in research goes beyond merely informing the research process on the real needs. It tackles questions concerning when and how the research on those needs should be undertaken. In complex health intervention research, involving patients in research has led to increased acceptability and adherence to interventions among patients and healthcare professionals (8). For DHIs, having end-users and stakeholders as research partners from early design to late implementation follow-up is one of the cornerstones of developing usable, used and useful interventions, adding value to standard care (8).

The vast number of strategies found in the methodological literature to enable such involvement reflects efforts to promote the communication, training and standardization of methods for involvement. Among them, participatory design (PD) has received particular attention in health technology research (22). PD approaches enable the engagement of end-users and stakeholders in creative and reflexive processes throughout the intervention research cycle, ultimately resulting in an artifact (e.g., website, MedTech device or app) (23). PD approaches might assist health researchers to plan and implement activities that promote the exploration of the specificities of DHIs in a rigorous and systematic way from the perspectives of all involved (24).

Establishing ownership

From our perspective, working on a business plan from an early stage is crucial for enhancing sustainability and spread of DHIs. A consensual strategy must be developed among the many stakeholders for the successful utilization, management and maintenance of the DHI beyond the project's lifetime and in clinical practice. Here, the Quadruple Helix model explored in a participatory logic might be an asset.

When considering innovation through health technology in current society, the relationship between academia, industry, regulatory bodies and civil society must be considered (25). The Quadruple Helix model highlights the social responsibility of innovation, thereby reinforcing the involvement of citizens in the research and development of technology. Evidence shows that the Quadruple Helix is an adequate model to explore innovation development with end-users and stakeholders and its sustainable translation into society (26), making it suitable for including the perspectives of developers (i.e., industry, healthcare services, and research centers), end-users (i.e., patients and healthcare professionals) and authorities (i.e., regulatory bodies, healthcare services administrators) (16).

Accounting for the context

From our perspective, equally important to ascertain whether an intervention works is to understand when it works, for whom and how, particularly in relation to the existing treatment and care journeys. Mastering the available evidence, the intervention theory and the context within which the intervention unfolds, is crucial for anticipating real-world contingencies in an effectiveness evaluation (6).

Moreover, conducting process evaluation alongside effectiveness trials is essential to understand the outcomes in light of the pathways leading to them (27). Such a strategy will likely inform the implementation process to more accurately fit the clinical context in which the DHI will unfold and highlight the complexity elements arising from the interplay between the DHI and the context.

Given that the specificities of self-paced access to DHI is dependent upon the participants' preference or need (e.g., patient's home, work, free-time setting), the traditional concept of context might need a reformulation. From our perspective, the context should comprise the setting in which the DHI is accessed, as well as the multi-level context where the treatment and care journey occur (e.g., outpatient care pathway). Accordingly, the multidisciplinary healthcare team, the organizational processes and the wider healthcare service are elements that must be carefully considered throughout the intervention research process. Here, the NASSSf offers systematic guidance to support the identification of complexity elements across micro-, meso- and macro domains of health technology innovation (6).

Future research and practice

The evidence on complex health interventions and DHIs reinforces the need to adopt research designs that enable exploring phenomena alongside the person experiencing them, and in their daily living contexts. Such an understanding might be enhanced through qualitative methods as a complement to quantitative approaches to evaluation, regardless of their focus on effectiveness or processes.

From our experiences, ensuring participation of all involved throughout the research process is crucial. Such involvement comprises the interpreting and acting phases and should occur in an academy-community collaborative processes that are endorsed by action research principles, designed to strengthen the richness, rigor and relevance of interventions for their users in their context (28).

Mixed-methods approaches are likely to allow us to elicit unique needs during DHI design and development by describing the effects with numbers and forming an understanding of the success or failure of implementation efforts (29). Aligned with this, the Most Significant Change Technique (30) has received attention in recent years as an innovative tool for monitoring and evaluating complex health interventions (31). The collection and discussion of stakeholders' stories of significant change regularly throughout the project allows for adaptative management (31). This technique might further support the establishment of the ownership of DHIs and is promising as a complementary effectiveness evaluation approach.

Given the many elements that DHIs portray, variability and heterogeneity are inevitable, and this might reduce their external validity. From our perspective, we need methodological strategies that enhance DHIs' sustainability and spread without reducing their internal validity. These principles position us in the realm of pragmatic trials (32). A pragmatic trial design allows for effectiveness evaluation methods that consider personal and contextual elements with the main goal of enhancing the knowledge transfer between settings. Pragmatic trials are likely to more adequately inform an adaptation or scale-up of the intervention to new contexts. In this sense, we move toward the realistic paradigm and its principles.

Ultimately, the alliance of paradigms should be considered throughout the intervention research cycle. Thoughtful reflection should consider their suitability for tackling the identified complexity elements, while rigorously and comprehensively addressing the phenomenon from the perspective of the people experiencing them and in context.

The transferability of our reflections and discussion should consider the sample of cases selected to inform this article. We based our analysis on three cases that had more commonalities than differences. Considering more cases with more differences would likely have led us to more in-depth and consolidated reflections. Moreover, as each is situated in the oncology domain, a judgment on the transferability of the complexity issues to other clinical areas cannot be made. Although further cases would be needed to inform that judgment, we believe that the complexity issues identified here are not specific to cancer care, they are rather related to the interplay between DHIs and the real-world context more broadly. The most

significant difference between the selected DHIs, i.e., the complexity framework, is, from our perspective, a strength of the analysis as it allowed the discussion to focus on multifaceted complexity elements.

Conclusion

This analysis of the identified challenges endorses the adoption of mixed-methods research designs to gather the perspectives of stakeholders and end-users, as well as pragmatic evaluation approaches that value effectiveness outcomes as much as process outcomes. Furthermore, the dissemination and sustainability agenda of DHIs must be considered from early-stage development with the inclusion of a business model. This business plan should be worked in partnership with healthcare services, regulatory bodies and industry, aiming to assure the management of the DHI over time.

DHIs are helpful and effectively complement healthcare. Yet high-quality research is still demanded. Methodological rigor must be maintained throughout the research lifecycle. Strategies to improve patient and health professional engagement in the design and delivery of these interventions must be put in place. DHIs entail many complexity dimensions that demand cooperative efforts and varied expertise. Such combinations should go beyond disciplinary boundaries to enable the successful design, evaluation, implementation and sustainability of DHIs.

Data availability statement

The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding author/s.

Author contributions

FV led the writing of the perspective article. All authors contributed equally to the idea conception, design, and discussion. All authors contributed with important intellectual content to the perspective article and approved the final version for publication.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Patient's decision and experience in the multi-channel appointment context: An empirical study

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Background: Long waiting time for treatment in the outpatient department has long been a complaint and has influenced patient's experience. It is critical to schedule patients for doctors to reduce patient's waiting time. Nowadays, multi-channel appointment has been provided for patients to get medical services, especially for those with severe illnesses and remote distance. This study aims to explore the factors that influence patient appointment channel choice in the context of multi-channel appointments, and how channel choice affects the waiting time for offline visiting.

Methods: We collected outpatient appointment records from both online and offline appointment channels to conduct our empirical research. The empirical analysis is conducted in two steps. We first analyze the relationship between appointment channel choice and patient's waiting time and then the relationships between three determinants and appointment channel choice. The ordinary least squares and the logistic regression model are used to obtain the empirical results.

Results: Our results show that a patient with an online appointment decision has a shorter consultation waiting time compared with a patient with on-site appointment ($\beta = -0.320$, $p < 0.001$). High-quality resource demand ($\beta = 0.349$, $p < 0.001$), high-severity disease ($\beta = 0.011$, $p < 0.001$), and high non-disease costs ($\beta = 0.039$, $p < 0.001$) create an obvious incentive for patients to make appointments *via* the Internet. Further, only the effect of non-disease cost on channel choice is lower for patients with multiple visit histories ($\beta = -0.021$, $p < 0.001$).

Conclusions: Our study confirms the effect of Internet use on reducing patient's waiting time. Patients consider both health-related risk factors and cost-related risk factors to make decisions on appointment channels. Our study produces several insights, which have implications for channel choice and patient's behavior literature. More importantly, these insights contribute to the design of appointment systems in hospitals.

KEYWORDS

patient experience, waiting time, multi-channel context, health-related factor, cost-related factor

Introduction

Patient's waiting time refers to the length of time from when the patient entered the waiting room or the consulting room to the time the patient received the services and left the doctor's consulting room, is closely related to the willingness to return for care and satisfaction ratings (1, 2), and affects the utilization of healthcare services (3). Patients may be less able to judge the technical quality of the care they receive, but they do judge their social interaction with the doctors (4). Among them, waiting time is usually regarded as indicator of service quality (5). Some patients even wait in line all night to ensure registration with a certain doctor (6). A long unnecessary waiting time can be a cause of stress for both patient and doctor (2, 7). Failure to incorporate patient-driven features into the design of service could lead to disharmonious patient–provider relationships (2).

Prior studies indicated that a key anecdotal source of dissatisfaction with medical services reported by patients is having to wait a long time in the office (1, 2). So, time spent waiting before the consultation has attracted much research attention, and researchers begin to explore the determinants of patient's waiting time (3, 8), including few healthcare workers, a large number of patients, and the use of computers. Among these factors, an effective appointment system is a critical component in controlling patient's waiting time (9). Researchers have simulated various appointment schedules by considering patient types and varied care needs and analyzed the corresponding patient's waiting times (9–12). However, these designs are difficult to generalize in practice because of the difficulty of implementing optimization models in healthcare systems, especially in China. In addition, patient's behavior and decision-making create greater uncertainty about waiting times (13, 14).

With the development of e-health, various medical services have been provided *via* the Internet and attracted a great number of patients (15–17). Among these services, the online appointment service is generally embraced by patients. Using survey data, the prior study has found that the online appointment system can significantly reduce patient's waiting time compared with the usual queueing method (6). To date, there are few studies about the efficacy of online appointments on reducing patient's waiting time that are conducted using a big sample size and real operation data. Most existing studies depend on the survey data [e.g., (6)]. In addition, although the benefits of the online appointment channel using have been recognized, its determinants have not been fully understood. In our previous study, we explored the impact of external resource status on patient mHealth adoption but did not delve into the influences of patient channel choice and the impact on waiting time (17). By identifying the determinants of patients' channel choice, hospitals can develop intervention strategies to further improve the usability of online channels.

Due to the limited and uneven distribution of medical resources in China, long waiting time for consultation is common in the healthcare system and seriously influence the patient's experience. Whereas previous studies have examined the issues such as factors that influence patient mHealth adoption and patient's experience, there are no studies that have considered patient service channel choice and the impact on patient's offline waiting time. Patient-centered health care aims to improve medical resource accessibility and user experience through information technology, as a part of the Healthy China strategy, which the Chinese government has already taken action on. To fill these gaps in existing research and practice, this study investigates the antecedents and consequences of patients' appointment decisions in the general outpatient department under the multi-channel appointment context by collecting a real dataset from a tertiary hospital in China. The specific research questions being addressed in this paper are as follows:

1) What is the average patient's waiting time in the consulting room?
2) Whether the appointment channel will affect patient's waiting time? And how?
3) What factors will influence the patient's decision on the choice of appointment channel?

The real operation data from 1,241 doctors from 119 departments, involving 308,085 patients, were used to answer these questions. This study is among the first to examine the relationship between appointment channel and patient's experience that is measured by patient's waiting time and the determinants of appointment channel selection. The empirical results provide a basis for theorizing the channel choice in the new context and these insights contribute to the designs of the appointment systems in hospitals.

Theoretical background and hypotheses development

Experience of waiting time in the outpatient department

Waiting time in the outpatient department is directly related to the patient's satisfaction with the medical services received. Long waiting time is a generally existent phenomenon in China as medical resources are limited. Figure 1 describes the general patient flow from appointment request to the moment of consultation (18). Once patients decide to obtain medical services in the hospitals, they must go through the registration process and consultation process. The waiting time can be divided into the following distinct categories:

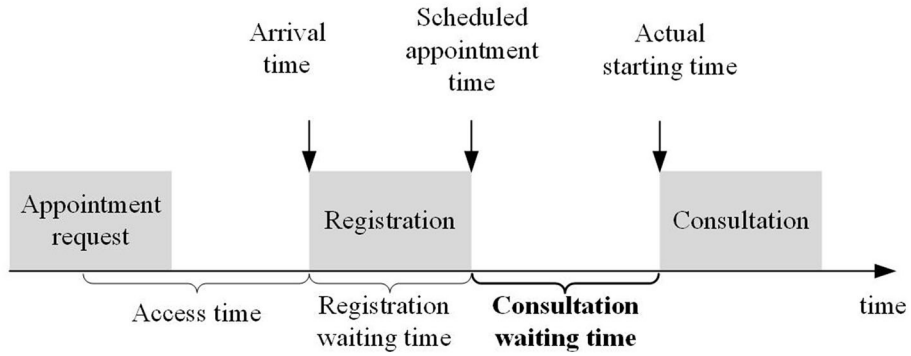

FIGURE 1
The general patient flow for getting medical services.

1) The registration waiting time. It measures the length of waiting time for registration. In the registration process, a patient who has chosen the offline appointment channel—on-site appointment—is required to queue up for filling in registration forms or presenting an identification card to the registration staff and designate a department or a doctor and then get a queue number for consultation. For a patient with an online appointment, s/he has to make an appointment based on the doctor's available dates *via* the Internet and show his/her appointment information and identification card to get a queue number for consultation in the hospital. Therefore, the processes of registration for making appointments online and offline are different.
2) The consultation waiting time. It measures the length of waiting time for consultation, namely, the waiting time between scheduled appointment time and the actual starting time. As patients with online and offline appointments have the same operation processes, the waiting time for the consultation is included in this study.

The registration waiting time for outpatients has already become a long-festering healthcare problem in China and has been fully studied (6). Compared with the registration waiting time, the consultation waiting time is often overlooked. In addition, the processes of registration for making appointments online and offline are different; therefore, our study focuses on consultation waiting time only, namely, the waiting time between scheduled appointment time and actual starting time.

Appointment channel and patient's waiting time

Outpatient services are an important component of health care and influence patient's satisfaction (19, 20). Long waiting time for treatment in the outpatient department has long been a complaint (21) and is a critical determinant of patients' choices in hospitals (22). In many service industries, the waiting time influences consumers' service experience and they often use the waiting time as a decisive factor in choosing a service provider (23). Therefore, researchers emphasized that the waiting time must be considered in designing an appointment system.

Existing studies mainly focus on how to design an appointment system to reduce the patient's waiting time (24) or no-show behavior (25). A longer waiting time relates to reneging behavior (23). Appointment scheduling systems are widely used by medical service providers to regulate their service capacity and demands. Providing pre-scheduled appointments helps to reduce the variability in demands and allows providers to better play their operations (25). The outpatient appointment service is provided through both online and offline channels. Online channels include the WeChat platform, APP, and third-party platforms such as haodf.com and Chutian mingyi platform, and offline channels include manual window service. To compare the differences between online and offline channels, we merge the multiple channels according to the online and offline dimensions. Using the online appointment channel, the medical services can be pre-scheduled, which brings benefits for both patients and doctors. Using a pre-scheduling mechanism, doctors can regulate their service capacity and balance the demands between online and offline channels, which helps to avoid overload situations. The overload of doctors is the main factor that influences patient's waiting time. Hence, we have:

H1. Compared with offline appointment, patients with online appointments have a lower length of waiting time for consultation.

Determinants of appointment channel choice

Although the Internet has radically changed public service delivery, the use of traditional service channels remains high, especially in health care. Based on the Media Richness Theory

(26), media differ in richness and have different capacities to provide cues. Compared with the offline appointment channel, patients can get more information *via* the online appointment channel and chances to choose a satisfied doctor.

The area of human–computer interaction has also discussed channel choice. The perceived accessibility and quality of information sources significantly influence channel choice (27). In addition, perceived usefulness and perceived ease of use are the primary relevance for computer acceptance behaviors based on the Technology Acceptance Model (28, 29). In marketing, the impact factors of channel choice have also been widely explored, with perceived risk, propensity, convenience, transaction costs, ease of use, complexity, trust, and flexibility which are the main factors discussed in existing studies (30). However, in no other field than marketing, channel choice received so much attention.

From the analysis of existing research in other fields, we can draw a major conclusion: we lack an understanding of what factors are relevant in the healthcare context. In health care, health-related risk factors and cost-related risk factors are two critical major concerns of patients (31, 32). For the health-related factors, since medical services deal with life and wellness, patients are eager to find high-quality physicians (4, 17, 33). For the cost-related factors, cost plays a vital role for consumers in deciding from whom to get the products/services, and higher costs decrease demand and increase switching in most circumstances (34). Patients in medical institutions show a very significant geographic distribution trend, which is also practical proof that cost-related factors affect patient service choices (17).

For the relationships between health-/cost-related factors and the patient's appointment choice, we conduct the following analysis. First, when the situation gets more ambiguous, people would try to find more reliable information sources to reduce uncertainty (35, 36). Therefore, when patients get serious diseases and need to find a high-quality (scarce) medical resource, they would tend to make appointments *via* the Internet as the Internet can provide certain results. Second, effort is the most important determinant of channel choice, namely people tend to choose the most convenient channel (17). The online channel provides more information conveniently and helps patients to make a satisfying choice easily, which could reduce the possibility of failing to choose a satisfied doctor and high costs. In this paper, resource type demand and disease severity are used to measure the health-related risk factors, and non-disease costs (including time cost, transportation cost, housing cost, etc.) are used to represent the cost-related risk factors (37, 38). Hence, we have:

Health-related risk factors:

H2a: High-quality resource demand is positively related to the online appointment choice.

H2b: High-severity disease is positively related to the online appointment choice.

Cost-related risk factor:

H2c: High non-disease cost is positively related to the online appointment choice.

The moderating effects of patients' visiting history

Perceived self-efficacy in the Theory of Planned Behavior has demonstrated people's judgment of their capabilities to organize and execute actions to attain designated performance (39). Both familiarity and domain expertise contribute to consumer's knowledge and influence their decision-making ability (40, 41). Internet experience creates a great sense of comfort with the online channel and thereby helps to reduce perceived uncertainty and increase decision-making ability (42).

Consumer behaviors change over time since the experience increases from past purchases (43). When consumers repeat purchase behavior several times, they feel more and more in control and change behavior correspondingly (44). Prior study has identified the moderating effect of prior experience on consumer's behavior (42). In this study, we use visiting history to represent patients' appointment channel choice experience. Each offline visit will be experienced as a channel choice. Therefore, we propose that when patients have a visit history in the hospital, they are familiar with the operation process and have low uncertainty, leading us to the following hypotheses:

H3a: Visiting history decreases the positive impact of resource type demand on online appointment choice.

H3b: Visiting history decreases the positive impact of the severity of diseases on online appointment choice.

H3c: Visiting history decreases the positive impact of the non-disease costs on online appointment choice.

Figure 2 shows our conceptual research model.

Methods

In this section, we describe our research context, data collection process, variables, and empirical models.

The research context and data collection

To answer the research questions, we collect a real dataset from a tertiary hospital in China which has been founded over 100 years ago. This hospital began to implement the online appointment service since 2014. Patients can make appointments *via* WeChat, the hospital's APP, and some third-party platforms. Besides the online appointment channel, patients can also make appointments *via* the traditional offline channel. As the hospital has superior doctors, advanced medical

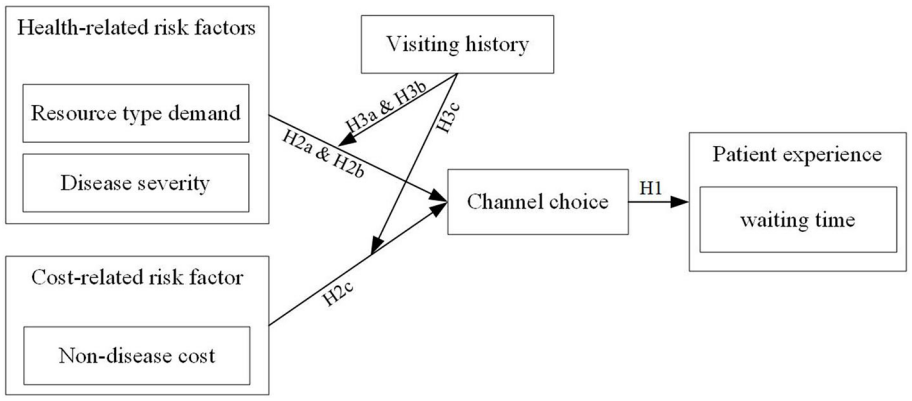

FIGURE 2
The conceptual model.

equipment, and technology, it has attracted many patients from all over the country, which provides a wide range of distance between the patient location and the hospital location and helps us to explore the impact of distance. The hospital has recorded sources for each patient, which helps us to distinguish appointment channels for each patient, and measure health-related risk factors, cost-related risk factors, and visiting history. In 2019, about one-third of the patients have made appointments *via* the Internet.

We extracted data from outpatient appointment records and collected all outpatient data for January 2019 to conduct our empirical research. Specifically, we used structured query language (SQL) query statements to retrieve data from the database, exported them to CSV format, and finally imported them to Rstudio version 1.2 for data cleaning and processing. Since there are many online channels and they are changing all the time, there is no uniform online appointment format template, and all of them interact with the backend database through the web interface, but the collected information includes all the data needed for this research. According to our problem, our data screening and processing procedures followed the following rules: First, patients in the emergency department were removed because emergency patients' waiting time was not subjected to various rules and were not eligible for this study. Second, we removed all no-show patients, who were not in the queue. Third, we removed anomalous data with a waiting time of more than 24 h, which accounts for a relatively small proportion of 1.9% and thus has less impact on our findings. Fourth, since the patient's channel selection and waiting time for each visit are independent, multiple visits of patients will be included in the study as multiple samples. Finally, the real operation data from 1,241 doctors from 119 departments, involving 308,085 patients from both online and offline appointment channels, were collected. The dataset contains information on the use of appointment channels for outpatient visits, demographic characteristics of patients, and disease-related information.

Variables and models

The definitions for all variables used in this study are presented in Table 1.

Patient's waiting time (WT)

It measures the length of consultation waiting time, namely, the waiting time between scheduled appointment time and actual starting time.

Appointment channel choice (CHANNEL)

A dummy variable is set to measure a patient's appointment channel choice. Zero represents the traditional on-site appointment and 1 represents appointment *via* the Internet, including WeChat, the hospital's APP, and third-party platforms.

Health-related risk factors

The resource type demand and severity of diseases are included to indicate health-related risk factors. The doctor's title is used to measure resource type demand (*RES_TYPE*), with the chief doctor representing high-quality resources. The total cost of a patient in the hospital is used to measure the severity of disease (*SEVERITY*).

Cost-related risk factor

The non-disease cost (*NonD_COST*) is measured, including time cost, transportation cost, housing cost, etc. The distance

TABLE 1 Variable definitions.

Variables	Symbols	Coding
Waiting time	*WT*	The logarithm of the consultation waiting time (in minutes) of patients.
Appointment channel	*CHANNEL*	Appointment channels for patients, offline is coded as 0 and online as 1.
Resource type demand	*RES_TYPE*	The title of the doctor that patient visit, 1 is the chief doctor, 0 is the associate chief doctor.
Disease severity	*SEVERITY*	The logarithm of the total cost of the current patient visit.
Non-disease cost	*NonD_COST*	The distance from patients to the clinic. Zero if the patient is in the city where the hospital is located and otherwise 1.
Visiting history	*HISTORY*	The logarithm of the number of previous visits.
Gender	*GENDER*	Males are coded as 0 and females as 1.
Age	*AGE*	Three dummy variables are used to measure the age of patients, AGE1 represents patients between 18 and 45 years old, AGE2 represents patients between 46 and 59 years old and AGE3 represents patients above 60 years old.
SITE	*SITE*	The hospital has three sites in the city, and two dummy variables are used to measure it.
Hour of day	*HOUR_ DAY*	The periods of patients want to see a doctor, including all-day, morning, and afternoon. Two dummy variables are used to measure it. HOUR_DAY1 represents morning and HOUR_DAY2 represents afternoon.

between the patient location and the hospital location is calculated to measure the non-disease cost. Specifically, a dummy variable is set for 0 if the patient is in the city where the hospital is located, and otherwise 1.

Visiting history (HISTORY)

It measures the number of patients' previous visits to the hospital.

Control variables

Prior studies have proved that demographic characteristics have significant impacts on consumers' preferences for different channels (45, 46). Therefore, gender, age, and site are included to control the model. In addition, the hour of the day that measures the period for the appointment is also included. Detailed descriptions can be found in Table 1.

The empirical analysis is conducted in two steps. We first analyze the relationship between appointment channel choice and patient's waiting time and then the relationships between three determinants and appointment channel choice. We used the lm function from the stats package in R language to fit our model.

Step 1. To test H1, a linear model was employed to estimate the effect of appointment channel choice on patient's waiting time. The ordinary least squares method was used to fit our models. The models were specified as follows:

$$WT_i = \beta_0 + \beta_1 CHANNEL_i + \beta_2 AGE_i + \beta_3 GENDER_i + \beta_4 SITE_i + \beta_5 HOUR\_DAY_i + \varepsilon_i$$

Step 2. Since CHANNEL is a binary variable, a logistic regression model was used to estimate the effect of three determinants on appointment channel choice. The multiple regression model is as follows:

$$\begin{aligned} CHANNEL_i = {} & \beta'_0 + \beta'_1 RES\_TYPE_i + \beta'_2 SEVERITY_i \\ & + \beta'_3 NonD\_COST_i + \beta'_4 HISTORY_i \\ & + \beta'_5 RES\_TYPE_i \times HISTORY_i + \beta'_6 SEVERITY_i \\ & \times HISTORY_i + \beta'_7 NonD\_COST_i \times HISTORY_i \\ & + \beta'_8 AGE_i + \beta'_9 GENDER_i + \beta'_{10} SITE_i \\ & + \beta'_{11} HOUR\_DAY_i + \varepsilon'_i \end{aligned}$$

where i=1,…,n indexes the patient. β are coefficients needed to be estimated. $RES\_TYPE \times HISTORY$, $SEVERITY \times HISTORY$, and $NonD\_COST \times HISTORY$ are interaction items. ε is the error term.

Results

The ordinary least squares and the logistic regression model are used to obtain empirical results. All our empirical models are done in RStudio version 1.2.

Descriptive statistic

Descriptive statistics for the key variables used in the analysis are presented in Tables 2–5. The average waiting time is 99.47 min, with 92.18 min for patients with the online appointment channel and 114.55 min for ones with the offline appointment channel. Nearly two-thirds of patients make appointments *via* the traditional on-site channel. The distribution of the doctors across various titles such as the chief doctor and associate chief doctor was even at approximately 60 and 40%. More than one-third of patients come from outside the city where the hospital locates. The average visiting time

TABLE 2 The descriptive statistics of waiting time for different groups.

	Average waiting time (min)	Observations
Total samples	99.47	308,085
Samples with online appointment channel	92.18	100,383
Samples with offline appointment channel	114.55	207,702

TABLE 3 Descriptive statistics for variables ($n = 308,085$).

Measure	Mean	St. Dev.
Ln(WT)/WT	3.965/99.47 min	1.273
CHANNEL (offline, online)	(0.674, 0.326)	
RES_TYPE (associate chief doctor, chief doctor)	(0.400, 0.600)	
Ln(SEVERITY)	5.302	1.639
NonD_COST (in the city, others)	(0.605, 0.395)	
Ln(HISTORY)/HISTORY	1.677/7.10	0.848
GENDER (male, female)	(0.426, 0.574)	
AGE (between 18 and 45 years old, between 46 and 59 years old and above 60 years old.)	(0.476, 0.233, 0.133)	
SITE (site 1, 2 and 3)	(0.732, 0.158, 0.111)	
HOUR_DAY (all day, morning, and afternoon)	(0.168, 0.518, 0.314)	

is 7.10 min. We find that there are 62.3% [=51.2/(51.2+31.4)] of patients want to see a doctor in the morning. The appointment channel is related to patient's waiting time, and three determinants are also related to patients' appointment channel choice. Also, the correlations between the independent variables and control variables are low, which helps yield stable results.

Data analysis

Empirical results are shown in Tables 5, 6. To make sure that the results are not driven by multicollinearity, we gradually added in different sets of independent and control variables.

Step 1. Results for the relationship between appointment channel choice and patient's waiting time

From Table 5, we find that making appointments *via* the Internet can significantly decrease patient's waiting time ($\beta = -0.320$, $p < 0.001$), the average reduced waiting time is 1.38 min. Therefore, H1 is supported.

Step 2. Results for the relationship between three determinants and appointment channel choice

Table 6 shows the impacts of health-related risk factors and cost-related risk factors on patients' appointment channel choices. We find that high-quality resource demand ($\beta = 0.349$, $p < 0.001$), the severity of disease ($\beta = 0.011$, $p < 0.001$), and the non-disease costs ($\beta = 0.039$, $p < 0.001$) positively improve patients' propensity to make appointments *via* the Internet. Among these three determinants, the influence of high-quality resource demand is the biggest. Therefore, H2a–c are supported.

For the moderating effects of patients' visiting history, we find that compared with patients without visiting history in the hospital, the impact of non-disease costs on appointment channel choice is small for patients with visiting history ($\beta = -0.021$, $p < 0.001$). However, no significant results are found for the moderating effects of visiting history on relationships between health-related risk factors (resource-type demand and severity of disease) and appointment channel choice. Therefore, H3a–b are not supported, and H3c is supported.

Heterogeneity tests

Based on the main results in Table 6, we find the impacts of independent variables and control variables are quite significant. Therefore, we further examine the heterogeneity of different patient groups. We divided patient samples based on gender, the period, and resource type demand and obtain the empirical results (shown in Table 7). We find that most results for independent variables are consistent with our main results. An interesting result is found for the male group. For male patients, they tend to make appointments directly on-site when getting serious diseases. The possible explanation is that males and females adopt different strategies in decision environments males are more risk-seeking than females (47).

Robustness checks

In the main analysis, one month of data was collected. To check the robustness of our results, we collected a new dataset with a 3-month interval ranging from January 2019 to March 2019 and used the new data to obtain empirical results (shown in Table 8). Consistent results are found, and the results appear to be robust.

Discussion and implications

To the best of our knowledge, our study is among the first that tests the effects of appointment channels (both

TABLE 4 Correlations of variables.

Variables	1	2	3	4	5	6	7	8	9
1. *WT*									
2. *CHANNEL*	−0.206***								
3. *RES_TYPE*	0.348***	0.375***							
4. *SEVERITY*	−0.037***	0.038***	0.053***						
5. *NonD_COST*	0.071***	0.037***	0.092***	0.034***					
6. *HISTORY*	−0.039***	−0.089***	−0.079***	0.067***	−0.083***				
7. *GENDER*	−0.005***	0.006***	−0.021***	−0.006***	−0.024***	0.076***			
8. *AGE*	−0.059***	−0.074***	0.004**	0.036***	0.044***	0.007***	0.024***		
9. *SITE*	−0.041***	−0.052***	−0.108***	−0.053***	−0.171***	0.047***	−0.012***	0.012***	
10. *HOUR_DAY*	0.366***	0.173***	0.384***	−0.060***	−0.015***	−0.085***	−0.067***	−0.086***	0.187***

*p < 0.05; **p < 0.01; ***p < 0.001.

TABLE 5 Results for appointment channel-patient's waiting time.

	WT	
	Model 1	Model 2
CHANNEL		−0.320***(0.005)
GENDER	0.088*** (0.004)	0.079***(0.004)
AGE1	−0.287*** (0.006)	−0.272***(0.006)
AGE2	−0.175*** (0.007)	−0.151***(0.007)
AGE3	−0.209*** (0.008)	−0.184***(0.008)
SITE1	−0.404*** (0.006)	−0.367***(0.006)
SITE2	−0.401*** (0.007)	−0.351***(0.007)
HOUR_DAY1	1.020*** (0.006)	0.902***(0.008)
HOUR_DAY2	1.532*** (0.007)	1.425***(0.008)
Adjusted R2	0.166	0.179
Residual Std. Error	1.163 (df = 308,076)	1.154 (df = 308,072)
F Statistic	7,665.500*** (df = 8; 308,076)	7,450.886*** (df = 9; 308,072)

*p < 0.05; **p < 0.01; ***p < 0.001.

online and offline) on patient's experience measured by patient's waiting time and investigates the determinants of channel choice in health care. Although the literature on online appointment is abundant, they all explore the factors that influence the adoption of mHealth and the impact of mHealth from a local perspective, without using a global perspective to delve into the influencing factors and mechanisms of action of the online channel in improving the patient's experience. Our study integrates previous research findings, conducts empirical studies based on a large amount of observational data, and provides new insights. Our findings have theoretical and practical support for policymakers and healthcare providers to promote mHealth services, improve service delivery, and enhance the patient's experience. In addition, our findings can help relevant people understand patient's appointment behavior.

Result analysis

Using a real dataset from a tertiary hospital in China, we find strong and robust evidence of the antecedents and consequences of channel choice. Our results confirm the effect of Internet use on reducing patient's waiting time. Patients consider both health-related risk factors and cost-related risk factors to make decisions on appointment channels, which is consistent with prior studies (30). Our empirical study generates several important results.

Patients who make appointments *via* the Internet have a shorter waiting time. Waiting time is a decisive factor in choosing service providers (23). Long waiting time is a common phenomenon in hospitals, especially these tertiary hospitals, and needs to be considered in designing appointment systems. Our results show that using the Internet to make appointments can substantially reduce their waiting time. The key reason may be that using a pre-scheduling appointment system, doctors can regulate their service capacity and balance the demands between online and offline channels, which helps to avoid overload situations and reduce patients' meaningless wait.

Health- and cost-related risk factors influence patients' channel choice**.** Our results suggest that both health- and cost-related risk factors are the two critical major concerns of patients, which is consistent with prior studies (31, 32). These factors significantly improve the patients' propensity to make appointments *via* the Internet. The possible reason is that the Internet improves information transparency and disclosure, which helps patients reduce uncertainty. When patients have higher health- or cost-related risk factors, such as getting a serious disease, they tend to choose a channel with higher perceived accessibility and information quality (27).

The moderating effects of patients' visiting history show heterogeneity. We further find that patients' visiting history only eliminates the positive relationship between the cost-related risk factor and channel choice (refer to Figure 3). No evidence

TABLE 6 Results for three determinants-appointment channel.

	CHANNEL		
	Model 1	**Model 2**	**Model 3**
RES_TYPE		0.312***	0.349***
		(0.002)	(0.004)
SEVERITY		0.006***	0.011***
		(0.0005)	(0.001)
NonD_COST		0.008***	0.039***
		(0.002)	(0.004)
HISTORY		−0.032***	−0.002
		(0.001)	(0.003)
GENDER	0.028***	0.024***	0.028***
	(0.002)	(0.002)	(0.002)
AGE1	−0.046***	−0.069***	−0.069***
	(0.002)	(0.002)	(0.002)
AGE2	−0.075***	−0.109***	−0.110***
	(0.003)	(0.003)	(0.003)
AGE3	−0.077***	−0.108***	−0.109***
	(0.003)	(0.003)	(0.003)
SITE1	−0.115***	−0.017***	−0.014***
	(0.002)	(0.002)	(0.002)
SITE2	−0.156***	−0.051***	−0.045***
	(0.003)	(0.003)	(0.003)
HOUR_DAY1	0.369***	0.104***	0.097***
	(0.002)	(0.003)	(0.003)
HOUR_DAY2	0.335***	0.086***	0.080***
	(0.003)	(0.003)	(0.003)
RES_TYPE×HISTORY			−0.025
			(0.003)
SEVERITY×HISTORY			−0.002
			(0.001)
NonD_COST×HISTORY			−0.021***
			(0.002)
Adjusted R^2	0.084	0.152	0.156
Residual Std. Error	0.448 (df = 308,076)	0.432 (df = 308,073)	0.431 (df = 308,069)
F Statistic	3,554.217*** (df = 8; 308,076)	5,027.065*** (df = 11; 308,073)	3,801.954*** (df = 15; 308,069)

*p < 0.05; **p < 0.01; ***p < 0.001.

has been found for his moderating effect on the relationship between health-related risk factors and channel choice. There are two possible explanations. First, compared with the cost-related risk factor, patients care about health-related risk factors more since medical services deal with life and wellness. High-quality medical services are valuable exchange resources and are greatly desired but scarce (48). As lacking relevant technical skills and professional medical knowledge, patients struggle to get high-quality medical resources *via* various means. The online channel helps patients get access to satisfied doctors. Second, the cost-related risk is easy to be measured compared with health-related risk. Thus, a channel with rich information is needed for patients to reduce their uncertainty. Therefore, even if patients have visiting history in the hospital, they still rely on the online channel to help reduce their perceived uncertainty.

Implications

This study produces several insights, which have implications for medical process optimization, channel choice, and patient's behavior literature. More importantly,

TABLE 7 Heterogeneity test results for appointment choice.

	Gender		HOUR_DAY		Resource type	
	Male	Female	Morning	Afternoon	Chief doctor	Associate chief doctor
RES_TYPE	0.429***	0.355***	0.374***	0.352***		
	(0.015)	(0.005)	(0.006)	(0.007)		
SEVERITY	−0.065***	0.013***	0.008***	0.013***	0.018***	0.010***
	(0.004)	(0.001)	(0.002)	(0.002)	(0.001)	(0.001)
NonD_COST	0.178***	0.041***	0.044***	0.039***	0.062***	0.005
	(0.015)	(0.005)	(0.005)	(0.007)	(0.005)	(0.004)
RES_TYPE×HISTORY	−0.031	−0.023	−0.043	−0.012		
	(0.015)	(0.004)	(0.005)	(0.006)		
SEVERITY×HISTORY	0.015	−0.003	−0.0001	−0.0005	−0.005	−0.003
	(0.002)	(0.001)	(0.001)	(0.001)	(0.0003)	(0.0002)
NonD_COST×HISTORY	−0.031***	−0.024***	−0.024***	−0.023***	−0.029***	−0.011***
	(0.008)	(0.002)	(0.003)	(0.004)	(0.003)	(0.002)
Observations	131,406	176,679	159,558	96,753	184,821	123,264
Adjusted R^2	0.206	0.167	0.099	0.110	0.011	0.098
Residual Std. Error	1.149 (df = 131,391)	0.429 (df = 176,664)	0.463 (df = 159,544)	0.453 (df = 96,739)	0.496 (df = 184,808)	0.298 (df = 123,251)
F Statistic	2,429.348*** (df = 14; 131,391)	2,523.347*** (df = 14; 176,664)	1,346.869*** (df = 13; 159,544)	921.329*** (df = 13; 96,739)	172.335*** (df = 12; 184,808)	1,122.707*** (df = 12; 123,251)

*p < 0.05; **p < 0.01; ***p < 0.001. Results for control variables are omitted.

these insights contribute to the design of appointment systems in hospitals.

Our study contributes to knowledge in several ways. First, our work extends our knowledge of the impact of IT in health care from the perspective of waiting time. Patient's waiting time is closely related to their willingness to return for care and satisfaction ratings (19, 20) and affects the utilization of healthcare services (3). However, to date, there are few studies about the efficacy of online appointments on reducing patient's waiting time that are conducted using a big sample size and real operation data. Most existing studies depend on survey data (6). Our results show that by implementing an online appointment channel, patient's waiting time can be decreased significantly.

Second, our study provides evidence on channel choice in health care. To date, studies on channel choice mainly focus on other fields (49, 50), and the determinants of channel choice have not been fully understood in health care. By considering the special characteristics of medical services, we include both health-related and cost-related factors and find heterogeneity in the results. Examination of the two dimensions of factors allows us to understand channel choice more comprehensively.

Third, this study enriches patient's behavior literature under the "Internet plus healthcare" background. With the application of information technology in health care, researchers have extensively investigated patient's behavior in the online channel context (32, 51) and overlooked patient's behavior in the multi-channel context. Driven by policies on the "Internet plus healthcare," a multi-channel strategy will be widely adopted. The findings of this study suggest that determinants of patient behavior can be divided into different dimensions and have different influences.

In practice, first, because of China's limited medical resources, long waiting time for consultation is common in the healthcare system and seriously influences the patient's experience. Understanding the impact factors of patient's waiting time helps administrators of hospitals take useful strategies to reduce waiting time and improve satisfaction. In particular, we provide practical insights into physicians and hospitals in the era of "Internet plus." This study emphasizes the effect of information technology use on reducing patient's waiting time and suggests that hospitals can improve their efficiency by integrating the online channel. The contribution of this study to the healthcare system includes the following three aspects: first, it will improve the efficiency of healthcare services by optimizing the online and offline processes. Second, it reduces the waste of medical resources by reducing the occurrence of patients leaving the waiting area without being seen by a physician due to long waiting times. Third, by reducing offline waiting time, it reduces the aggravation of patients' conditions caused by unnecessary waiting time and reduces the additional burden on the healthcare system.

TABLE 8 Robustness check results.

	WT		CHANNEL	
	Model 1	Model 2	Model 2	Model 3
CHANNEL		0.185***		
		(0.003)		
RES_TYPE	0.622***	0.558***	0.344***	0.384***
	(0.003)	(0.003)	(0.001)	(0.002)
SEVERITY	−0.044***	−0.044***	0.004***	0.009***
	(0.001)	(0.001)	(0.0003)	(0.001)
NonD_COST	0.139***	0.138***	0.007***	0.039***
	(0.003)	(0.003)	(0.001)	(0.002)
RES_TYPE×HISTORY				−0.027
				(0.002)
SEVERITY×HISTORY				−0.002
				(0.0003)
NonD_COST×HISTORY				−0.023***
				(0.001)
Adjusted R^2	0.165	0.169	0.166	0.171
Residual Std. Error	1.144 (df = 850,124)	1.141 (df = 850,123)	0.429 (df = 850,124)	0.428 (df = 850,120)
F Statistic	1.144 (df = 850,124)	14,447.190*** (df = 12; 850,123)	15,430.130*** (df = 11; 850,124)	11,710.860*** (df = 15; 850,120)

*p < 0.05; **p < 0.01; ***p < 0.001. Results for control variables are omitted.

The contribution of this study to patients includes the following two aspects: First, it will improve offline waiting time and reduce the cost of care for patients through multi-channel service. The second is to improve the patient's experience by reducing offline waiting time and anxiety in crowded environments.

Second, this study has revealed the determinants of online channel choice and found different effects. Based on our dataset, there only one-third of patients use the online channel to make appointments. There's still a lot of room for hospitals to develop the online channel. By identifying the determinants of patients' channel choice, hospitals can develop intervention strategies to further improve the usability of online channels. To facilitate the use of the online channel, the management of hospitals should set encouraging mechanisms to appeal to their patients to make appointments *via* Internet, such as putting more resources into developing online channels or establishing cooperative relationships with third-party platforms.

Third, based on our dataset, we find that there are 62.3% of patients want to see a doctor in the morning, which makes it very difficult to obtain appointments during this period. Hospitals can regulate it by introducing the distribution mechanism of appointment sources in the online channel to regulate demands evenly and encourage patients to make appointments during periods with a lower outpatient load.

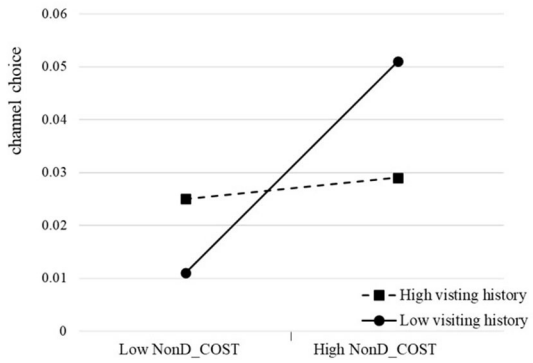

FIGURE 3
The moderating effect of visiting history on channel choice.

Limitations

Although this research has highlighted several notable findings and contributions, we acknowledge some limitations. First, we only obtained data from a hospital, and the results need to be cross-validated in other hospitals. Second, this study, as in most cross-sectional research, cannot infer causality and the dynamic effects. Future researchers should design longitudinal studies to replicate the research findings. Despite these potential limitations, our study demonstrates that the online appointment

channel is an efficient means to reduce patient's waiting time. By identifying the determinants of patients' channel choice, hospitals can develop intervention strategies to further improve the usability of online channels.

Conclusions

To the best of our knowledge, our study is among the first that tests the effects of appointment channels on patient's experience measured by patient's waiting time and investigates the determinants of channel choice in health care. By collecting real operation data from 1,241 doctors from 119 departments, involving 308,085 patients from a tertiary hospital in China, we find that first, the average patient's waiting time in the consulting room is 99.47 min, with 92.18 min for patients with online appointment channel and 114.55 min for ones with offline appointment channel. Second, our results confirm the effect of Internet use on reducing patient's waiting time. Patients consider both health-related risk factors and cost-related risk factors to make decisions on appointment channels. Third, the moderating effects of patients' visiting history show heterogeneity. Patients' visiting history only eliminates the positive relationship between the cost-related risk factor and channel choice, but no evidence has been found for his moderating effect on the relationship between health-related risk factors and channel choice. Because of China's limited medical resources, long waiting time for consultation is common in the healthcare system and seriously influence patient's experience. Our findings can help relevant people understand the effects of information technology on reducing patient's waiting time and these insights contribute to the designs of the appointment systems in hospitals.

Data availability statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author contributions

HW is responsible for framework development, model design, and first draft writing. QY is responsible for data processing, model design, and review. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Breast awareness mobile apps for health education and promotion for breast cancer

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Background: Lack of knowledge, poor awareness, and attitude are barriers to breast cancer (BC) screening participation. The ubiquitous usage of mobile phones makes it a perfect platform for delivering interventions to increase knowledge and awareness in screening, a strategy for early identification of BC. However, although numerous applications for BC prevention are available on major mobile phone platforms, relatively few have been tested in scientific studies to determine their efficacy.

Objective: This study aimed to assess the efficacy of BrAware Apps in increasing the knowledge of BC risk factors, awareness of warning signs and confidence in breast self-examination (BSE) among women in northeast peninsular Malaysia.

Methods: A quasi-experimental pre and post-test research design were conducted with 41 women participants in Kelantan, Malaysia, before and after using the BrAware apps. Participants were given an online, adapted Breast Cancer Awareness Measure questionnaire. Post-test was 2 months after using the BrAware apps. Comparison using paired *T*-tests were conducted to evaluate the change in knowledge of risk factors, warning signs awareness and confidence level for BSE.

Results: The mean age of women was 39.71(SD = 8.80). The participants' mean knowledge score of BC warning signs differs before using BrAware (mean 70.62, SD 11.74) and after using the BrAware app (mean 79.83, SD 10.15) at the <0.001 level of significance.

Conclusions: The BrAware mobile app had a positive effect in increasing the women's knowledge of risk factors of BC, warning signs awareness and confidence level for BSE. It can be concluded that the mobile app may be an adjunct in educating women on BC.

KEYWORDS

mobile phone apps, breast cancer, early detection of breast cancer, breast self-examination, knowledge, awareness

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Introduction

Breast cancer (BC) is the most common cancer globally (1). It accounts for about 30% of female cancers and a mortality-to-incidence ratio of 15% as women's first oncological cause of death (2). Similarly, BC was the most often diagnosed malignancy among Malaysian women from 2007 to 2011, accounting for roughly 32.1% of all cases. According to the National Cancer Institute, the 5-years survival rate for BC in Malaysia is around 87.5% for stage I, 80.7% for stage II, 59.7% for stage III, and 23.3% for stage IV from 2007 to 2016 (3).

Screening for BC is available in Malaysia, and diagnosing the disease sooner and treating it in its early stages is feasible. Many measures have been launched in Malaysia to prevent BC mortality and morbidity by raising awareness through campaigns and screening programmes offered by government institutions. BC awareness month, often known as "Pink October," has aided in raising awareness among women. However, the number of women who regularly get screened is far from satisfactory. A lack of knowledge of the various cancer screening methods, cultural attitudes, and a lack of encouragement by family members and doctors are the major reasons for the poor response to screening. Despite being an upper-middle-income nation with a robust healthcare system and effective socioeconomic initiatives, Malaysia's cancer survival rates are lower than the global average. The rate is attributable to several factors, including poor cancer awareness and screening rates, delays in seeking medical help, delays in detection and diagnosis, and insufficient access to high-quality care. These barriers are particularly obvious for people who live in rural areas because cancer centers are typically located near major cities (4). Therefore, Malaysia's awareness program for BC and health promotion and education needs to be reinforced.

As the use of mobile phones grows, so does the need for mobile phone apps. These applications might be used for various purposes, including social engagement, education, entertainment, and personal health. Mobile applications have positively impacted health-related behaviors and clinical health outcomes. Application users were more satisfied with using mobile health applications to manage their health than users of conventional care (5). A mobile app for the women population at risk in Malaysia was developed as a new tool for BC's health education and promotion. This study has shown its usability (6). However, we do not know whether this mobile app can improve users' knowledge, attitudes, and behavioral changes on BC. Therefore, this study aimed to assess the efficacy of the BrAware mobile app in improving the knowledge of risk factors of BC, warning signs awareness and confidence level for BSE among women aged 18 years and older who are the population at risk for the disease in northeast peninsular Malaysia.

Methods

Research design and study participants

A quasi-experimental pre and post-test research design were conducted among women in Kelantan, Malaysia, to measure the efficacy of a mobile application (BrAware) in increasing the knowledge of BC risk factors, awareness of warning signs, and confidence in breast self-examination (BSE). The state of Kelantan is largely rural, and its culture is quite distinct from other Malaysian states (7). The inclusion criteria were women aged 18 years and above who owned a smartphone and had never been diagnosed with BC. No age range was specified because the risk of BC increases with age. In addition, participants were excluded if their self-reported mobile app literacy was low and the phone did not run appropriately after downloading the mobile application. Low mobile app literacy is the inability to find, use, understand and evaluate the apps (8). A non-probability sampling method using social media such as Facebook and WhatsApp group were used to recruit public women living in Kelantan. The sampling technique was considered because it was more cost-effective and time-effective than probability sampling, and it was also impossible to do a probability sampling (9).

Instrument

The questionnaire consisted of two sections: sociodemographic and BC awareness. Sociodemographic variables included age, occupation, monthly household income, ethnicity, race, highest education level, BC family history, trained BSE, and period to seek medical help if there was a change in the breast). The Breast Cancer Awareness Measure (B-CAM) and B-CAM-M (M for Malay language) were validated in the United Kingdom (10), and Malaysia (11) were adapted. The content and response format were modified to make it more culturally relevant for the local women. Of the seven domains of the B-CAM, three domains were included: Knowledge of risk factors, awareness of warning signs, and BSE. Nineteen items were adapted for BC awareness (9 items on knowledge of risk factors, eight items on awareness of warning signs and two items on confidence in BSE). A 5-point Likert scale was used: strongly agree, agree, neutral, disagree, and strongly disagree. The total score for each domain was summated into a percentage score. The mean percentage score of BC awareness before and after using the BrAware App was computed and compared. Findings showed that the BC awareness Cronbach alphas coefficient was 0.89, indicating good internal consistency (12). The instruments were pilot tested on ten women similar to the samples but not included in the final sample. No changes were made to the instruments.

Procedure

Using the Malay language, data was collected online using the Google Forms platform between October 1, 2021, and December 1, 2021. This study applied various strategies to maintain social distance and observe the Movement Control Order. These include relying on the researchers' professional and personal networks to publicize and disseminate the advertisement *via* posters and social media like Facebook and WhatsApp and sharing the poster through email. An introduction statement and instructions for completing the pre and post-test online and a link for participants to download the BrAware App are included in the information. Participants were expected to become familiar with the BrAware App. The researchers would remind the subjects to complete a post-test 2 months after the pre-test date through Whats App text message or phone call. Instructions for completing the questionnaire online were also supplied by clicking the "Continue" button. Participants were given a choice to respond to the survey using the "Yes/No" option to confirm their willingness to participate. The participant was instructed to finish the online questionnaire after receiving confirmation to continue "Yes," whilst "No" indicates a refusal to participate in the survey. To avoid duplicated or exaggerated data, participants were limited to one response. The survey took ∼10–15 min to complete. For the post-test, the same instrument was employed. Therefore, the data set only included participants who completed both the pre-test and post-test.

BrAware app

The mobile app, BrAware, from the abbreviation of Breast Awareness, was developed based on the Android platform by the researchers (6). The app was user-friendly, constructed with simple point form sentences, including a share button, infographic images or video, dual language capabilities (English and Malay language), a Google Map navigator and a reminder function. BrAware App content includes information about breast anatomy, BC, risk factors of BC, treatment modalities, BSE, screening examination, doctor examination, survival rate, finding support group, hotline number, screening reminders and myths and facts based on Malaysian cultural beliefs.

Statistical analysis

Collected data were coded and analyzed using IBM Statistical Package for Social Sciences (SPSS) (version 26, IBM Corp., Armonk, NY). Descriptive data were used to describe the characteristics of sociodemographic variables. The test score is

TABLE 1 Socio-demographic characteristics of participants ($n = 41$).

Variables	Mean (SD)	*n*	%
Age (years)	39.71 (8.80)		
20–29		7	17.1
30–39		10	24.4
40–49		21	51.2
≥50		3	7.3
Range	22–63		
Occupation			
Housewife		7	17.1
Self-employed		5	12.2
Working (private)		13	31.7
Working (government)		16	39.0
Monthly household income (MYR)	5582.93 (8158.21)		
Range	0–50000		
Median	2800	24	58.5
≤RM 4850.00		17	41.5
>RM 4850.00			
Ethnicity			
Malay		39	95.1
Non-malay		2	4.8
Marital status			
Single		2	4.9
Married		32	78.0
Widowed		7	17.1
Highest education level			
Postgraduate		6	14.6
Degree		10	24.4
Diploma		4	9.8
Secondary		21	51.2
BC family history			
Yes		4	9.8
No		37	90.2
Trained BSE			
Yes		31	75.6
No		10	24.4
Period to seek medical help if found a change in breast (days)			
Range	6.29 (10.72)		
Median	0–60		
Immediate	3	10	24.4
≤3 days		12	29.3
>3 days		19	46.3

MYR, The Malaysian Ringgit, the currency of Malaysia (MYR4.22 equal to 1 United State Dollar as of April 7th 2022).

TABLE 2 Breast cancer awareness ($n = 41$).

Variable	Knowledge		95% CI for mean different	*r*	*t* statistic (df)	*p*-value*
	Pre (mean, SD)	Post (mean, SD)				
BC warning signs	70.62 (11.74)	79.83 (10.15)	−13.79, −4.64	0.130	−4.07 (40)	<0.001
Knowledge of BSE	73.66 (18.94)	83.41 (10.63)	−16.69, −2.84	−0.026	−2.84 (40)	0.007
Knowledge of risk factors for BC	65.79 (14.63)	77.07 (16.57)	−18.95, −3.61	−0.209	−2.97 (40)	0.005

*Paired t-test.

presented as means ± standard deviation (SD) and analyzed by a paired *t*-test. $P < 0.05$ is considered statistically significant.

Results

A total of 41 women completed the online survey questionnaire. Sociodemographic characteristics are shown in Table 1. The mean age was 39.71 (SD = 8.80). The ethnic distribution of participants was 95.1% Malay while the remainder, 4.8%, was non-Malay. More than half (51.2%) of the participants obtain a secondary education. Most of the participants (78%) were married women. The mean household income of participants was 5,582.93 (SD = 8,158.21), and 9.8% had a BC family history, whilst 24.4% were not trained in BSE. The mean period to seek medical help if found a change in the breast was 6.29 (SD = 10.72).

Results of the paired *t*-test show that the mean knowledge score of BC warning signs differs before using BrAware (mean 70.62, SD 11.74) and after using BrAware (mean 79.83, SD 10.15) at the <0.001 level of significance. On average, knowledge of BC warning signs was about 9.21 points higher after using BrAware. However, for BSE knowledge, the mean score before and after using BrAware was increased to 9.75 ($p = 0.007$). In addition, the mean knowledge of risk factors for BC changed before (mean 65.79, SD 14.63) and after (mean 77.07, SD 16.57) using BrAware at the 0.005 level of significance. Therefore, this implies that it makes sense to conclude that the intervention might be responsible for improving knowledge of BC risk factors, awareness of warning signs, and confidence in breast self-examination (BSE) among the participants (Table 2).

Discussion

The pre and post-tests show an improvement in knowledge of BC among the women population after using the BrAware app. As Nasution et al. (6) mentioned, it is best to approach their knowledge and awareness to change human behavior and promote early BC detection in the community (6). Therefore, the BrAware app can be considered feasible in a real clinical context to promote behavioral changes in the lifestyles of women in performing BSE and screening. The plausible explanation was the regular practice of correct skills while using the app may increase the users' memorisation (13, 14). Most of the participants who had secondary-level education would easily understand simple point-form sentences in the app. This study highlights the importance of mobile apps based on how people's health and well-being can be improved *via* monitoring (15). This result matches those observed in a study in Iran that implemented the smartphone app, which improved BSE practice and even reported abnormal findings among participants by mass palpation or visually inspected nipple retraction (16). According to the Health Belief Model (HBM), an individual's opinion that she is vulnerable to BC, the severity of BC, and the benefits, as well as a barrier to preventative action such as doing the BSE and screening at the hospital, all influence health-seeking behavior toward BC prevention (6). In addition, to our knowledge, no BC awareness support apps are targeting Malaysian women.

A combination of dual language strategies of knowledge dissemination will help facilitate the knowledge transfer to the user as most apps do not provide educational content in the local language. The Malay language is used widely in ASEAN as the official language of Indonesia, Brunei, Singapore and Malaysia, and a lingua franca spoken by communities in southern Thailand, southern Philippines, and parts of Myanmar and Cambodia (17). Therefore, the BrAware app can be a user-friendly tool for the Malaysian community and ASEAN countries on BC. This app provides credible information on breast anatomy, BC, risk factors of BC, treatment modalities, BSE, screening examination, doctor examination, survival rate, finding support group, hotline number, screening reminders and myths and facts based on Malaysian cultural beliefs. The credibility of the BrAware app content is supported by the source of reference info on each page.

Meanwhile, another study promotes the app's credibility by enabling direct communication with the therapist (16). Furthermore, the reminder feature notifications as cues in the app improve user engagement and BSE routine in a time duration set according to the user's menstrual cycle (18). Many studies have supported mobile apps in improving the user's or patient's knowledge and awareness of the diseases (6). A study in China suggested that using a mobile app could

improve the user's experience, especially on the accessibility to health information, leading to positive health outcomes (19). Another time-intervention effect study involving 50 years and older group population in Kedah, Malaysia, showed a significantly improved overall knowledge among participants in the intervention group compared with the control group about colorectal cancer (20). Therefore, this study shows that the BrAware app can be fully used to deliver health education and promotion to intended users and enhance the effect of education to change people's behavior.

In the present advancement in communication and digital technology, it can be concluded that the BrAware app is a way forward for health promotion and education, particularly in preventing and early detection of BC. However, there are potential limitations of this study that should be noted. First, the results may not be generalisable to all women in Malaysia as only one state was selected. Therefore, the participants need to be expanded to urbanized women in Malaysia. Also, since this study evaluated the outcomes after 2 months, it is not certain what the knowledge of BC awareness retention is and how long it will be retained. Therefore, we will need to evaluate the app's effectiveness over the long term in the future.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by Human Research Ethics Committee (HREC) of Universiti Sains Malaysia (USM/JEPeM/18080380). The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

AY, YP, IA, and SL contributed to the conception and design of the study. AY and AN implemented the methods and execution of the study. AY performed the statistical analysis. AY, AN, and SL wrote the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Age-related circadian rhythm and variability of large- and small-airway function in healthy non-smoking adults: Data from 7-day diurnal and nocturnal home monitoring using an electronic portable spirometer

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Background: The aim of the study was to investigate the possible influencing factors of the large- and small-airway function variation in healthy non-smoking adults.

Methods: Healthy non-medical non-smoking adults were enrolled in this prospective cohort study. Each participant took the portable spirometer test relying only on video teaching. Then conventional spirometry and bronchodilation test were conducted using a Jaeger spirometer, followed by 7-day diurnal and nocturnal home monitoring using a portable spirometer.

Results: A drop in both large- and small-airway function began at about 25 years of age, and a rapidly decline at about 50 years. The CV of FEV_1 ($r = 0.47$, $P = 0.0082$) and small-airway function variables correlated with age ($r \geq 0.37$, $P < 0.05$ for both MEFs and MEFs/FVC), especially for evening small-airway function variables. The CV of large (4.666 ± 1.946, $P = 0.002$ for FEV_1; 4.565 ± 2.478, $P = 0.017$ for FEV_3) and small airways (10.38 ± 3.196, $P = 0.031$ for MEF50 and 11.21 ± 4.178, $P = 0.023$ for MMEF) was higher in the 45- to 60-year subgroup than in the 30- to 45-year and 18- to 30-year subgroups.

Interpretation: Age was the main influencing factor of both central and peripheral airway function variability, especially for the small-airway function in the evening. The LLN of small-airway variables varies depending on the age and circadian rhythm. People older than 45 years should pay more attention to monitoring small-airway function in the evening, which will be helpful for early clinical detection of those at high risk for asthma.

Trial registration number: ChiCTR2100050355.

KEYWORDS

age, small airway function, variation, circadian rhythm, home monitoring

Highlights

- What factors influence the circadian rhythm and variability of both large- and small-airway function in non-smoking healthy adults?
- Pulmonary function varies with circadian rhythm day to day and seasonally, age, standing height, sex, and ethnicity; however, there is a relative dearth of information regarding the possible influencing factors of the pulmonary function variation over time in healthy adults, especially the circadian rhythm and variation of both large- and small-airway function.
- Age was the main influencing factor of both large- and small-airway function variability, especially for the small-airway function in the evening after 45 years, indicating people older than 45 years should pay more attention to monitoring small-airway function nocturnally, which will be helpful for early clinical detection of those at high-risk for asthma.

Introduction

Asthma is a common chronic airway disease, affecting estimated 400 million people worldwide and 45.7 million people in China (1–3). Although asthma is prevalent, the misdiagnosis rate, especially underdiagnosis in mild asthma, is massive (3). Objective evidence of variable expiratory airflow limitation is a key component in the asthma diagnosis process (1). However, the heterogeneity of the asthma compound is achallenge in diagnosis. Moreover, lack of effective objective monitoring contributes to uncontrolled symptoms, acute exacerbation, and death due to asthma, which have a substantial impact on healthcare costs.

Asthma is also a highly rhythmic airway disease, with clinical symptoms, lung function, and airway hyperresponsiveness varies in a circadian rhythm, day to day, seasonally, as well as from year to year (4–7). Spirometry, including central and peripheral airway function, fulfills a pivotal role in diagnosis, treatment response, and acute attack monitoring of patients with asthma. While comparison of an individual spirometry result with an appropriate reference or predicted value may identify abnormal lung function, it is often more clinically valuable according to normal variation range of lung function over time in an individual's level (8).

A laboratory spirometer (Jaeger spirometer) is too large and inconvenient to carry and too expensive for timely monitoring of lung function. Although peak expiratory flow (PEF) monitoring has been strongly recommended to demonstrate diurnal variability in asthma (9), the peak flow meters (PFMs) also have some limits, including low adherence, low accuracy, insensitivity to changes, and lack of large- and small-airway function indicators (10, 11). Thus, a portable spirometer with good quality control and concordance similar to that of a Jaeger spirometer serves as essential equipment of normal variation range monitoring, and the all-round management of asthma, is needed. Several portable spirometers have been validated to date (12–18), but most of them only show large-airway variables including PEF, forced expiratory volume in 1 s (FEV_1), and forced vital capacity (FVC). Small-airway function indicators, which are increasingly important in the diagnosis, treatment, and monitoring of patients with asthma, are lacking in those spirometers (19–23). In our previous prospective cohort study based on data from 7-day morning and evening home monitoring using an electronic portable spirometer (GOSPT2000), we had validated GOSPT2000 is a reliable device and can serve as an alternative to a Jaeger spirometer for dynamic monitoring of lung function.

Recently, researchers have emphasized the significance of time (the fourth dimension) in asthma diagnosis. We have also investigated healthy individuals' circadian rhythm and variation features of large- and small-airway function in a previous study and found the FEV_1, FVC, and FEV_3 in the morning were higher than those at night, while no significant day–night difference was observed in small-airway variables. Pulmonary function varies with age, standing height, sex, and ethnicity; however, there is a relative dearth of information regarding the possible influencing factors of the pulmonary function variation over time in healthy adults, especially the circadian rhythm and variation of both large- and small-airway function.

The aim of this study was to investigate the possible influencing factors of the large- and small-airway function variation in healthy adults; whether professional training could improve the performance of a portable spirometer and whether factors such as age, sex, height, body mass index (BMI), or education degree affected the portable spirometer outcomes after professional training were also evaluated.

Materials and methods

Participants

This is a prospective cohort study approved by the Ethics Committee of Shanghai General Hospital, Shanghai Jiao Tong University (No. 2021KY073). We recruited participants

Abbreviations: BMI, body mass index; CI, confidence interval; CV, coefficient of variation; df, degrees of freedom; MEF50, forced expiratory flow at 50% of forced vital capacity; MEF25, forced expiratory flow at 75% of forced vital capacity; MMEF, forced expiratory flow between 25 and 75%; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 s; FEV_3, forced expiratory volume in 3 s; HRCT, high-resolution computerized tomography; IQR, interquartile range; LLN, lower limit of normal; PEF, peak expiratory flow; SD, standard deviation; ULN, upper limits of normal.

from healthy adult volunteers, and 36 participants who met the inclusion criteria, had preserved lung function, and homogeneous with respect to gender, age, and educational levels—were enrolled. Informed consent was obtained for all the subjects.

To be included in the study, participants had to meet the inclusion criteria given as follows: 18–65 years old, no clinical symptoms within 8 weeks, normal comprehensive medical examination report (including routine laboratory tests such as complete blood counts, biochemistry tests, tumor markers such as carcinoma embryonic antigen and alpha fetal protein, B-ultrasonic examination, electrocardiography, and chest high-resolution computed tomography scan) within 1 month, no smoking history in their lifetimes, no allergic medical history such as allergic rhinitis or allergic dermatitis, no chronic respiratory disease, no previous pulmonary function test experience, and no medical background.

Subjects were excluded if they had systemic diseases, including the presence of unstable cardiovascular status; diabetes; gastroesophageal reflux; nausea; vomiting; abdominal pain; stress urinary incontinence; surgery of the chest, abdomen, or eye within the past 2 weeks; history of syncope associated with forced exhalation; unsuitable for lung function examination; or oral or facial pain aggravation when chewing. Subjects who had mental illness and cognitive disorders were also excluded.

Study design

A schematic representation of our study is presented in Figure 1. After providing written informed consent, participant demographics, occupation, education, height, weight, smoking status, and current medical status (including acute illnesses in the previous 4 weeks) were assessed. After reconfirming subjects were free of respiratory symptoms, we asked each participant to take a portable GOSPT2000 test relying only on video teaching. No guidance on the detection method of the GOSPT2000 equipment was given by trained medical technicians during the measurement.

After the first pre-training portable GOSPT2000 test, the subjects were asked to complete spirometry and a bronchodilation test using a hospital spirometer (Jaeger Co., Hoechberg, Germany) under the guidance of a trained medical technician on the same morning. The quiescent period was over 20 min before the spirometry and bronchodilation test. Then, the subjects took the GOSPT2000 device home and completed the pulmonary function monitoring in the home setting for the next 7 consecutive days. The detection time followed the setting of the software system and was carried out between 08:00 and 09:00 in the morning and between 20:00 and 21:00 in the evening. The GOSPT2000 equipment was returned after 7 consecutive days of measurements.

Portable spirometer (GOSPT2000)

GOSPT2000, a product of GoSprio (Monitored Therapeutics Inc., Dublin, OH, USA) has been approved by the FDA in the United States (K163249).

The GOSPT2000 portable spirometer is a small, handheld device consisting of a vertical turbine volume sensor. The turbine transducer measures expired air directly at body temperature and pressure with saturated water vapor (BTPS), thus avoiding inaccuracies in temperature corrections. The GOSPT2000 performs full flow–volume loops, including inspiration and expiration data. It has built-in quality control measurements and transmits indices of measurement quality including time to peak flow, BEV, total expiratory time, end-expiratory flow detection, and identification of cough during the measurement. It transmits real-time lung function data to computers, tablets, or smartphones over a Bluetooth connection for telehealth applications.

Measurements were performed following the detailed and standardized operation video after subjects responded to a symptoms questionnaire. Forced expiratory maneuvers that met all acceptability criteria were performed until the two best efforts were reproducible (minimum of three). The test curve with the highest sum of the FVC and FEV_1 was considered the best one, and the largest FVC and FEV_1 measurements were recorded. Between each set of measurements, the subjects rested 5–10 mins.

Data on PEF, FVC, FEV_1, FEV_3, forced expiratory flow at 50% of forced vital capacity (MEF50), forced expiratory flow at 75% of forced vital capacity (MEF25), and forced expiratory flow between 25 and 75% (MMEF) were collected for analysis. According to the latest standardization of spirometry in the 2019 update (24), the back-extrapolated volume (BEV) must be 5% of the FVC or 0.100 L to ensure that FEV_1 results from a maximal effort.

Diurnal variation was calculated from twice-daily spirometry variables as highest value of the day minus lowest value of the day/mean of highest and lowest values of the day, averaged for 1 week.

Spirometry and bronchodilation test

Salbutamol (400 ug) with a metered dose inhaler was used as a bronchodilator in the bronchodilation test, and spirometry was performed before and 20 min after bronchodilator use. The improvement of the FEV_1 was calculated and expressed as percentage changes compared with the baseline values.

Spirometry was performed by using a spirometer (Jaeger Co., Hoechberg, Germany) following the performance criteria recommended in the ATS/ERS Standardization of Spirometry (9). The following parameters were collected: PEF, FVC, FEV_1, FEV_3, MEF50, MEF25, and MMEF expressed as absolute

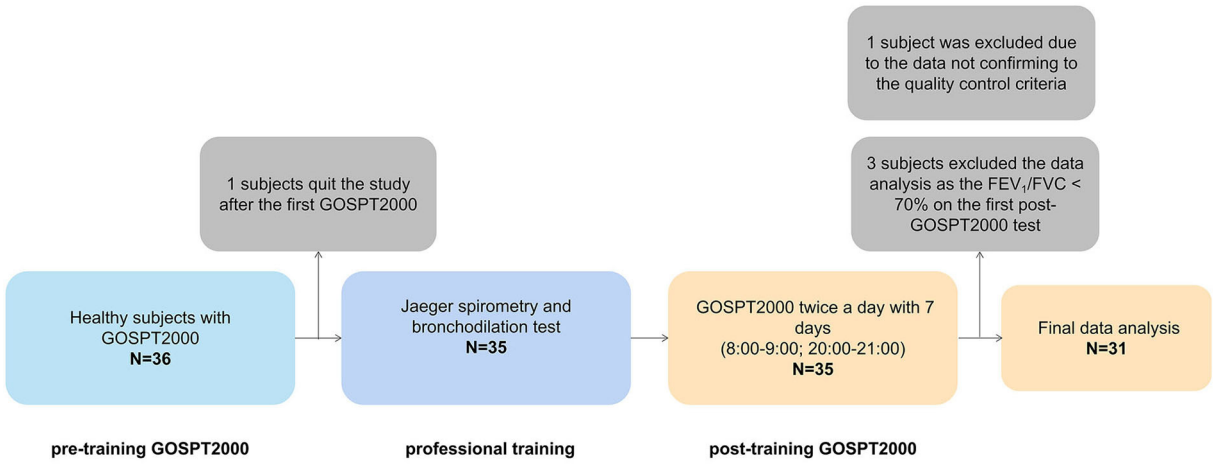

FIGURE 1
Schematic presentation of study design. A total of 36 adults were invited to participate, among which one participant quit the study after conducted the first GOSPT2000 test and 35 adults attended and completed the 7-day portable spirometer and laboratory pulmonary function tests; of these, three participants were excluded from the data analysis as their FEV_1/FVC was <70% on the first GOSPT2000 test, and one person was excluded from final analysis as data did not meet the quality control criteria, leaving 31 participants for the final data analysis in the present study. After the first portable GOSPT2000 test, the subjects were asked to complete the spirometry and bronchodilation test using a Jaeger spirometer under the guidance of a trained medical technician on the same morning. The quiescent period between measurements was 20 mins after completing the spirometry and bronchodilation test. Then, the subjects took the GOSPT2000 device home and completed the pulmonary function monitoring in the home setting for the next 7 consecutive days. FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 s; FEV_3, FEV in 3 s; MEF50: forced expiratory flow at 50% of forced vital capacity; MEF25, forced expiratory flow at 75% of forced vital capacity; MMEF, forced expiratory flow between 25 and 75%; PEF, peak expiratory flow; SD, standard deviation; CI, confidence interval; t-, total; m-, morning; e-, evening.

value. FEV_1/FVC, FEV_3/FVC, MEF50/FVC, MEF25/FVC, and MMEF/FVC were the ratio of two parameters.

PEF, FEV_1, FEV_1/FVC, and MEF75 represent large-airway function; MEF50, MEF25, and MMEF represent small-airway function.

Statistical analysis

Analyses were performed by GraphPad Prism version 9.01 (GraphPad Software, San Diego, CA, USA), SPSS version 20.0 (SPSS Inc, Chicago, Illinois, USA), and R version 4.1.1 (Innovative Solutions, St. Louis, MO, USA).

Baseline data are presented descriptively. Normality of distribution was checked using the Shapiro–Wilk test. Normally distributed data were expressed as mean ± standard deviation (SD) or 95% confidence interval (CI). Non-normally distributed data were expressed as median and interquartile ranges (IQR). The coefficient of variation (CV) and diurnal variation were calculated for each continuous variable.

A Mann–Whitney U test was performed to compare inter-group differences between two medians of categorical variables (gender). A Kruskal–Wallis test was performed to compare inter-group differences between four medians of categorical variables (age and education degree). The Spearman correlation coefficient matrix and Spearman rank correlation tests were performed by R version 4.1.1. The correlation between different variables was determined using Spearman analysis; $r > 0.4$ or <-0.4 was defined as strong correlation, and r between -0.4 and 0.4 as weak correlation, if $P < 0.05$. Splines of large- and small-airway function with age were smoothed using the LOESS method. Simple linear regression was also performed by GraphPad Prism version 9.01. The threshold for statistical significance for all analyses was set at $P < 0.05$.

Results

Demographic and baseline characteristics

Of the 36 healthy adults invited to participate, one participant quit the study after the first pre-training GOSPT2000 test; thereafter, 35 adults attended and completed the laboratory pulmonary function tests and the spirometry test for next 7 days morning and evening using the portable spirometer GOSPT2000. A total of three participants were excluded from data analysis because the FEV_1/FVC was <70% on the first post-training GOSPT2000 spirometry test, and one more was excluded because the BEV was >5% and >0.100 L of the FVC according to the built-in quality control of GOSPT2000 device, leaving 31 participants for final data analysis (Figure 1). No subject quit the home monitoring during the 7 days. Of the

448 sets of spirometry data, only 16 sets (10 sets from one person excluded for final analysis; four sets from another person excluded for analysis of diurnal variation) did not conform to the acceptability and repeatability criteria. All the participants had normal Jaeger spirometer measurement results and negative bronchodilation tests with improvement of $FEV_1 < 200$ ml and $FEV_1/FVC < 20\%$.

The mean age of subjects analyzed was 36.68 (SD 11.64) years, and 58.06% (18 of 31) were female. The average height of the subjects was 168.9 (SD 8.791) cm, the average body weight was 65.55 (SD 10.38) kg, and the average BMI was 22.95 (SD 2.950) kg/m^2 (Table 1). Overall, 29.03% (9 of 31) of the study population graduated from junior high school, 35.48% (11 of 31) graduated from senior high school, and 35.48% (11 of 31) had a university-level education. All their home-monitoring pulmonary function measurement variable (FVC, FEV_1, FEV_3, PEF, MEF50, MEF25, MMEF, FEV_1/FVC, FEV_3/FVC, MEF50/FVC, MEF25/FVC, and MMEF/FVC) descriptive data are presented in Table 1.

Factors associated with large- and small-airway function both in the morning and evening for 7 consecutive days

The Spearman correlation coefficient matrix and Spearman rank correlation tests were performed (Figure 2A; Supplementary Table 1). Both large- and small-airway function variable values were strongly negatively related to age ($P \leq 0.0001$ for tMEF25 and tMEF25/FVC; $P < 0.001$ for $tFEV_3/FVC$; $P < 0.01$ for $tFEV_1$, $tFEV_1/FVC$, tMEF50, and tMMEF; and $P < 0.05$ for $tFEV_3$ and tMMEF/FVC) and were dramatically positively related to height ($P < 0.0001$ for PEF, tFVC, $tFEV_1$, $tFEV_3$, tMEF50, tMEF25, and tMMEF; $P < 0.05$ for $tFEV_3/FVC$ and tMEF25/FVC). No significant correlations between age and FVC, PEF, or MEF50/FVC, and no significant correlations between height and FEV_1/FVC, MEF50/FVC, or MMEF/FVC were found ($P > 0.05$). The MEF/FVC ratio, which reflects effort-independent expiratory airflow in the context of lung volume, reflected less correlation with age, height, and weight, especially with the height and weight. Both large- and small-airway function absolute values of male adults were dramatically higher than those of female adults (Supplementary Figure 1); however, FEV_1/FVC (Supplementary Figure 1E) and MEFs/FVC (Supplementary Figures 1J–L) showed no difference across sex ($P > 0.05$).

Then, we further compared the morning and evening variable values of large- and small-airway function, separately, and similar correlation in the morning and in the evening was found (Figure 2B; Supplementary Table 1).

Age-related features in large- and small-airway function in non-smoking healthy adults

A smoothing age spline was generated to illustrate characteristics of large- and small-airway function values by age (Figure 3). A small increasing trend of both large- and small-airway function from 18 years of age to 25 years of age was found. There was then a drop in the trend until about 35 years of age, followed by a small but steady increase till 50 years of age, followed by a rapid decline in both large- and small-airway function till old age (Figure 3).

All their 7-day GOSPT2000 pulmonary function measurement variable descriptive data grouped by age are presented in Table 2. There were no difference in sex, height, weight, and BMI among the groups across age. In the 30- to 45-year and 45- to 60-year subgroups, both large- ($P = 0.047$ for FVC; $P = 0.007$ for FEV_1; and $P = 0.019$ for FEV_1/FVC) and small-airway function variable ($P = 0.014$ for MEF50; $P < 0.001$ for MEF25; and $P = 0.004$ for MMEF) values were lower than those in the 18- to 30-year subgroup. For the tMEF/FVC ratio, tMEF25/FVC values in the 18- to 30-year subgroup were higher than those in the other two subgroups. No significant age-related differences were found between the subgroups for PEF ($P > 0.05$).

We further compared the morning and evening variable values of large- and small-airway function, separately. We found a similar phenomenon both in the morning and the evening, and non-smoking healthy adults ≥30 years had lower large- and small-airway function values than adults <30 years (Table 2).

The variation features of large- and small-airway function in non-smoking healthy adults were also correlated with age

We then analyzed the relationships between the CV of lung function variables and age, height, weight, or BMI. A strong relationship between age and both large- ($r = 0.47$, $P = 0.0082$ for $tFEV_1$) and small-airway (tMEF25, tMMEF, and tMMEF/FVC) function variables was found (Figure 4; Supplementary Table 2, $r \geq 0.4$, $P < 0.05$ for all). tMEF50, $tFEV_3/FVC$, tMEF50/FVC, and tMEF25/FVC were weekly correlated to age ($0.36 \leq r \geq 0.38$, $P < 0.05$ for all); no significant relationships between height, weight, or BMI and both large- and small-airway function variables were found ($P > 0.05$). There was also no significant difference across sex (except $P < 0.05$ for MMEF/FVC only, $P > 0.05$ for all other variables, Supplementary Figure 2).

To validate the influence of age on the CV of lung function variables, we compared the CV of lung function variables in

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TABLE 1 Demographic data and portable spirometry variable values of non-smoking healthy adults.

Variables	25% Percentile	Median, %	75% Percentile	Mean	SD	Lower 95% CI of mean	Upper 95% CI of mean	P^b	*df*
Age, years	24	37	46	36.68	11.64	32.41	40.95	0.1338	30
Height, cm	163	167	177	168.9	8.791	165.7	172.1	0.811	30
Weight, kg	60	65	72	65.55	10.38	61.74	69.36	0.3095	30
BMI, kg/m^2	20.2	23.24	24.34	22.95	2.95	21.86	24.03	0.1727	30
tFVC	3.189	3.622	4.504	3.853	0.8661	3.535	4.171	0.2367	30
$tFEV_1$	2.621	2.929	3.651	3.147	0.7721	2.864	3.431	0.1477	30
$tFEV_1$/FVC	0.773	0.8193	0.8548	0.8154	0.05681	0.79.45	0.8362	0.5599	30
$tFEV_3$	3.058	3.462	4.390	3.715	0.8817	3.392	4.038	0.1802	30
$tFEV_3$/FVC	**0.9458**	**0.9676**	**0.9815**	0.9620	0.0287	0.9515	0.9725	**0.0146**	30
tPEF[a]	**6.502**	**7.181**	**9.378**	7.978	1.816	7.311	8.644	**0.0113**	29
tMEF50	2.960	3.841	4.219	3.700	1.063	3.311	4.090	0.3475	30
tMEF50/FVC	0.8188	0.9982	1.097	0.9680	0.2106	0.8907	1.045	0.7233	30
tMEF25	**1.001**	**1.250**	**1.762**	0.7038	1.085	1.213	1.729	**0.0125**	30
tMEF25/FVC	0.2826	0.3667	0.4497	0.3735	0.1305	0.3256	0.4213	0.1211	30
tMMEF	2.522	3.174	3.742	3.267	1.085	2.869	3.665	0.4763	30
tMMEF/FVC	0.6790	0.8683	0.9874	0.8471	0.2013	0.7733	0.9210	0.7791	30
mFVC	3.208	3.666	4.573	3.823	0.8907	3.497	4.15	0.1731	30
eFVC	3.161	3.543	4.434	3.765	0.9028	3.434	4.096	>0.1	30
$mFEV_1$	2.627	2.988	3.654	3.141	0.7934	2.85	3.432	0.1668	30
$eFEV_1$	2.577	2.876	3.653	3.096	0.8074	2.8	3.392	0.0946	30
$mFEV_3$	3.07	3.487	4.45	3.692	0.9134	3.357	4.027	0.1598	30
$eFEV_3$	3.001	3.42	4.33	3.639	0.9233	3.3	3.977	>0.1	30
$mFEV_1$/FVC	0.7825	0.8217	0.8587	0.8199	0.05072	0.8013	0.8385	0.9448	30
$eFEV_1$/FVC	0.7894	0.8232	0.8551	0.8201	0.04953	0.8019	0.8382	0.9241	30
$mFEV_3$/FVC	0.9416	0.9651	0.9874	0.9633	0.02795	0.953	0.9735	0.054	30
$eFEV_3$/FVC	0.9463	0.9682	0.9821	0.9638	0.02576	0.9544	0.9733	0.0869	30
mPEF[a]	**6.311**	**7.093**	**9.149**	7.796	1.851	7.117	8.475	**0.0231**	29
ePEF[a]	**6.457**	**7.157**	**9.527**	7.939	1.914	7.237	8.641	**0.0001**	29
mMEF50	2.946	3.851	4.184	3.691	1.039	3.309	4.072	0.3922	30
eMEF50	3.034	3.733	4.184	3.717	1.079	3.321	4.113	>0.1	30
mMEF25	**1.007**	**1.297**	**1.793**	1.489	0.7069	1.229	1.748	**0.0199**	30
eMEF25	1.003	1.253	1.761	1.458	0.7018	1.201	1.715	>0.1	30
mMMEF	2.639	3.23	3.7	3.279	1.081	2.883	3.676	0.3559	30
eMMEF	2.633	3.197	3.784	3.268	1.078	2.873	3.664	>0.1	30
mMEF50/FVC	0.8175	0.9866	1.086	0.9734	0.193	0.9025	1.044	0.5711	30
eMEF50/FVC	0.8794	0.9833	1.112	0.9945	0.1996	0.9213	1.068	0.4387	30
mMEF25/FVC	0.2737	0.3589	0.4542	0.3806	0.1282	0.3336	0.4276	0.0995	30
eMEF25/FVC	**0.2895**	**0.3795**	**0.4354**	0.3769	0.1243	0.3313	0.4225	**0.0189**	30
mMMEF/FVC	0.7007	0.8925	0.9737	0.8565	0.1868	0.788	0.9251	0.8277	30
eMMEF/FVC	0.718	0.8717	0.9978	0.8659	0.1848	0.7982	0.9337	0.9922	30

df, degrees of freedom; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 s; FEV_3, FEV in 3 s; MEF50: forced expiratory flow at 50% of forced vital capacity; MEF25: forced expiratory flow at 75% of forced vital capacity; MMEF: forced expiratory flow between 25 and 75%; PEF, peak expiratory flow; SD, standard deviation; CI, confidence interval; t-, total; m-, morning; e-, evening.

[a]n = 30.

[b]P-values in this table show whether the data conform to a normal distribution. P < 0.05 indicates that the data conform to a normal distribution; otherwise, the data conform to non-normal distribution.

Bold values indicates statistical significance.

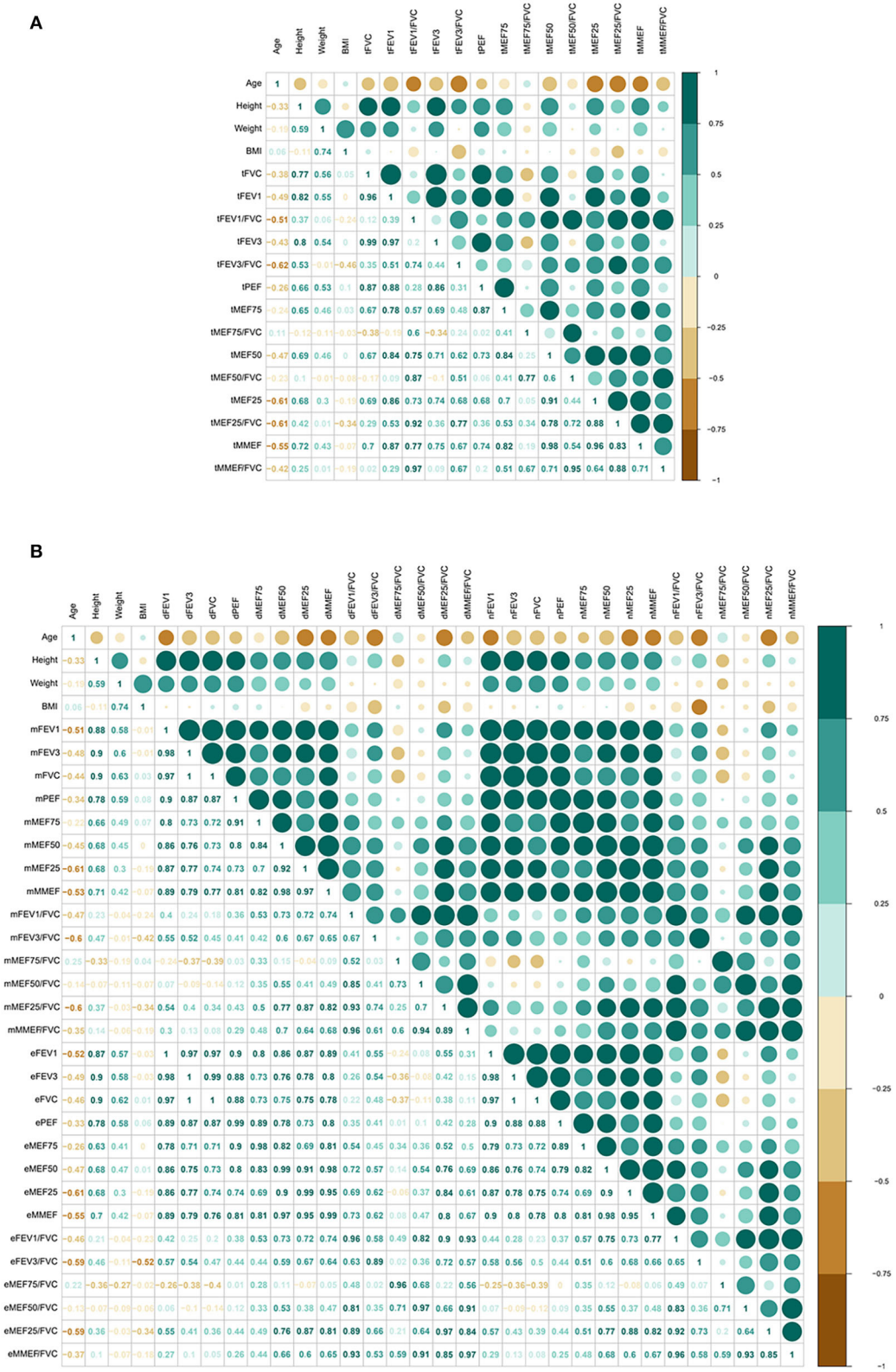

FIGURE 2
Correlation of pulmonary function (total, morning, and evening) with age, height, weight, and BMI ($N = 31$, except $N = 30$ for PEF). Both large- and small-airway function variable values were strongly negatively related to age, and were dramatically positively related to height **(A)**. Similar correlation both in the morning and the evening was found **(B)**. FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 s; FEV_3, FEV in 3 s;
(Continued)

FIGURE 2 (Continued)
MEF50: forced expiratory flow at 50% of forced vital capacity; MEF25: forced expiratory flow at 75% of forced vital capacity; MMEF: forced expiratory flow between 25 and 75%; PEF, peak expiratory flow; SD, standard deviation; CI, confidence interval; t-, total; m-, morning; e-, evening.

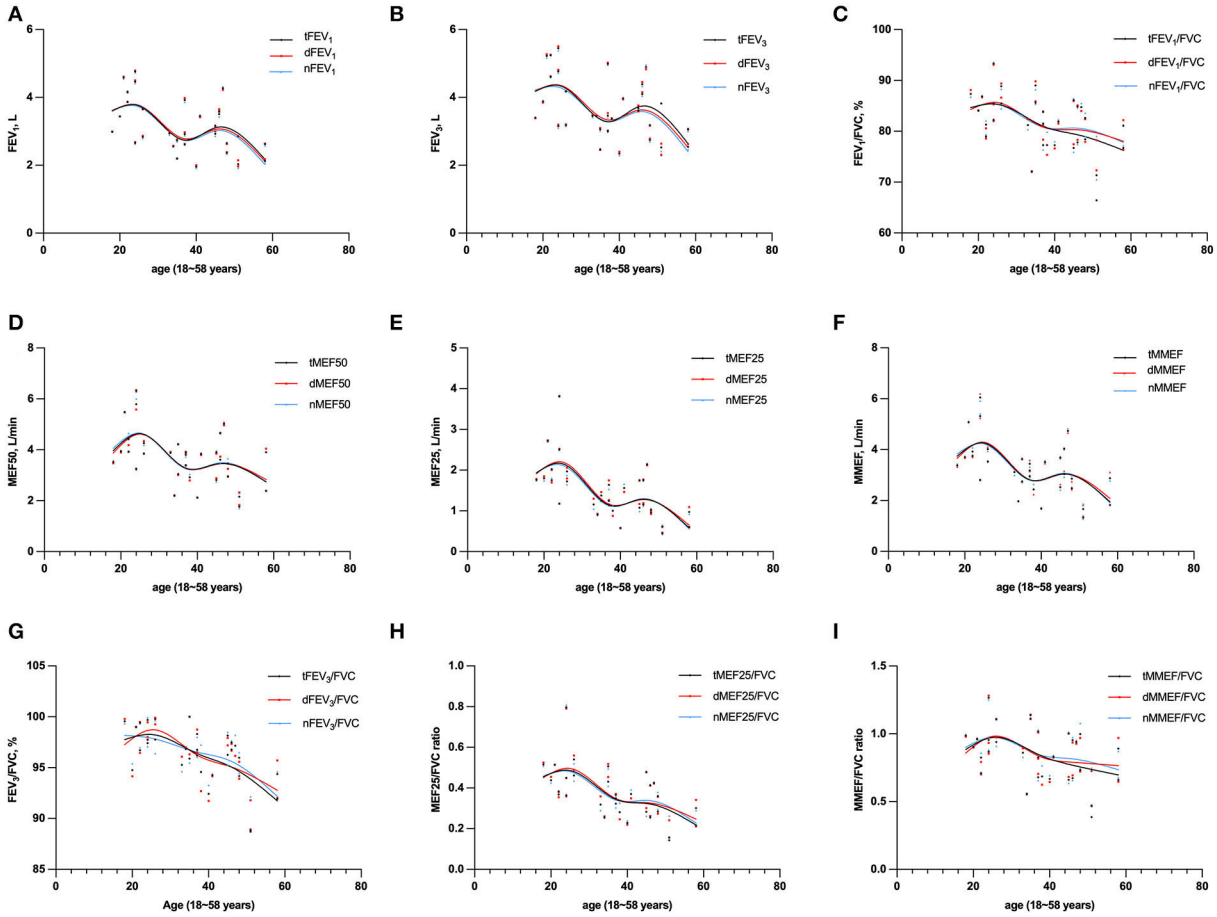

FIGURE 3
Absolute values for FEV_1 **(A)**, FEV_3 **(B)**, MEF50 **(D)**, MEF25 **(E)**, and MMEF **(F)**, ratio values for FEV_1/FVC **(C)**, FEV_3/FVC **(G)**, MEF25/FVC **(H)**, and MMEF/FVC **(I)** by age ($N = 31$, except $N = 30$ for PEF). Graphs were generated to illustrate characteristics of large- and small airway function values by age. FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 s; FEV_3, FEV in 3 s; MEF50: forced expiratory flow at 50% of forced vital capacity; MEF25: forced expiratory flow at 75% of forced vital capacity; MMEF: forced expiratory flow between 25 and 75%; PEF, peak expiratory flow; SD, standard deviation; CI, confidence interval; t-, total; m-, morning; e-, evening.

the three subgroups across age. Of the values of large-airway function, the CV was significantly higher in the 45- to 60-year subgroup (4.666 ± 1.946, $P = 0.002$ for FEV_1; 4.565 ± 2.478, $P = 0.017$ for FEV_3, Table 3) than in the 30- to 45-year subgroup (2.906 ± 0.8121 for FEV_1; 2.739 ± 0.8813 for FEV_3) and the 18- to 30-year subgroup (2.489 ± 0.8739 for FEV_1; 2.648 ± 0.8069 for FEV_3).

For MEFs, the 45- to 60-year subgroup showed higher CV values of MEF50 (10.38 ± 3.196, $P = 0.031$) and MMEF (11.21 ± 4.178, $P = 0.023$) than the 30- to 45-year subgroup (7.385 ± 2.392 for MEF50; 7.951 ± 4.535 for MMEF) and 18- to 30-year subgroup (7.990 ± 1.951 for MEF50; 6.603 ± 1.752 for MMEF, Table 3).

When circadian rhythms were considered, only the evening CV values of small-airway function variables were higher in the 45- to 60-year subgroup (11.18 ± 3.427, $P = 0.002$ for MEF50; 19.04 ± 10.59, $P = 0.028$ for MEF25; 11.90 ± 4.640, $P = 0.001$ for MMEF, Table 3), while there were no age-related differences for large-airway function variables ($P > 0.05$ for FVC, FEV_1, and FEV_3, Table 3) and for morning variable values ($P > 0.05$ for all).

TABLE 2 Portable spirometry variable values according to age.

Variables	Age, years				*P*
	18–30	30–45	45–60	All subjects	
N	10	10	11	31	–
Height, m	1.734 (0.0757)	1.660 (0.0908)	1.675 (0.0866)	1.689 (0.0879)	0.134
Weight, kg	68.7 (12.54)	65.6 (11.94)	62.64 (5.853)	65.55 (10.38)	0.423
BMI, kg/m^2	22.76 (3.256)	23.71 (3.369)	22.41 (2.328)	22.95 (2.950)	0.600
Sex (female)	4/10 (40%)	7/10 (70%)	7/11 (63.64%)	18/31 (58.06%)	>0.05
tFVC, L	**4.3872 (0.8870)**	**3.4918 (0.7638)**	**3.696 (0.7578)**	**3.853 (0.8661)**	**0.047**
tFEV$_1$, L	**3.742 (0.7549)**	**2.805 (0.5665)**	**2.919 (0.6775)**	**3.147 (0.7722)**	**0.007**
tFEV$_3$, L	**4.307 (0.8777)**	**3.3556 (0.7528)**	**3.5032 (0.7742)**	**3.715 (0.8817)**	**0.027**
tPEF*, L/min	8.9687 (1.806)	7.1167 (1.165)	7.8593 (1.999)	7.9776 (1.816)	0.067
tMEF50, L/min	**4.4752 (1.032)**	**3.3325 (0.7384)**	**3.3301 (1.025)**	**3.700 (1.062)**	**0.014**
tMEF25, L/min	**2.123 (0.7311)**	**1.1857 (0.3112)**	**1.137 (0.5374)**	**1.471 (0.7038)**	**<0.001**
tMMEF, L/min	**4.155 (1.004)**	**2.8673 (0.6568)**	**2.8226 (1.036)**	**3.267 (1.085)**	**0.004**
tFEV$_1$/FVC	**0.8539 (0.0408)**	**0.8069 (0.049)**	**0.7880 (0.0603)**	**0.8154 (0.0568)**	**0.019**
tFEV$_3$/FVC	**0.9818 (0.0163)**	**0.9605 (0.0213)**	**0.9453 (0.0334)**	**0.9620 (0.0287)**	**0.009**
tMEF50/FVC	1.027 (0.1542)	0.9763 (0.2355)	0.9065 (0.2325)	0.968 (0.2106)	0.432
tMEF25/FVC	**0.4831 (0.1269)**	**0.3430 (0.0825)**	**0.3015 (0.1088)**	**0.968 (0.2106)**	**0.002**
tMMEF/FVC	0.9523 (0.1522)	0.8370 (0.1990)	0.7607 (0.2137)	0.8471 (0.2013)	0.088
tFVC%	93.19 (6.760)	92.7023 (10.33)	106.8 (26.93)	97.86 (18.24)	0.128
tFEV$_1$%	93.02 (7.753)	87.3655 (7.399)	99.30 (18.52)	93.42 (13.18)	0.114
tPEF%	100.5 (11.71)	95.83 (10.01)	108.7 (21.47)*	101.9 (15.96)	0.173
tMEF50%	85.29 (14.01)	74.1309 (15.58)	78.0096 (19.18)	79.11 (16.61)	0.322
tMEF25%	**84.58 (24.77)**	**58.21 (11.50)**	**64.18 (23.21)**	**68.83 (23.06)**	**0.021**
tMMEF%	87.77 (15.58)	72.54 (14.70)	78.52 (22.90)	79.58 (18.76)	0.19
mFVC, L	**4.403 (0.9005)**	**3.523 (0.7583)**	**3.574 (0.7947)**	**3.825 (0.7947)**	**0.038**
eFVC, L	**4.371 (0.8750)**	**3.463 (0.7722)**	**3.490 (0.8208)**	**3.766 (0.9021)**	**0.03**
mFEV$_1$, L	**3.755 (0.7583)**	**2.828 (0.5696)**	**2.868 (0.7213)**	**3.141 (0.7930)**	**0.007**
eFEV$_1$, L	**3.728 (0.7523)**	**2.784 (0.5652)**	**2.807 (0.7539)**	**3.097 (0.8071)**	**0.007**
mFEV$_3$, L	**4.329 (0.8903)**	**3.38 (0.7528)**	**3.398 (0.8250)**	**3.693 (0.9132)**	**0.022**
eFEV$_3$, L	**4.286 (0.8663)**	**3.333 (0.7540)**	**3.331 (0.8666)**	**3.639 (0.9228)**	**0.021**
mFEV$_1$/FVC	**0.8545 (0.0432)**	**0.8071 (0.0525)**	**0.8002 (0.0421)**	**0.8199 (0.0507)**	**0.025**
eFEV$_1$/FVC	**0.8539 (0.0393)**	**0.8079 (0.0464)**	**0.8004 (0.0481)**	**0.8201 (0.0495)**	**0.024**
mFEV$_3$/FVC	**0.9833 (0.0183)**	**0.9596 (0.0253)**	**0.9484 (0.0284)**	**0.9633 (0.0280)**	**0.01**
eFEV$_3$/FVC	**0.9805 (0.0157)**	**0.9625 (0.0195)**	**0.9498 (0.0305)**	**0.9638 (0.0257)**	**0.018**
mPEF, L/min	8.904 (1.777)	7.031 (1.086)	7.486 (2.111)*	7.796 (1.851)	0.056
ePEF, L/min	9.033 (1.839)	7.212 (1.251)	7.606 (2.164)*	7.939 (1.913)	0.076
mMEF50, L/min	**4.431 (1.017)**	**3.323 (0.7548)**	**3.332 (0.9809)**	**3.684 (1.037)**	**0.016**
eMEF50, L/min	**4.519 (1.056)**	**3.318 (0.7141)**	**3.356 (1.043)**	**3.719 (1.080)**	**0.012**
mMEF25, L/min	**2.143 (0.7298)**	**1.203 (0.3385)**	**1.147 (0.5327)**	**1.486 (0.7082)**	**<0.001**
eMEF25, L/min	**2.103 (0.7346)**	**1.175 (0.3039)**	**1.130 (0.5425)**	**1.458 (0.7017)**	**0.001**
mMMEF, L/min	**4.149 (1.040)**	**2.870 (0.6922)**	**2.848 (0.9908)**	**3.275 (1.082)**	**0.004**
eMMEF, L/min	**4.160 (0.9730)**	**2.861 (0.6321)**	**2.830 (1.049)**	**3.269 (1.078)**	**0.003**
mMEF50/FVC	1.015 (0.1573)	0.9668 (0.2383)	0.9414 (0.1884)	0.9734 (0.1930)	0.691
eMEF50/FVC	1.041 (0.1550)	0.9822 (0.2321)	0.9638 (0.2146)	0.9945 (0.1996)	0.674
mMEF25/FVC	**0.4874 (0.1280)**	**0.3467 (0.0914)**	**0.3143 (0.0981)**	**0.3806 (0.1282)**	**0.002**
eMEF25/FVC	**0.4806 (0.1283)**	**0.3428 (0.0775)**	**0.3136 (0.0991)**	**0.3769 (0.1243)**	**0.002**
mMMEF/FVC	0.9483 (0.1620)	0.8325 (0.2048)	0.7950 (0.1737)	0.8565 (0.1868)	0.153
eMMEF/FVC	0.9581 (0.1444)	0.8442 (0.1952)	0.8020 (0.1896)	0.8659 (0.1848)	0.139

FVC, forced vital capacity; FEV$_1$, forced expiratory volume in 1 s; FEV$_3$, FEV in 3 s; MEF50: forced expiratory flow at 50% of forced vital capacity; MEF25: forced expiratory flow at 75% of forced vital capacity; MMEF: forced expiratory flow between 25 and 75%; PEF, peak expiratory flow; SD, standard deviation; CI, confidence interval; t-, total; m-, morning; e-, evening.
* n = 10.
Bold values indicates statistical significance.

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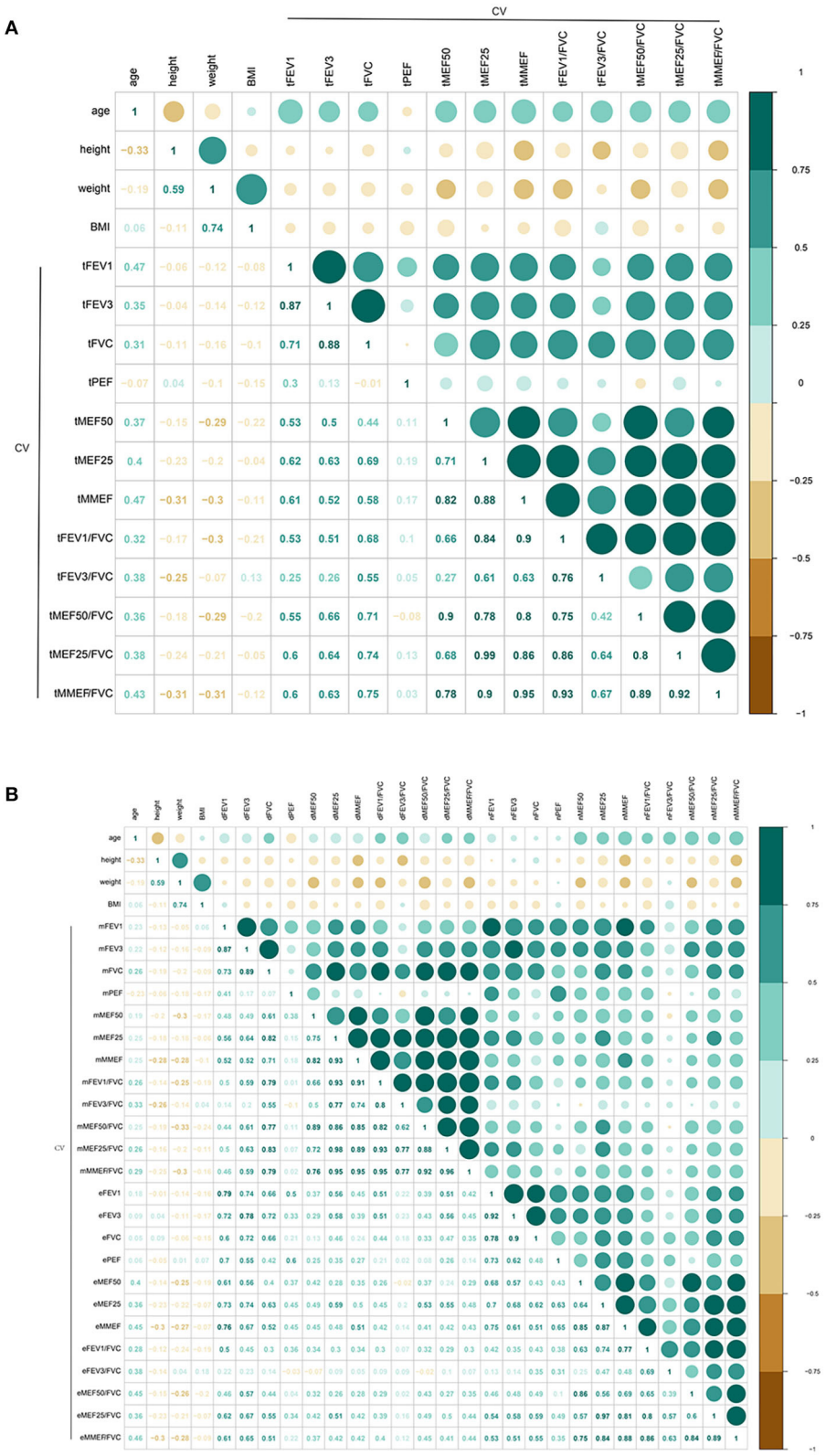

FIGURE 4
Correlation of CV of pulmonary function variable values with age, height, weight, and BMI (total, morning, and evening) ($N = 31$, except $N = 30$ for PEF). A strong relationship between age and both large- [**(A)**, $r = 0.47$, $P = 0.0082$ for $tFEV_1$] and small-airway (tMEF25, tMMEF, and

(Continued)

FIGURE 4 (Continued)
tMMEF/FVC) function variables [**(A)**, $r \geq 0.4$, $P < 0.05$ for all]. tMEF50, $tFEV_3$/FVC, tMEF50/FVC, and tMEF25/FVC was weekly correlated to age [**(A)**, $0.36 \leq r \geq 0.38$, $P < 0.05$ for all], no significant relationships between height, weight, or BMI and both large- and small-airway function variables were found [**(A)**, $P > 0.05$]. Similar correlation both in the morning and the evening was found **(B)**. FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 s; FEV_3, FEV in 3 s; MEF50, forced expiratory flow at 50% of forced vital capacity; MEF25, forced expiratory flow at 75% of forced vital capacity; MMEF, forced expiratory flow between 25 and 75%; PEF, peak expiratory flow; SD, standard deviation; CI, confidence interval; t-, total; m-, morning; e-, evening.

TABLE 3 Comparison of the CV of large- and small-airway function variables according to age.

CV of variables, %	Age, years				*P*
	18∼30	30∼45	45∼60	All subjects	
N	10	10	11	31	–
tFVC	2.821 (0.7225)	3.572 (1.668)	4.712 (2.562)	3.734 (1.954)	0.078
$tFEV_1$	**2.489 (0.8739)**	**2.906 (0.8121)**	**4.666 (1.946)**	**3.396 (1.623)**	**0.002**
$tFEV_3$	**2.648 (0.8069)**	**2.739 (0.8813)**	**4.565 (2.478)**	**3.357 (1.818)**	**0.017**
tPEF	4.846 (1.698)	4.588 (1.335)	4.496 (1.937)*	4.639 (1.635)	0.888
tMEF50	**7.99 (1.951)**	**7.385 (2.392)**	**10.38 (3.196)**	**8.641 (2.834)**	**0.031**
tMEF25	10.59 (4.202)	14.44 (7.357)	17.82 (8.521)	14.40 (7.406)	0.078
tMMEF	**6.603 (1.752)**	**7.951 (4.535)**	**11.21 (4.178)**	**8.674 (4.108)**	**0.023**
mFVC	2.289 (1.185)	3.562 (1.882)	4.248 (3.352)	3.395 (2.432)	0.1790
eFVC	3.009 (0.9634)	3.098 (1.689)	3.856 (2.306)	3.338 (1.750)	0.4861
$mFEV_1$	2.386 (1.381)	2.455 (0.7676)	3.744 (2.145)	2.89 (1.642)	0.0960
$eFEV_1$	2.413 (0.7666)	2.939 (1.328)	3.866 (2.218)	3.098 (1.651)	0.122
$mFEV_3$	2.348 (1.178)	2.414 (0.7558)	4.058 (3.349)	2.976 (2.234)	0.1350
$eFEV_3$	2.643 (1.021)	2.691 (1.323)	3.533 (2.356)	2.974 (1.693)	0.408
mPEF	5.209 (2.465)	3.752 (1.520)	3.829 (2.589)*	4.249 (2.281)	0.2790
ePEF	4.173 (1.777)	4.043 (1.512)	4.686 (1.859)*	4.313 (1.693)	0.667
mMEF50	8.054 (3.132)	7.837 (3.926)	9.516 (3.687)	8.502 (3.562)	0.5130
eMEF50	**7.291 (2.855)**	**6.359 (2.655)**	**11.18 (3.427)**	**8.371 (3.621)**	**0.002**
mMEF25	9.919 (3.911)	15.44 (11.91)	16.38 (8.862)	13.99 (9.036)	0.2220
eMEF25	**11.18 (5.631)**	**11.05 (3.809)**	**19.04 (10.59)**	**13.93 (8.133)**	**0.028**
mMMEF	6.586 (2.288)	8.612 (7.248)	10.18 (5.087)	8.516 (5.312)	0.3100
eMMEF	**6.43 (2.122)**	**6.459 (2.286)**	**11.90 (4.640)**	**8.380 (4.139)**	**0.001**

FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 s; FEV_3, FEV in 3 s; MEF50: forced expiratory flow at 50% of forced vital capacity; MEF25, forced expiratory flow at 75% of forced vital capacity; MMEF, forced expiratory flow between 25 and 75%; PEF, peak expiratory flow; SD, standard deviation; CI, confidence interval; t-, total; m-, morning; e-, evening.
*n = 10.
Bold values indicates statistical significance.

Diurnal variations of FEV_1 and FEV_3 were positively related to age ($P = 0.0109$, $r = 0.47$, $df = 29$ for FEV_1 and $P = 0.0215$, $r = 0.43$, $df = 29$ for FEV_3, Figures 5, 6). There was no significance between age and FVC, PEF, MEF50, MEF25, and MMEF ($P > 0.05$ for all, Figure 5). No significant correlations were found between height, weight, or BMI and both large- and small-airway function variables ($P > 0.05$ for all, Figure 5).

Diurnal variation of variables in the different age subgroups has also been analyzed. Age-related differences were found, but no statistical significance in large- and small-airway function variables was demonstrated ($P > 0.05$ for all, Table 4).

Professional spirometry training improved the performance in spite of the age, sex, height, weight, BMI, and education degree

The subjects had lower FEV_1 ($\Delta = 0.117$ L, $P < 0.001$), FVC ($\Delta = 0.117$ L, $P < 0.001$), FEV_3 ($\Delta = 0.121$ L, $P < 0.001$), and MEF50 ($P < 0.01$) before training than using the Jaeger spirometer (Supplementary Figure 3). A significant improvement of accuracy in FVC, FEV_1, FEV_3, and MEF50 was found, which was consistent with that using a Jaeger

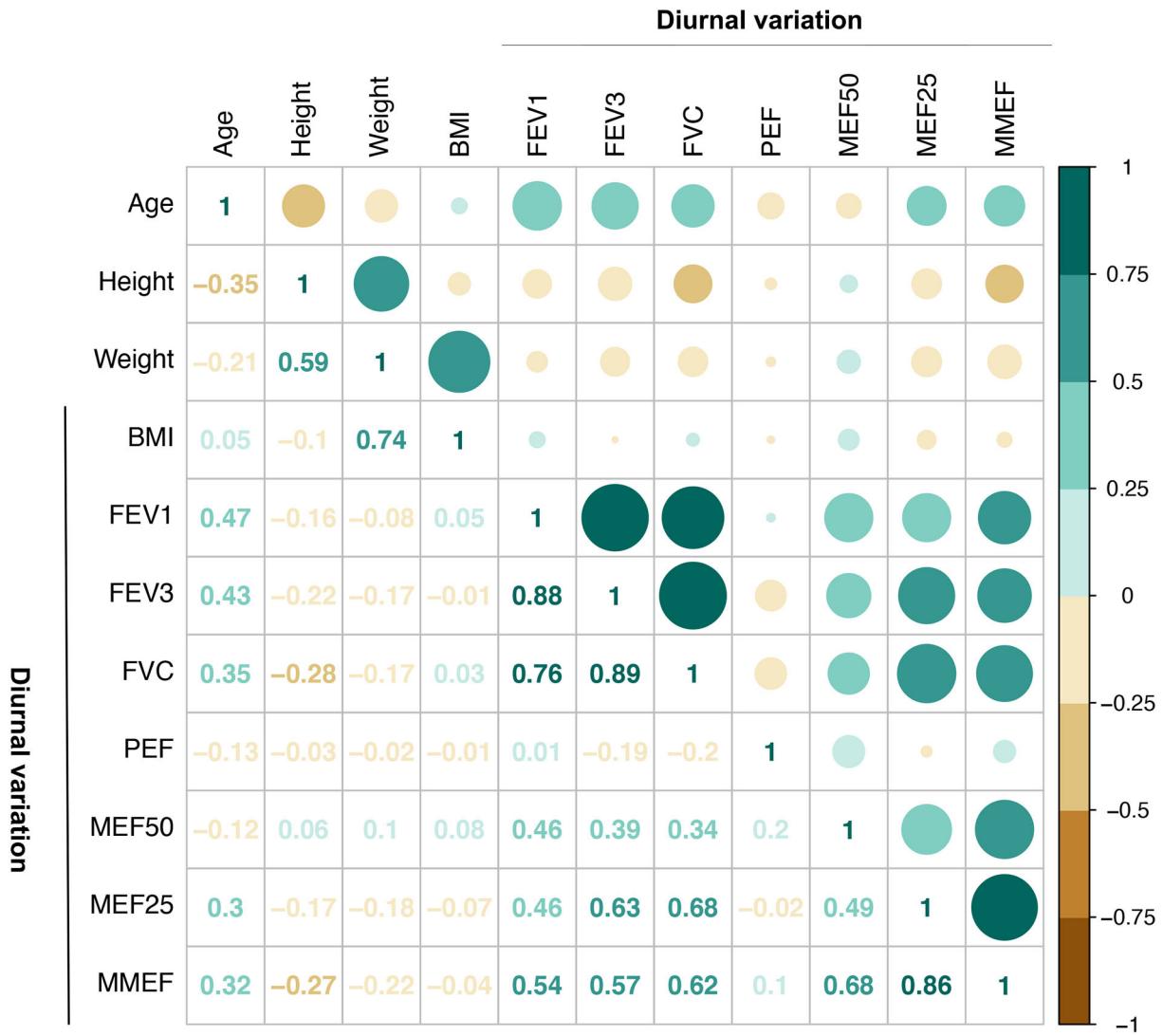

FIGURE 5
Correlation of diurnal variation of pulmonary function variable values with age, height, weight, and BMI ($N = 30$). A strong relationship between age and FEV_1 as well as FEV_3 ($r = 0.47$, $P = 0.0109$ for FEV_1 and $r = 0.43$, $P = 0.0215$ for FEV_3) was found. There was no significance between age and FVC, PEF, MEF50, MEF25, and MMEF ($P > 0.05$ for all). No significant correlations were also found among height, weight, or BMI and both large- and small-airway function variables ($P > 0.05$ for all). BMI, body mass index; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 s; FEV_3, FEV in 3 s; MEF50, forced expiratory flow at 50% of forced vital capacity; MEF25, forced expiratory flow at 75% of forced vital capacity; MMEF, forced expiratory flow between 25 and 75%; PEF, peak expiratory flow.

spirometer (Figure 5, $P > 0.05$ for all). PEF, MEF25, and MMEF were also consistent with those of a Jaeger spirometer (Supplementary Figure 3, $P > 0.05$ for all).

No significant relationships were found between improvement values, including both large- and small-airway variables, and age, height, weight, or BMI ($P > 0.05$ for all, Supplementary Figure 4). Furthermore, there were no sex- and education degree-related differences between the subgroups for both large- and small-airway variables ($P > 0.05$ for all, Supplementary Figures 5, 6).

Discussion

To our best knowledge, no relevant studies have been published regarding the influencing factors of both large- and small-airway function variation features using a portable spirometer for 7 days (including morning and evening values) in non-smoking healthy adults. What is new about our study: (1) using a portable spirometer for 7 days (including morning and evening values) to monitor large- and small-airway function in non-smoking healthy adults; (2) investigating factors affecting

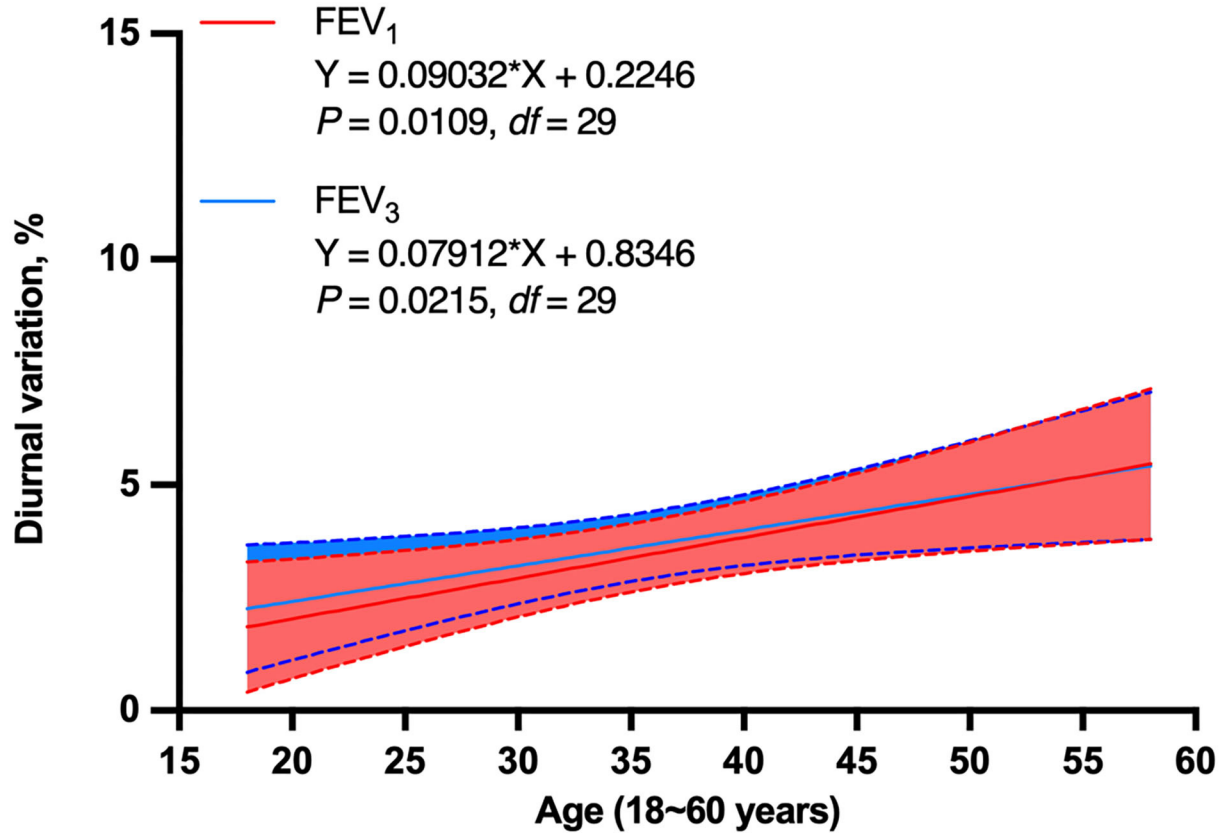

FIGURE 6
Simple linear regression of diurnal variation of FEV_1 and FEV_3 with age in non-smoking healthy adults ($N = 30$). Diurnal variation of FEV_1 and FEV_3 were positively related to age in non-smoking healthy adults ($P = 0.0109$, $df = 29$ for FEV_1 and $P = 0.0215$, $df = 29$ for FEV_3). FEV_1, forced expiratory volume in 1 s; FEV_3, FEV in 3 s; *df*, degree of freedom.

TABLE 4 Comparison of the diurnal variation of large- and small-airway function variables according to age.

Variables	Age, years			All subjects	*P*
	18–30	30–45	45–60		
N	10	10	10[#]	30	–
FVC, %	3.002 (1.019)	4.137 (2.394)	4.700 (2.883)	3.940 (2.275)	0.244
FEV_1, %	2.434 (1.207)	3.279 (1.411)	4.713 (2.972)	3.482 (2.196)	0.058
FEV_3, %	2.842 (1.195)	3.222 (1.526)	4.955 (2.741)	3.688 (2.107)	0.053
PEF, %	5.035 (1.997)	5.230 (1.901)	4.031 (2.074)	4.749 (1.996)	0.377
MEF50, %	8.788 (3.004)	7.030 (2.125)	7.940 (3.639)	7.950 (2.995)	0.458
MEF25, %	11.99 (5.250)	16.20 (9.404)	19.33 (15.35)	15.83 (10.93)	0.334
MMEF, %	7.237 (3.112)	8.486 (5.067)	10.47 (5.126)	8.741 (4.561)	0.288

FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 s; FEV_3, FEV in 3 s; FEV_3, FEV in 6 s; MEF50, forced expiratory flow at 50% of forced vital capacity; MEF25, forced expiratory flow at 75% of forced vital capacity; MMEF, forced expiratory flow between 25 and 75%; PEF, peak expiratory flow; SD, standard deviation.
[#]Four sets of spirometry data from one person did not conform to the acceptability and repeatability criteria and excluded from analysis of diurnal variation.

the morning and evening variability of central and peripheral airway function; and (3) evaluating whether professional training could improve performance of the portable spirometer and possible factors. We found that (1) age, sex, height, and weight all influenced the spirometry values, especially in absolute values; (2) there was a drop until about 35 years of age, followed by a very small but steady increase till 50 years of age, and then a rapid decline in both large- and small-airway function

till old age; (3) age was the main influencing factor of both central and peripheral airway function variability, especially for the small-airway function in the evening after 45 years; and (4) professional spirometry training improved the performance in spite of age, sex, height, weight, BMI, and education degree.

Pulmonary function varies with age, standing height, sex, and ethnicity (25). In our study, we also analyzed the influencing factors of home-monitoring spirometry values and validated the appreciable impact of sex, age, height, and weight on both large- and small-airway function variable values, especially on absolute values. Therefore, spirometry results need to be compared with predicted values or FVC, and lower and upper limits of normal (LLN and ULN, respectively) that are appropriate for the individuals being tested. Furthermore, we found no morning and evening differences relate to those influences on lung function. Height was proved more strongly correlated with both large- and small-airway function; however, the effect of height and weight was significantly reduced when BMI was calculated.

There was a steady age-related decline in lung function in adults, which was in concordance with previous findings (24). We discovered that a drop in lung function begins at 25 years of age, followed by a rapidly decline in both large- and small-airway function from about 50 years of age, which is similar to previous research results that show there is an accelerating cross-sectional decline in FEV_1 after age 30 years in Caucasian adult men, with a nadir at age 62 years when the annual loss ranges between 32 and 46 ml (24), indicating lung function protection may need to start more earlier and aging may contribute to this rapid decline in lung function.

In our previous study, we had reported the healthy individuals' baseline and variation features of large- and small-airway function, low intra-individual variations of central and small-airway variables both in morning and evening, and a slightly higher value of evening variation relative to the corresponding morning variation value. Through the data reanalysis, we found that the CVs of both large- and small-airway function variable values were most affected by age. The CV of lung function values is relatively stable in the 18- to 30-year and 30- to 45-year groups, but significantly increased after 45 years of age, suggesting the LLN is not constant but varies depending on age, especially for the 45- to 60-year group. Then, the correlation of CVs of morning and evening lung function values was calculated separately. Among the CVs of morning lung function values, only the CV of FEV_3/FVC was strongly positively related to age, indicating that FEV_3/FVC, which is an indicator of mild airway obstruction and mild lung injury (25–27), may be more sensitive to detect the age-related early airway obstruction than FEV_1/FVC. Dramatically higher CVs of small-airway function variables (MEF50, MEF25, MMEF, and MMEF/FVC) at night were observed after 45 years of age, suggesting people older than 45 years should pay more attention to monitoring small-airway function in the evening, which will be helpful for early clinical detection of those at high risk for asthma.

Spearman correlation and linear regression analysis exhibited that the diurnal variation of FEV_1 and FEV_3 dramatically increased with age, which further verified the influence of age on circadian variation of lung function in the healthy population. Diurnal variation of lung function variables was further explored across age stratification. There was no significant difference in diurnal variation of lung function among age-groups; however, an increasing trend with age was observed. In addition to that, the diurnal variation difference of FEV_1 and FEV_3 in different age-groups was very close to significance ($P = 0.058$ for FEV_1 and $= 0.053$ for FEV_3), indicating diurnal variation of these two variables increased with age, especially for the 45- to 60-year population. One possible explanation for these inconsistencies may be related to the small sample size, especially considering the multiple age strata, which included only 30 healthy adult subjects. The sample size limitation in the current study was mainly due to the difficulty in recruitment. It was very difficult to recruit healthy non-smoking adults for continuously monitoring lung function in the morning and at night for 7 days, especially because gender, age, and education degree were homogenized simultaneously. Also, based on the results of this study, we will further carry out a multicenter prospective study to monitor large- and small-airway function with a larger sample size, longer duration, and more time points so as to obtain more accurate reference values of both large- and small-airway function variability in the healthy population of China.

We further explored the improvement of portable spirometer performance after professional training. In our study, lower mean values for FVC, FEV_1, and FEV_3 were observed in the GOSPT2000 test, which was in concordance with previous findings (20–22). Nevertheless, those differences were all dispelled after professional training, proving more accuracy and clinical stability of portable spirometer testing than traditional Jaeger spirometer testing. A significant advantage of the GOSPT2000 spirometer over several validated portable spirometers is that both large- and small-airway function variables can be measured (20, 23–27). The values of small-airway function measured by using a portable spirometer were more consistent with those of a Jaeger spirometer in this study, indicating more accuracy of small-airway function variable values of the portable spirometer. Moreover, the improvement was observed after professional spirometry training independent of age, sex, height, weight, BMI, and education degree, indicating the high universality and operability of the portable spirometer, and the results showed that it can be widely used in home settings and primary hospitals.

There are several limitations to our study. First, our study did not include the pediatric population 5–18 years and older

population aged more than 60 years. Second, the sample size in our current study is relatively small, and the collection of large numbers of lung function test results in lifelong healthy non-smokers should be performed to ensure the accuracy of the inspection results.

In conclusion, morning and evening lung function values, calculated separately, and sex, age, height, and weight all influenced the spirometry values, especially in absolute values. There was a drop in both large- and small-airway function at about 25 years of age, followed by a rapid decline at about 50 years. Age was the main influencing factor of both central and peripheral airway function variability, especially for the small-airway function in the evening after 45 years. People older than 45 years should pay more attention to monitoring small-airway function in the evening. Education and training improved the portable spirometer accuracy in both large- and small-airway variables independent of age, sex, BMI, and education degree.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Ethics Committee of Shanghai General Hospital, Shanghai Jiao Tong University (No. 2021KY073). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

XZ, YZha, YZho, WB, and MZ conceptualized and designed the study, verified the data, and drafted the manuscript. XZ, YZha, and YZho searched the literature. DY, CL, JL, and YZho acquired the data. XZ independently performed the statistical analyses. WB and MZ verified the statistical analyses. An external mathematical statistician verified all data and statistical analyses. All authors analyzed, visualized, interpreted the data, critically revised, reviewed, and approved the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.946988/full#supplementary-material

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Promotion strategy for online healthcare platform during the COVID-19 pandemic: Evidence from Spring Rain Doctor in China

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Introduction: Online healthcare platform (OHP) is a new form of medical treatment that solves the problems of an unbalanced distribution of medical resources in China. Especially during the COVID-19 pandemic, OHP has greatly reduced the medical pressure of the hospital and the risk of cross-infection.

Methods: Based on self-determination theory (SDT) (Ryan and Deci, 2000), privacy calculus theory (PCT) (Culnan, 1999) and perceived value theory (PVT) (Choi, 2004), this study uses evolutionary game theory to analyze behavioral strategies and their dynamic evolution in the promotion of OHP. Moreover, we conduct numerical simulations with the help of program compilation.

Results: The results demonstrate that (1) both the qualification inspection of doctors and the investment in information protection influence doctors' participation in and patients' usage of OHP; (2) both the initial probabilities of doctor participation and patient usage influence the multi-game results; (3) the trend of doctors joining OHP is affected by registration cost, time cost, and reputation loss; and (4) the trend of patients using online healthcare is mainly decided by the cost.

Conclusion: This study takes the Spring Rain Doctor as an example to verify the game results. To further popularize online medical treatment among patients, the platform should attach importance to the inspection of doctors and the protection of privacy information and strengthen its publicity in remote places.

KEYWORDS

online healthcare platform, evolutionary game theory, tripartite stakeholders, COVID-19, China

Introduction

In the wake of the COVID-19 outbreak, the international environment has become more complex and uncertain. The new scientific and technological revolution and industrial transformation continue to evolve, and new challenges and opportunities keep emerging. Digital technology and the digital economy are the forerunners of the world scientific and

technological revolution and industrial transformation. Online healthcare is an important way in which the digital economy works during the COVID-19 pandemic. The online healthcare platform (OHP) is an Internet platform wherein doctors provide healthcare services and scientific knowledge to patients directly without time and space restrictions. Patients seek targeted treatment solutions through online medical consultation services (Ye et al., 2022). In 2020, the outbreak of novel coronavirus pneumonia (COVID-19) has seriously affected people's health and normal life (Wang et al., 2021). Due to the outbreak of the COVID-19, the public was mostly anxious about going to the hospital, especially for patients with mild cold symptoms. Therefore, the OHP has received unprecedented attention due to its benefits such as convenience, cost, flexibility, and time savings (Whitten et al., 2007; Jung and Padman, 2015). Compared with traditional offline health care, the OHP can prevent COVID-19 infections, as patients can communicate with doctors and obtain health information anytime and anywhere (Ren and Ma, 2020). In the process of prevention and control of the epidemic, the Chinese OHP has played the unique advantages of online consultation. OHP has reduced the risk of patients' infection and alleviated the situation of medical resources shortage in some areas (Wang et al., 2021). Simultaneously, the COVID-19 epidemic catalyzed the expansion of OHP, represented a major opportunity for internet-based medical treatment in the medium and long term. According to China Internet Network Information Center's 49th statistical report on the Development of Internet in China, by the end of 2021, the scale of online medical care in China had reached 298 million, with a year-on-year growth of 24.2%. It shows that OHPs are a valuable resource in dealing with large-scale public health emergencies (Jiang et al., 2021).

In China, the Chinese government had adopted a series of administrative measures to encourage the development of OHP, especially during the COVID-19 pandemic. The State Council, the National Health Commission and other departments have issued a series of policies related to Internet healthcare, including the "Opinions on Promoting the Development of Internet + Medical and Health," aiming to build and standardize the domestic Internet healthcare system. The online healthcare industry continued to maintain rapid development, and more Internet companies joined the competition. As of December 2021, the utilization rate of online healthcare in China was 28.9%, an increase of 7.2 percentage points compared with December 2020 (China, Internet Network Information Center, 2022). The promotion of OHP can bring many benefits to patients and doctors. For patients, OHP can reduce transaction costs brought by geographical and time constraints, while improving convenience (Deng and Liu, 2017; Wu and Lu, 2018). OHP can support patient self-health management by promoting the sharing of health-related knowledge with patients (Yang et al., 2019b). By browsing the doctor's homepage on the platform, patients can view the doctor's information and understand his/her training, professionalism, and treatment effectiveness (Cao et al., 2017). After the outbreak of COVID-19, online health services satisfied peoples' needs for convenient and contactless health services (Jiang et al., 2021). In addition, according to self-determination theory (SDT; Ryan and Deci, 2000), doctors take the behavior of participating in OHP because they can obtain the relevant value to satisfy their inner needs. Doctors can improve the usage of their time by answering patients' questions in their spare time through OHP (Lu et al., 2019). They can also actively use OHP to obtain economic and social benefits (Jiang et al., 2021; Zhang et al., 2021). Simultaneously, OHP can promote doctor–patient communication to a certain extent, reduce the pressure of hospital diagnosis and treatment, and resolve medical resource shortages and doctor–patient disputes (Luo et al., 2019; Li C. R. et al., 2020). Patients in remote and severely affected areas can receive remote diagnosis and treatment, so as to realize information sharing and diagnosis and treatment across regions and departments (Liang et al., 2020). Therefore, the promotion of OHP is of great significance for the prevention and control of the COVID-19 pandemic.

However, the rapid development of online healthcare has also brought many problems caused by the imperfection of relevant laws and regulations for OHP in China, such as the lack of effective supervision of platform, uneven quality of online medical platforms, low barriers to entry, and the low degree of specialization (Zhang and Feng, 2019). Some platforms have underinvested in information maintenance, leading patients to face the risk of private information leakage (Zhu et al., 2018a). Leaks of disease-related information can lead to social stigma, disease discrimination, mental stress, and a series of other issues (Backerman, 2008). Privacy calculus theory (PCT) points out that when users disclose personal information in exchange for some economic or social benefits, they will make an evaluation to ensure that their private information will not be used illegally and they will not be negatively affected (Culnan and Armstrong, 1999). Therefore, patients' concern about privacy risks is an important factor affecting their use of OHP. Moreover, the OHP lacks strict inspection of doctors' qualifications and trainings, and the quality of doctors' medical services varies, leading to misdiagnosis and reduction in patient satisfaction (Yang et al., 2019a). Meanwhile, this will damage the reputation of doctors. According to perceived value theory (PVT), perceived value refers to the comparison of benefits and costs in the process of using a product or service. Perceived values are considered to have positive effects on actual users' attitudes and long-term usage behavior (Hu, 2021). Perceived value can be measured by perceived benefits and perceived costs (Dong, 2019). Patients and doctors will use and participate in OHP when the perceived benefits outweigh the perceived costs. Therefore, we need to explore the influencing factors of doctor participation and patient use from the perspective of benefits and costs.

Based on SDT, PCT and PVT, we collated the factors that influence patient use and doctor participation. But the spread of OHP among patients and doctors is a long-term process. In this process, the behaviors of patients, doctors and platforms will interact with each other. Information asymmetry exists among participants, and the behavior of subjects is characterized by bounded rationality. Therefore, there is a game between the three participants. The evolutionary game model is based on the assumption of incomplete

rationality of human beings, which can better reflect the complexity and uncertainty of the subject's behavior, and describe the detailed process of the subject's decision-making eventually reaching dynamic equilibrium over time (Weibull, 1995). Therefore, this article integrated evolutionary game theory, SDT, PCT and PVT to construct a tripartite evolutionary game model of doctor, patient and platform. We used numerical simulation to verify the accuracy of the model and evolution results. Finally, we used the case of Spring Rain doctor platform to verify the simulation results, and put forward management suggestions for the promotion of OHP and the improvement of Internet medical treatment.

Literature review

Scholars usually study OHP from the perspectives of patients, doctors, and platforms. We can also determine the factors affecting the promotion of OHP from these three aspects.

Existing literature has mainly focused on the influence factors of patients' behavior from different theoretical perspectives. Based on PVT, Choi et al. (2004) showed that in the choice of online medical services, customer perceived value has a significant impact on their satisfaction and behavioral intentions. Deng et al. (2014) determined that perceived value, attitude, perceived behavior control, technology anxiety, and self-actualization need positively affect the behavior intention of older users. Gu et al. (2018) founded a positive effect of perceived usefulness on patient satisfaction with OHP. Moreover, the performance expectations, social influence, and credibility of network health information are the key factors affecting patients' acceptance and use of OHP (Sun and Lu, 2014). Yang et al. (2019c) proposed that the response time, interaction depth and service content of the first consultation affected the patient's perceived trustworthiness of the doctor, which had a significant impact on the patient's follow-up consultation behavior. Simultaneously, service prices also affect satisfaction, and they show an inverted U-shaped relationship (Wu and Lu, 2018). Shao et al. (2022) examined the impacts of different incentive levels including identity incentive, privilege incentive, and material incentive on user perceived value, user engagement, and user loyalty. Based on PCT. Wang et al. (2017) founded that privacy calculation has an important impact on the willingness to use OHP. Individuals will weigh the disclosure of privacy information and the acquisition of benefits, and decide whether to use OHP. Sun et al. (2022) supposed that patients tend to feel insecure when using the OHP to participate in various activities. They believed that security control of OHPs negatively influences privacy concerns and patients' trust in platform, and further influences patients' satisfaction and willness to use. Aligned with the unified theory of acceptance and use of technology (UTAUT), Nunes et al. (2019) examined the moderating roles of age, gender, and smartphone experience in the relationship between technology acceptance determinants (performance expectancy, effort expectancy, social influence, and facilitating conditions) and the intention to use mobile health applications.

Most studies have been conducted from the perspective of patients. Although understanding how patients benefit from OHP is imperative, OHP will be viable only when participating doctors also gain returns from OHP (Guo et al., 2017). OHP requires significant engagement from doctors, as they provide doctor-driven services (Liu Q. B. et al., 2020). In OHP, doctors provide consultation services, knowledge, and information to help patients understand their diseases and obtain treatments (Li et al., 2019). Doctors' contributions, such as providing consultation services and healthcare information, promote the development of such platforms in the long term (Yang et al., 2019c). Therefore, some scholars have paid attention to the influencing factors of doctors joining OHP based on different theoretical perspectives. For instance, Guo et al. (2017) used social exchange theory to argue thatdoctor participation in OHCs is a social exchange behavior, and studied the impact of status capital and decision capital on the social and economic returns of different doctor groups. The results show that the doctor's decision capital is a professional component, which is important to the platform maintaining exchange returns. Meanwhile, Chen et al. (2020) combined the expectancy theory and the model of Bagozzi, Dholakia, and Basuroy. The results reveal that extrinsic motivations (i.e., extrinsic rewards, expected relationships, and image) and intrinsic motivation (i.e., a sense of self-worth) significantly influence the desire to serve patients well, which in turn positively affects the willingness to offer free and paid services. Ma and Wang (2018) determined the positive impact of performance expectations, effort expectations, social impact, and convenience conditions on doctors' willingness to use and usage behavior. Based on SDT, Yang and Zhang (2019) thought that doctors would obtain social support from interaction with patients, and this support could promote doctors' behaviors in OHP. Meanwhile, Yang et al. (2019c) determined that reputation, monetary rewards, and doctor–patient interaction positively influence doctors' contribution to OHP, and that the doctor's professional status moderates the relationship between motivators and the resulting contribution. Moreover, doctors participate in OHP to provide healthcare services to patients and become popular among users (Liu S. et al., 2020). Furthermore, doctors deliver heightened reputation and other returns while improving the provision of healthcare services (Li J. Y. et al., 2020).

From the perspective of platforms, scholars usually study the impact of platforms on society. For instance, Yang et al. (2015) determined that OHP can solve the problem of information asymmetry between doctors and patients. Moreover, in a study on the information transfer between patients and doctors, OHP is found to increase the communication between patients and doctors and improve the quality of care (Mcgeady et al., 2008). Meanwhile, Goh et al. (2016) studied the social value of OHP services. He believed that the OHP can make medical information break through the geographical boundaries and pass from the city to the countryside, which greatly improve the rural medical environment and achieved social value. Moreover, Venkatesh et al. (2016) found that the emergence of Internet medical services could help pregnant women in rural areas obtain online healthcare

information. It can alleviate the problem of uneven distribution of medical resources in urban and rural areas and greatly reduce the infant mortality rate. Furthermore, Wu and Zhou (2017) found that the OHP can use the Internet to promote the flow of high-quality doctor resources and medical information services across regions, which is beneficial to improve the uneven distribution of medical resources in China.

To sum up, online healthcare research has mainly focused on the willingness and motivation of patients and doctors. Scholars have studied the behavior and motivation of patients, doctors and other users according to relevant theories of psychology, economics and management. Although some scholars have studied the impact of platforms on society, few studies have focused on the influencing factors of platforms' behaviors. Meanwhile, there has been little in-depth analysis of the game between doctors, patients and platforms.

There are three innovations in this study compared with other studies. First, although many scholars have studied the influencing factors of patients' use and doctors' participation in OHP, due to the information asymmetry among doctors, patients and platforms, the behavioral decisions of all parties show the characteristic of bounded rationality. Some scholars have used evolutionary game theory to study the behavioral evolution of OHP subjects before (Hu, 2020), but few studies have discussed the behavioral interaction and strategy evolution of doctors, patients, and platforms. Therefore, this article introduces evolutionary game theory into the study of OHP promotion strategy, and discusses how to promote OHP from the perspectives of patient use and physician participation.

Secondly, through literature review, we found that most of the factors affecting patients' willingness to use and satisfaction are related to perceived value and privacy leakage, and most of the factors affecting doctors' participation in OHP are related to economic benefits, time costs and reputation benefits. Therefore, based on the PVT and PCT, we conducted a study on the influencing factors of patients' use of OHP. SDT can explain the motivation of individual behavior, so it can be the theoretical basis for influencing factors of doctor participation behavior. This article integrates evolutionary game theory, SDT, PVT and PCT, uses evolutionary game model and numerical simulation method to explore the law of behavioral evolution of the three participants. At the same time, factors such as economic benefits, privacy leakage, perceived value, reputational risk are incorporated into the game model.

Thirdly, based on the use of evolutionary game and numerical simulation, this article verifies the numerical simulation results through case analysis of Spring Rain Doctor platform. Spring Rain Doctor is the first Internet enterprise in China to try online healthcare. We believe that Spring Rain Doctor is representative among Chinese OHPs. The case analysis makes the conclusions and suggestions more practical and more in line with the specific situation of China. This work is of great importance to improving the imbalance of medical resources during the COVID-19 pandemic.

Materials and methods

Evolutionary game theory in healthcare

Evolutionary game theory is derived from the concept of evolutionary stability strategy (Smith, 1974). It was originally developed in the economics field to study social interactions (Li, 2011). This method takes the group of participants with limited rationality as the research object and examines the evolution trend of group behavior from the viewpoint of system theory. Over the last few decades, the evolutionary game theory has been widely adopted by economists, sociologists, social scientists, and the philosophers (Xia et al., 2017).

The concept of evolutionary game theory has also been used to study the actions of players in healthcare systems. Chen et al. (2018) leveraged the evolutionary game theory to build a novel model to capture the behaviors of hospitals and patients in mHealth. Then, they analyzed the payoff matrix between hospitals and patients such that a replicator dynamic system can be built. Moreover, Yu et al. (2020) used evolutionary game theory to analyze behavioral strategies and their dynamic evolution in the implementation and operation of telemedicine. From the perspective of privacy disclosure, Xu et al. (2022) constructed an evolutionary game model of privacy disclosure behavior with users and online health communities as the main participants. Zheng and Xu (2021) discussed the complex institutional environment faced by OHP, believed that there was a dynamic game among the government, platform and doctors, and used the evolutionary game method to build a game model of the government, doctors and platform. Taking the mHealth system as the context, Zhu et al. (2018b) builded an evolutionary game to model three types of entities (including system providers, hospitals and governments) under the conditions of incomplete information and bounded rationality.

However, no research has used evolutionary game method to model doctors, patients and platforms. Each of the three participants had a choice of two strategies. Firstly, doctors can choose to participate in OHP, but doctors also pay time costs and registration costs, and may also lose reputation. Secondly, patients can choose to use OHP, but when patients face the risk of privacy leakage and misdiagnosis, patients can also not use OHP and look for alternative solutions. Thirdly, platforms can choose to increase qualification review and privacy protection, but at the same time, platforms need to pay economic costs. There may be situations where the platform sells or discloses users' private information to third parties for the benefit of third parties. Meanwhile, the strategic choices of the three participants will have an impact on each other's strategic choices. Therefore, we believe that the evolutionary game method is suitable for this study. By building an evolutionary game model, we can fully consider the benefits and costs of the three participants of OHP, so as to explore the action strategies of the three participants, and finally put forward suggestions for the application and promotion of OHP.

Evolutionary stable strategy

Smith (1976) devised a central concept of evolutionary game theory called the evolutionary stable strategy (ESS). ESS is the strategy when game players continuously learn and imitate successful strategies in the evolution process and finally reach a stable state after improving their own strategies. The replication dynamic equation is a dynamic differential equation, which is used to express the frequency that a particular strategy is selected by a class of groups. It can be expressed by the following equation:

$$\frac{dx_i}{dt} = x_i\left(u_{si} - \bar{u}\right)$$

where x_i denotes the frequency of strategy s_i, u_{si} denotes the expected return of strategy s_i selected by this group, and $\bar{u}$ denotes the average expected return of this group. When interference factors make x smaller than x^*, $\mathrm{d}x/\mathrm{d}t$ needs to be bigger than 0. Moreover, when x is bigger than x^*, $\mathrm{d}x/\mathrm{d}t$ needs to be smaller than 0 to achieve a stable state.

In summary, evolutionary game theory is based on the assumption of bounded rationality, considering the interaction between game players. Through multiple games, players constantly learn and improve their strategies and finally reach an evolutionary stable state.

Tripartite evolutionary game model of stakeholders in OHP

The hypothesis of the tripartite evolutionary game model

In China, the enterprise-based mode is the main mode of online healthcare, accounting for 70% of the total. Internet companies build OHP and cooperate with doctors. The platforms need to contact doctors and inspect the qualifications of doctors. During this time, the platforms should pay more costs. In addition, the platform must invest in information protection. The higher platforms invest, the higher the risk of cost recovery that platforms confront.

From the perspective of doctors, doctors can obtain economic and social benefits by joining OHP (Guo et al., 2017). Specifically, doctors can obtain additional income and build a reputation by providing good online healthcare services (Chang et al., 2019; Chen et al., 2020). In OHP, reputational reward obtained by doctors mainly comes from the patients' feedback such as their ratings and reviews (Liu et al., 2016). The reputation reward is especially crucial for doctors to enhance their own career and occupational influence (Liu et al., 2016; Yang and Zhang, 2019). Simultaneously, doctors must pay the time and registration costs. When the platforms do not strictly inspect or evaluate doctors, doctors will face reputation loss due to misdiagnosis and low patient satisfaction. Moreover, when the platforms' investment in information protection is insufficient, doctors will face the risk of leakage of private information.

From the patients' perspective, patients can save time and money by using OHP. However, patients may face the risk of being misdiagnosed and privacy.

The following hypotheses were tested in this study:

1. Doctors take two courses of action: One strategy is to join OHP (joining), and the other is not to join OHP (not joining). Thus, the strategy space of doctors is S1 (joining, not joining). Patients take two courses of action: One strategy is to use OHP, and the other is not to use OHP. Thus, the strategy space of patients is S2 (using, not using). OHPs take two courses of action: One strategy is to provide standardized online healthcare services, and the other is not to provide standardized online healthcare services. Thus, the strategy space of platforms is S3 (providing, not providing).
2. The assumptions are that doctors with x probability may adopt the "joining" strategy, and those with $(1-x)$ probability may adopt the "not joining" strategy. Patients with y probability may adopt the "using" strategy, and those with $(1-y)$ probability may adopt the "not using" strategy. Platforms with z probability may adopt the "providing" strategy, and those with $(1-z)$ probability may adopt the "not providing" strategy, in which $0<x<1$, $0<y<1$, and $0<z<1$, respectively.
3. When the doctors join and the patients use OHP, the doctor's income is represented by r_1, the costs of the doctor's OHP registration and qualification certification are c_1, and, the doctor's time costs are c_2. Moreover, α and β denote the platforms' qualification inspection strength coefficient (QISC) and information protection investment strength coefficient (IPISC), respectively. When the platforms do not provide standardized online healthcare services, the QISC of doctors is less than 1. It may lead to misdiagnosis or low patient satisfaction. The reputation loss suffered by the doctor is denoted by $(1-\alpha)c_3$. Simultaneously, the platforms' IPISC is less than 1, and the information leakage loss suffered by doctors is denoted by $(1-\beta)c_4$.
4. The health benefit of patients using OHP is denoted by e_1. When patients choose to go to the hospital instead of using OHP, the health benefit they obtain is e_2, $e_1<e_2$. The time and money saved by patients using OHP are represented by e_3. When doctors join OHP, patients use OHP, and platforms provide standard online healthcare services, a solid trust relationship is established among patients, doctors, and platforms. At this time, the patients obtain an additional benefit of L. The costs of patients using OHP are h_1. However, when doctors join OHP, patients use OHP, and the platforms do not provide standardized online healthcare services, the health loss of patients is $(1-\alpha)h_2$, and the loss of patients' disease information leakage is

$(1-\beta)h_3$. Regardless of whether doctors join OHP, when patients use OHP and the platforms do not provide standardized online healthcare services, the loss of the patient's identity information leakage is $(1-\beta)h_4$.

5. When the platforms provide standardized online healthcare services, doctors join OHP, and patients use OHP, the economic benefit obtained from the platform is w_1. At this point, the social reputation income obtained by the platforms is M. When the platforms provide standardized online healthcare services, the platforms' QISC for doctors is 1, and the its IPISC is 1. The costs of platforms' inspection of doctors' qualification and information protection investment are t_1 and t_2, respectively. When the platforms do not provide standardized online healthcare services, the cost of inspecting doctor qualification is αt_1, and the cost of information protection investment is βt_2, $0<\alpha<1$, $0<\beta<1$. When the platforms do not provide standardized online healthcare services, the compensation for the patients' health loss is $(1-\alpha)F_1$, and the compensation for the patients' disease information leakage is $(1-\beta)F_2$. Meanwhile, the compensation for the leakage of patients' identity information and the doctors' information is denoted by $(1-\beta)F_3$ and $(1-\beta)G$, respectively. When patients use OHP, doctors join OHP, and the platforms do not provide standardized online healthcare services, the social reputation loss suffered by the platforms is denoted by N.

Payoff matrix of the tripartite evolutionary game in OHP

Based on the above assumptions, a tripartite evolutionary game model including doctors, patients, and platforms under bounded rationality was constructed. The payoff matrix of the three groups is shown in Table 1.

TABLE 1 Payoff matrix.

	Provide (z)		Not provide ($1-z$)	
	Join (x)	**Not join ($1-x$)**	**Join (x)**	**Not join ($1-x$)**
Use (y)	$r_1-c_1-c_2$	0	$r_1-c_1-c_2-(1-\alpha)c_3-(1-\beta)c_4$	0
	$e_1+e_3-h_1+L$	e_2	$e_1+e_3-h_1-(1-\alpha)h_2-(1-\beta)(h_3+h_4)$	$e_2-(1-\beta)h_4$
	$w_1-t_1-t_2+M$	$-t_1-t_2$	$w_1-\alpha t_1-\beta t_2-(1-\alpha)F_1-(1-\beta)(F_2+F_3+G)-N$	$-\alpha t_1-\beta t_2-(1-\beta)F_3$
Not use ($1-y$)	$-c_1$	0	$-c_1-(1-\beta)c_4$	0
	e_2	e_2	e_2	e_2
	$-t_1-t_2$	$-t_1-t_2$	$-\alpha t_1-\beta t_2-(1-\beta)G$	$-\alpha t_1-\beta t_2$

Analysis of the tripartite evolutionary game model in OHP

Replicator dynamics equation of the tripartite evolutionary game

According to the payoff matrix, we separately listed the replication dynamic equations of doctors, patients and platforms.

Under the aforementioned assumption, when doctors implement the "join" strategy, the marginal expected revenue is

$$\begin{aligned} P_{11} = {} & yz(r_1-c_1-c_2)+y(1-z) \\ & \left[r_1-c_1-c_2-(1-\alpha)c_3-(1-\beta)c_4\right]+ \\ & (1-y)z(-c_1)+(1-y)(1-z)\left[-c_1-(1-\beta)c_4\right] \end{aligned}$$

Meanwhile, when doctors implement the "not join" strategy, the marginal expected revenue is

$$P_{12} = yz(0)+y(1-z)(0)+(1-y)z(0)+(1-y)(1-z)(0)$$

Moreover, the expected revenue of the doctors is calculated as follows:

$$P_1(x) = xP_{11}+(1-x)P_{12}$$

Thus, the replicator dynamics equation of doctors can be written as $P_1(x)$ in Equation (1):

$$P_1(x) = \frac{dx}{dt} = x(1-x)\begin{Bmatrix} y\left[r_1-c_2-(1-\alpha)c_3\right]- \\ c_1-(1-\beta)c_4+z(1-\beta)c_4 \end{Bmatrix} \quad (1)$$

When patients implement the "use" strategy, the marginal expected revenue is

$$\begin{aligned} P_{21} = {} & xz(e_1+e_3-h_1+L)+x(1-z)\begin{bmatrix} e_1+e_3-h_1-(1-\alpha) \\ h_2-(1-\beta)(h_3+h_4) \end{bmatrix}. \\ & +(1-x)z(e_2)+(1-x)(1-z)\left[e_2-(1-\beta)h_4\right] \end{aligned}$$

Meanwhile, when patients implement the "not use" strategy, the marginal expected revenue is

$$P_{22} = xz(e_2)+x(1-z)(e_2)+(1-x)z(e_2)+(1-x)(1-z)(e_2)$$

The expected revenue of the patients is

$$P_2(y) = yP_{21}+(1-y)P_{22}$$

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Thus, the replicator dynamics equation of patients can be written as in Equation (2):

$$P_2(y)=\frac{dy}{dt}=y(1-y)\begin{Bmatrix}x\begin{bmatrix}e_1-e_2+e_3-h_1-\\(1-\alpha)h_2-(1-\beta)h_3\end{bmatrix}\\+xz\left[(1-\alpha)h_2+(1-\beta)h_3+L\right]-\\(1-\beta)h_4+z(1-\beta)h_4\end{Bmatrix} \quad (2)$$

When the platforms implement the "provide" strategy, the marginal expected revenue is

$$\begin{aligned}P_{31}=&xy(w_1-t_1-t_2+M)+x(1-y)(-t_1-t_2)\\&+(1-x)y(-t_1-t_2)+(1-x)(1-y)(-t_1-t_2).\end{aligned}$$

However, when platforms implement the "not provide" strategy, the marginal expected revenue is

$$\begin{aligned}P_{32}=&xy\begin{bmatrix}w_1-\alpha t_1-\beta t_2-(1-\alpha)\\F_1-(1-\beta)(F_2+F_3+G)-N\end{bmatrix}+\\&x(1-y)\left[-\alpha t_1-\beta t_2-(1-\beta)G\right]\\&+(1-x)y\left[-\alpha t_1-\beta t_2-(1-\beta)F_3\right]+\\&(1-x)(1-y)(-\alpha t_1-\beta t_2).\end{aligned}$$

The expected revenue of the platforms is

$$P_3(z)=zP_{31}+(1-z)P_{32}.$$

Thus, the replicator dynamics equation of platforms can be written as $P_3(z)$ in Equation (3):

$$P_3(z)=\frac{dz}{dt}=z(1-z)\begin{Bmatrix}xy\begin{bmatrix}M+(1-\alpha)F_1+\\(1-\beta)F_2+N\end{bmatrix}-(1-\alpha)t_1\\-(1-\beta)t_2+x(1-\beta)\\G+y(1-\beta)F_3\end{Bmatrix}. \quad (3)$$

Stability analysis

The above three replication dynamic equations describe the dynamic adjustment process of the strategy selection of doctors, patients, and platforms. The game system has reached a stable state when the three groups continue to learn and imitate to reach the Nash equilibrium. To find the stability point of the evolutionary game among the three stakeholders, we assume:

$$\begin{Bmatrix}\frac{dx}{dt}=0\\\frac{dy}{dt}=0\\\frac{dz}{dt}=0\end{Bmatrix}.$$

Then, within the range of the equilibrium solution domain $W=\{(x,y,z)|0\le x\le 1;;0\le y\le 1;;0\le z\le 1|\}$ are the following eight special equilibrium solutions: V0(0,0,0), V1(1,0,0), V2(1,1,0), V3(1,0,1), V4(0,1,0), V5(0,1,1), V6(0,0,1), V7(1,1,1). Another equilibrium point $E(x^*,y^*,z^*)$ is also in the above solution domain and satisfies:

$$y\left[\eta_1-c_2-(1-\alpha)c_3\right]-c_1-(1-\beta)c_4+z(1-\beta)c_4=0 \quad (4)$$

$$x\begin{bmatrix}e_1-e_2+e_3-\\h_1-(1-\alpha)\\h_2-(1-\beta)h_3\end{bmatrix}+xz\begin{bmatrix}(1-\alpha)h_2+\\(1-\beta)h_3+L\end{bmatrix}-(1-\beta)h_4+z(1-\beta)h_4=0 \quad (5)$$

$$\begin{aligned}&xy\left[M+(1-\alpha)F_1+(1-\beta)F_2+N\right]-\\&(1-\alpha)t_1-(1-\beta)t_2+x(1-\beta)G+y(1-\beta)F_3=0\end{aligned} \quad (6)$$

Then, the three equations above are differentiated to obtain:

$$P_1'(x)=(1-2x)\begin{bmatrix}y(\eta_1-c_2-(1-\alpha)c_3)-\\c_1-(1-\beta)c_4+z(1-\beta)c_4\end{bmatrix},$$

$$\begin{aligned}P_2'(y)=&(1-2y)\{x\left[e_1-e_2+e_3-h_1-(1-\alpha)h_2-(1-\beta)h_3\right]\\&+xz\left[(1-\alpha)h_2+(1-\beta)h_3+L\right]-(1-\beta)h_4+z(1-\beta)h_4\},\end{aligned}$$

$$\begin{aligned}P_3'(z)=&(1-2z)\{xy\left[M+(1-\alpha)F_1+(1-\beta)F_2+N\right]\\&-(1-\alpha)t_1-(1-\beta)t_2+x(1-\beta)G+y(1-\beta)F_3\}.\end{aligned}$$

According to the stability theorem of the evolutionary game, when $P_1'(x)<0$, $P_2'(y)<0$, $P_3'(z)<0$ in the above three formulas, x^*, y^*, and z^* represent the stable strategies that doctors, patients, and platforms should adopt in the evolution process.

Replicator dynamic analysis of the doctor group

According to equation (4),

$$y\left[\eta_1-c_2-(1-\alpha)c_3\right]-c_1-(1-\beta)c_4+z(1-\beta)c_4=0.$$

This equation represents the boundary of the steady state. When the following conditions are met

$$y\left[\eta_1-c_2-(1-\alpha)c_3\right]-c_1-(1-\beta)c_4+z(1-\beta)c_4>0,$$

then we obtain.

$P_1^{'}(0)>0$, $P_1^{'}(1)<0$.

This indicates that joining OHP is stable, and not joining OHP is unstable.

In contrast, when the following conditions are met.

$$y\left[\eta_1-c_2-(1-\alpha)c_3\right]-c_1-(1-\beta)c_4+z(1-\beta)c_4<0,$$

then we obtain.

$P_1^{'}(0)<0$, $P_1^{'}(1)>0$.

This indicates that not joining OHP is stable, and joining OHP is unstable. When $x\in(0,1)$, $P_1(x)>0$. The phase evolution diagram of its stability depends on the shape of the quadratic curve of equation (4).

Replicator dynamic analysis of the patient group

According to equation (5),

$$x\left[e_1-e_2+e_3-h_1-(1-\alpha)h_2-(1-\beta)h_3\right]+$$
$$xz\left[(1-\alpha)h_2+(1-\beta)h_3+L\right]-(1-\beta)h_4+z(1-\beta)h_4=0.$$

This equation represents the boundary of the steady state. When the following conditions are met

$$x\left[e_1-e_2+e_3-h_1-(1-\alpha)h_2-(1-\beta)h_3\right]+$$
$$xz\left[(1-\alpha)h_2+(1-\beta)h_3+L\right]-(1-\beta)h_4+z(1-\beta)h_4>0,$$

then we obtain.

$P_2^{'}(0)>0$, $P_2^{'}(1)<0$.

This indicates that using online medical treatment is stable, and not using online medical treatment is unstable.

In contrast, when the following conditions are met

$$x\left[e_1-e_2+e_3-h_1-(1-\alpha)h_2-(1-\beta)h_3\right]+$$
$$xz\left[(1-\alpha)h_2+(1-\beta)h_3+L\right]-(1-\beta)h_4+z(1-\beta)h_4<0,$$

then we obtain.

$P_2^{'}(0)<0$, $P_2^{'}(1)>0$.

This indicates that not joining online medical treatment is stable, and joining online medical treatment is unstable. When $x\in(0,1)$, $P_2(x)>0$. The phase evolution diagram of its stability depends on the shape of the quadratic curve of equation (5).

Replicator dynamic analysis of the platform group

According to equation (6),

$$xy\left[M+(1-\alpha)F_1+(1-\beta)F_2+N\right]-$$
$$(1-\alpha)t_1-(1-\beta)t_2+x(1-\beta)G+y(1-\beta)F_3=0$$

This equation represents the boundary of the steady state. When the following conditions are met,

$$xy\left[M+(1-\alpha)F_1+(1-\beta)F_2+N\right]-$$
$$(1-\alpha)t_1-(1-\beta)t_2+x(1-\beta)G+y(1-\beta)F_3>0,$$

then we obtain.

$P_3^{'}(0)>0$, $P_3^{'}(1)<0$.

This indicates that using OHP is stable, and not using OHP is unstable.

In contrast, when the following conditions are met,

$$xy\left[M+(1-\alpha)F_1+(1-\beta)F_2+N\right]$$
$$-(1-\alpha)t_1-(1-\beta)t_2+x(1-\beta)G+y(1-\beta)F_3<0,$$

then we obtain.

$P_3^{'}(0)<0$, $P_3^{'}(1)>0$.

This indicates that not joining OHP is stable, and joining OHP is unstable. When $x\in(0,1)$, $P_3(x)>0$. The phase evolution diagram of its stability depends on the shape of the quadratic curve of equation (6).

Simulation analysis

To explore the evolution of OHP under different parameter values, based on the established evolutionary game model, we analyze the platforms' QISC, IPISC, the initial state of doctors and patients, the doctor's registration costs, time costs, and reputation loss, and the patients' online healthcare costs. To determine the simulation parameters, we refer to the relevant data on the Spring Rain Doctor platform, consult experts who study simulation in related fields, and combine relevant literature research. These simulation parameters can reflect the general trend to some extent.

The influence of QISC α on the OHP evolutionary game behavior

α takes the value of 0.1, 0.5, and 0.9 for low, medium, and high QISC, respectively. As shown in Figure 1A, doctors doubt the credibility of the platform due to the platforms' medium and low QISC, and they tend to use the strategy of not joining OHP. The lower the QISC, the faster the rate of evolution to the strategy of not joining. When the platform has a higher degree of QISC, doctors tend to believe the operation level of the platform. Therefore, OHP can improve the healthcare efficiency of doctors and their additional income. Eventually, doctors will tend to join OHP.

As shown in Figure 1B, when the platforms' QISC is low, patients doubt the healthcare level of the doctors on the platform and the reliability of the platform based on the doctors'

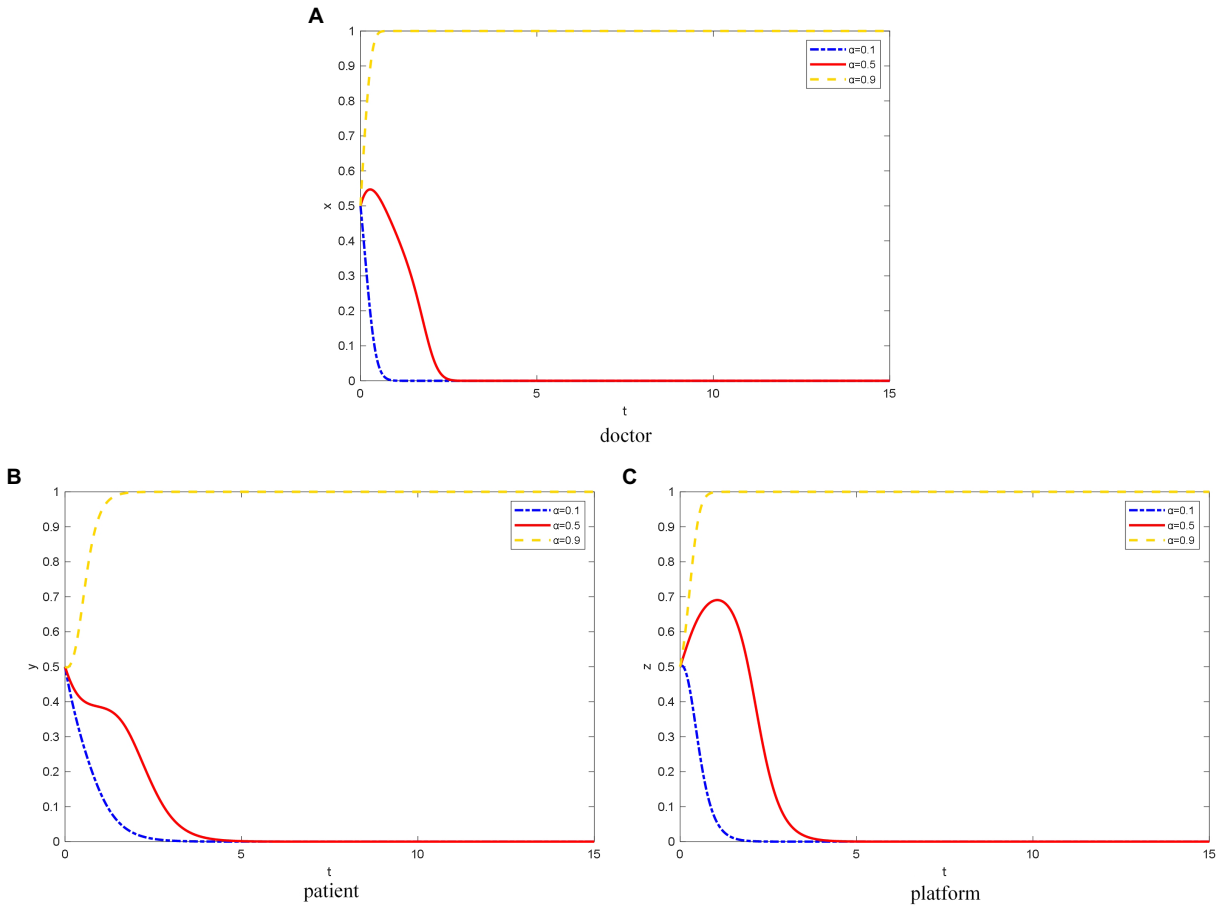

FIGURE 1
The evolution path of different objects' strategy under different QISC. **(A)** Doctor, **(B)** patient, **(C)** platform.

information. Due to the fear of misdiagnosis, the patients are likely to choose the strategy of not using OHP. When the platforms' QISC is moderate, the patients initially tend to not use OHP due to the psychology of observation. However, after patients can accurately judge the qualifications of doctors through the patient and peer evaluation mechanism on the platform, they exhibit a tendency to use OHP.

When the platforms' QISC is high, patients can learn about the doctors' healthcare level through the doctor-related information published on the platform, such as the medical institution, region, and professional title. Because patients can save time and money by using OHP, they can enjoy healthcare resources that were not previously available due to several factors such as region and income level. Therefore, patients will tend to use OHP.

As shown in Figure 1C, when the platforms' QISC is low, the platforms' inspection of doctors and its construction are relatively negative. Thus, the platform tend to not provide standardized online healthcare services.

Meanwhile, when the platforms' QISC is moderate because the platforms consider reputation, they will invest part of the funds to build the platforms' qualification inspection and information protection mechanism. However, over time, the platforms' revenue is not as expected, and the platforms do not pay much attention to the brand and popularity. Eventually, platforms tend to use the strategy of not providing standardized online healthcare services.

However, when platforms have a high degree of QISC, they pay more attention to its own construction, social reputation, and long-term development. They invest heavily in doctor qualification inspection and information protection, and they are willing to take certain risks. Thus, the platforms eventually tend to provide standardized online healthcare services.

The influence of IPISC β on OHP evolutionary game behavior

β takes the value of 0.1, 0.5, and 0.9 for low, medium, and high IPISC, respectively.

As shown in Figure 2A, when the platforms' IPISC is low, doctors concern about their own information security, which will lead to the evolution of not joining OHP.

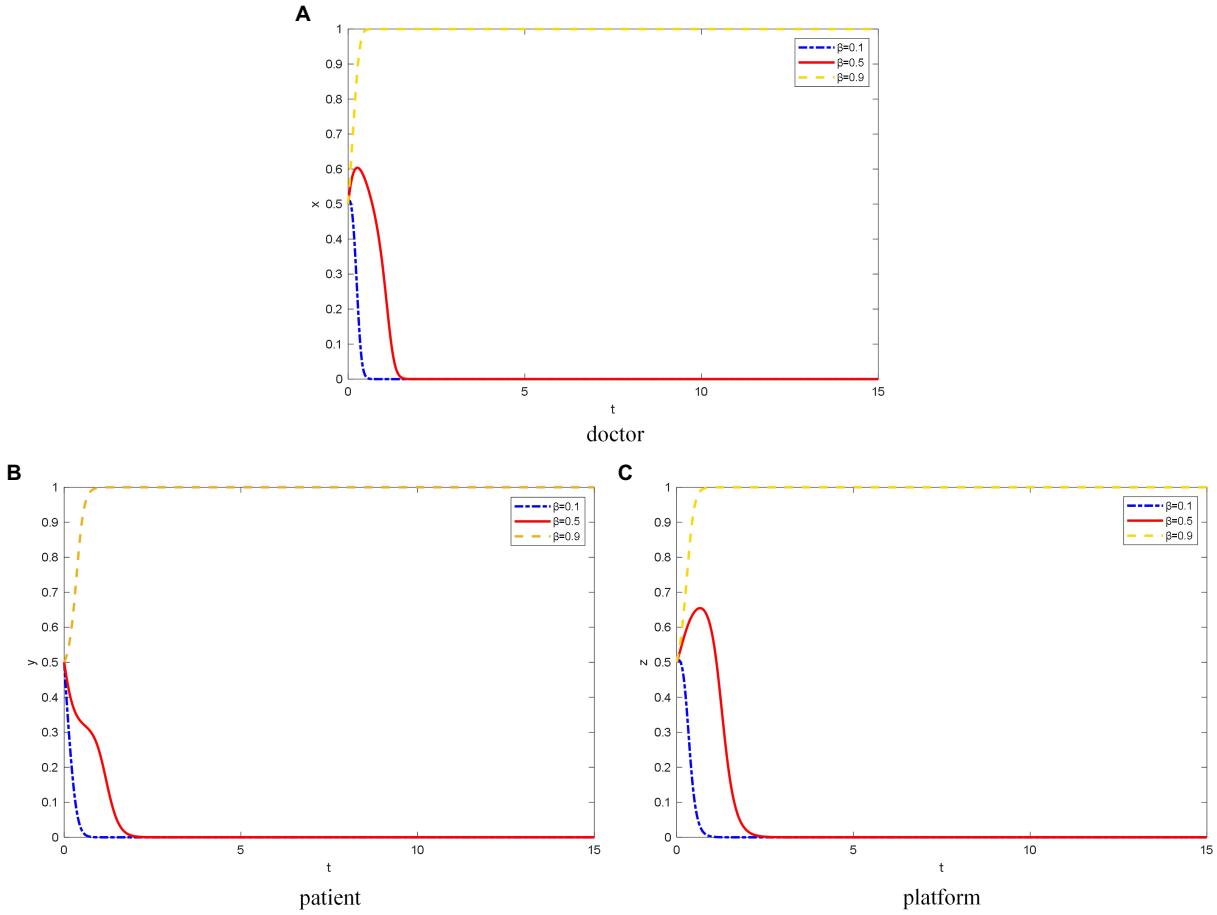

FIGURE 2
The evolution path of different objects' strategy under different IPISC. **(A)** Doctor, **(B)** patient, **(C)** platform.

However, when the platforms' IPISC is moderate, doctors will choose to join OHP for a certain period to observe the quality of the platforms' operation. However, the platforms' investment in information protection cannot meet the needs of doctors for their information security protection. Thus, the doctors finally choose not to join the OHP.

When the platforms invest heavily in information protection, doctors elect to trust the platforms' information protection mechanism and join OHP. In addition, the greater the IPISC, the faster doctors elect to join OHP.

For patients, when the IPISC is low, they are concerned about the leakage of their private and identity information, and they tend to not use OHP (Figure 2B). The lower the platforms' IPISC, the faster the patients choose not to use it. When the platforms' IPISC is moderate or high, patients elect to trust the platforms' information protection mechanism and choose to use OHP.

As shown in Figure 2C, when platforms' IPISC is low, they lack attention to the construction of information protection mechanisms. Thus, the platforms ultimately choose not to provide standardized online healthcare services.

In the case of moderate investment in platform information protection, the platforms initially elect to provide standardized online healthcare services because they want to attract doctors and patients. Over time, after a large number of doctors and patients join and use OHP, respectively, the platform thinks investing heavily in doctor qualification inspection and information protection is not necessary because of the cost. Thus, platforms ultimately choose not to provide standardized online healthcare services.

When the platforms' IPISC is high, they pay more attention to the protection of doctors' and patients' privacy information and invest more funds to protect it. At this time, the platforms care more about long-term interests, so they choose to provide standardized online healthcare services. The higher the platforms' IPISC, the faster they choose to provide standardized online healthcare services.

Influence of the different initial states of doctors on the OHP evolution game behavior

As shown in Figure 3, when the probability of doctors' initial choice to join the OHP is 0.2, doctors' attitude toward joining the OHP is negative. Therefore, patients concern about OHP and doubt the reliability of the platform. Eventually, the patients elect not to use OHP. Because doctors do not join OHP, platforms

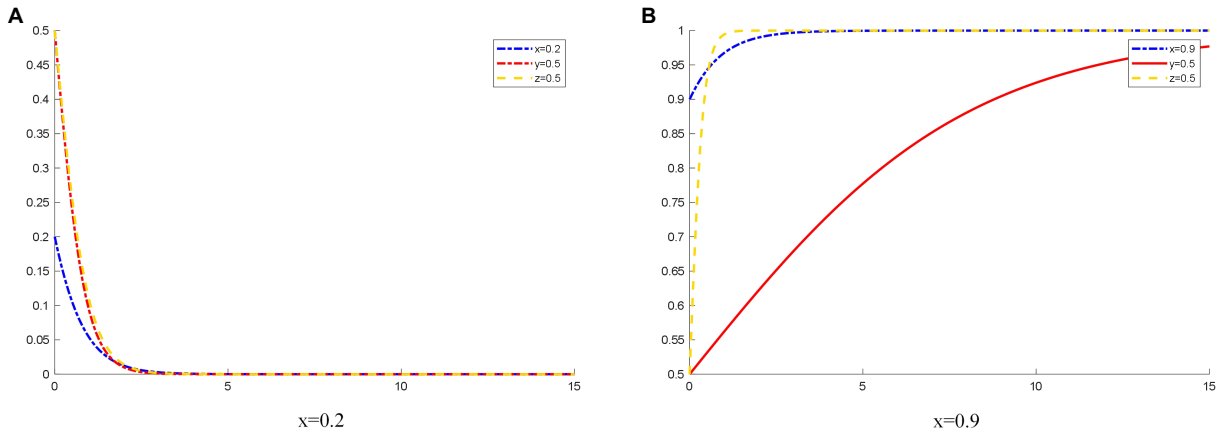

FIGURE 3
The evolution track of three-party strategy selection under different initial states of doctors. **(A)** *x* (1)=0.2; **(B)** *x* (1)=0.9.

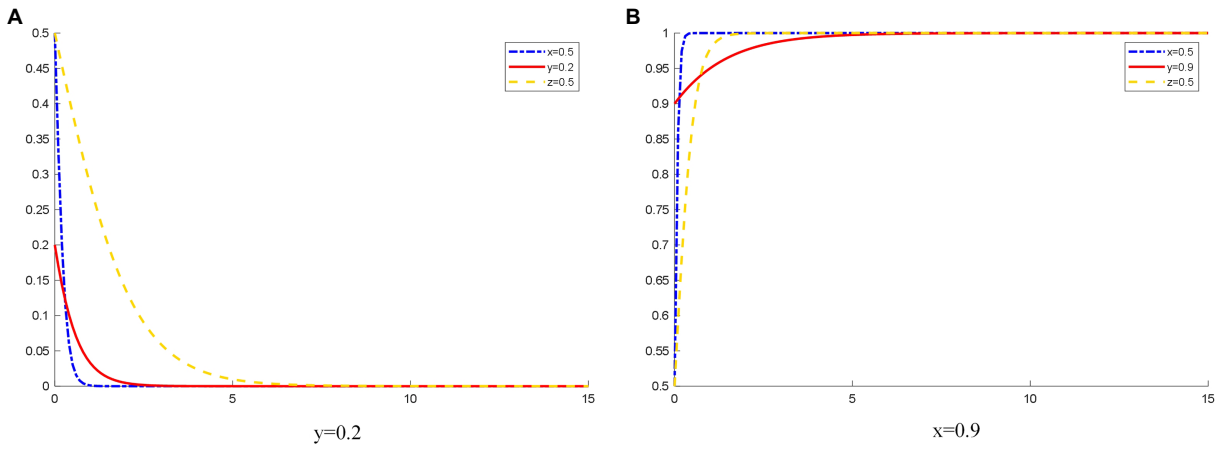

FIGURE 4
The evolution track of three-party strategy selection under different initial states of patients. **(A)** *y* (1)=0.2; **(B)** *y* (1)=0.9.

cannot attract patients, and they quickly choose not to provide standardized online healthcare services.

Meanwhile, when the probability that the doctors initially choose to join OHP is 0.9, the doctors' willingness to join OHP is relatively strong. Moreover, many doctors signed the contracts with the platform. The platform has rich medical resources. These resources enable patients to trust the platforms, so they choose to use OHP. At this time, the platform has good thinking, and they choose to provide standardized online healthcare services much faster than patients choose to use OHP.

Influence of the different initial states of patients on the OHP evolution game behavior

As shown in Figure 4, when the probability that the patients initially choose to use OHP is 0.2, the patients' willingness to use OHP is low due to the platforms' operation, publicity, and other factors. OHP has not been popularized in society. The platform lacks a large number of users. At this time, the platform is reluctant to spend too much cost on operating online healthcare services and tends to not provide standardized online healthcare services.

When the probability that patients initially choose to use OHP is 0.9, most patients choose to use OHP. This form of OHP is popular among the public. At this time, a large amount of online medical resources is required. A large number of patients choosing to use OHP would improve the medical efficiency of doctors and reduce the pressure on hospitals. Doctors can also obtain additional income. Therefore, doctors choose to join OHP. Moreover, a large number of users registered on the platform provide opportunity for the platforms to obtain huge profits. They further improve the quality of platform services for their reputation and patients, strictly inspect the qualifications of doctors, and actively protect the safety of patient information.

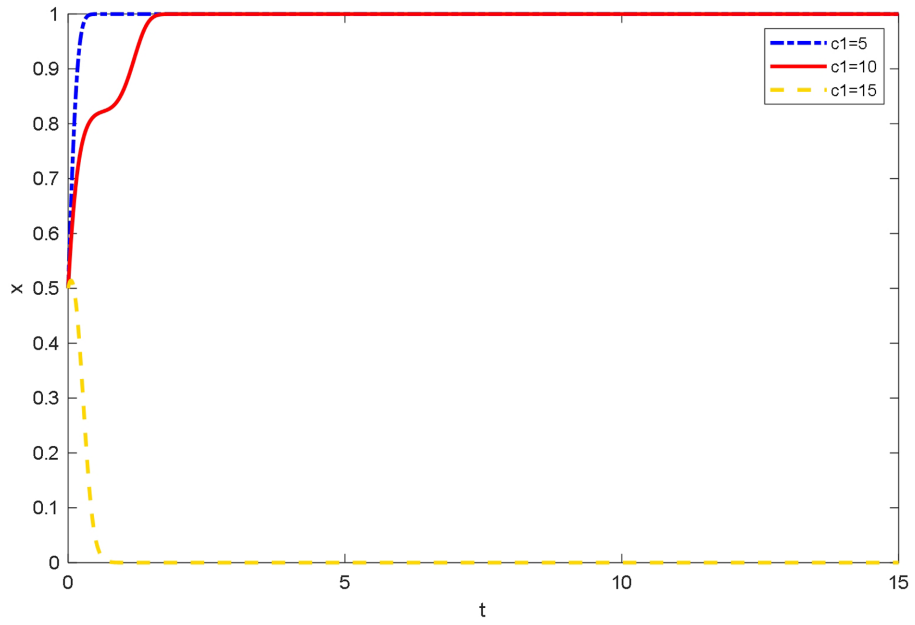

FIGURE 5
Evolutionary trajectory of doctor's strategy selection under different registration costs.

Eventually, platforms tend to provide standardized online healthcare services.

Influence of different registration costs on the evolutionary behavior of doctors

As shown in Figure 5, when the qualification registration costs are high, doctors tend not to join OHP. Doctors are faced with the difficulty of registration. When inspecting the qualifications of doctors, the platforms require doctors to upload qualification and work certificates. Some doctors think that registration and cancelation procedures are cumbersome. Therefore, they ultimately tend not to join OHP. However, when the qualification registration costs are low, doctors tend to join OHP. This reflects that doctors' satisfaction and joining costs are important to the joining behavior of doctors.

Influence of different time costs on the evolutionary behavior of doctors

Figure 6 shows that when the time costs are low, doctors are willing to use their free time to join OHP to increase their income and reputation. Doctors can have online medical treatment any time, which is why doctors choose to join OHP. When the time costs are medium, at first, doctors try to choose joining OHP, and then because of lack of time and energy, they finally elect not to join OHP. However, they tend to do their jobs in the hospital when the time costs are high. At this time, they are unwilling to spend too much time on OHP and ultimately choose not to join OHP.

Influence of different reputation loss on the evolutionary behavior of doctors

Figure 7 shows that the reputation loss of doctors among patients is small because the evaluation mechanism of patients on doctors set by the platforms is more reasonable and objective, and the professional level and working attitude of doctors can be evaluated fairly. At this time, the doctor has a greater willingness to join OHP. When the doctors' reputation is greatly lost, in addition to the medical level, the patients' requirements for the doctors' service level are also higher, and the doctor is more likely to receive negative evaluations about communication skills, timeliness, and service attitudes. For example, the experience mechanism of doctors will be questioned by patients; patients are more willing to trust the opinions of doctors in offline hospitals than OHP. Moreover, due to the availability of online knowledge, patients' psychological expectations for OHP are too high, which will lead to patient's provision of negative comments. Initially, doctors choose to join OHP. Over time, negative online reviews will put pressure on doctors, and they ultimately choose not to join OHP.

Influence of different online healthcare costs on the evolutionary behavior of patients

As shown in Figure 8, when the online healthcare costs are low, using OHP can save patients time and money to go to the hospital for medical treatment. This is because many patients'

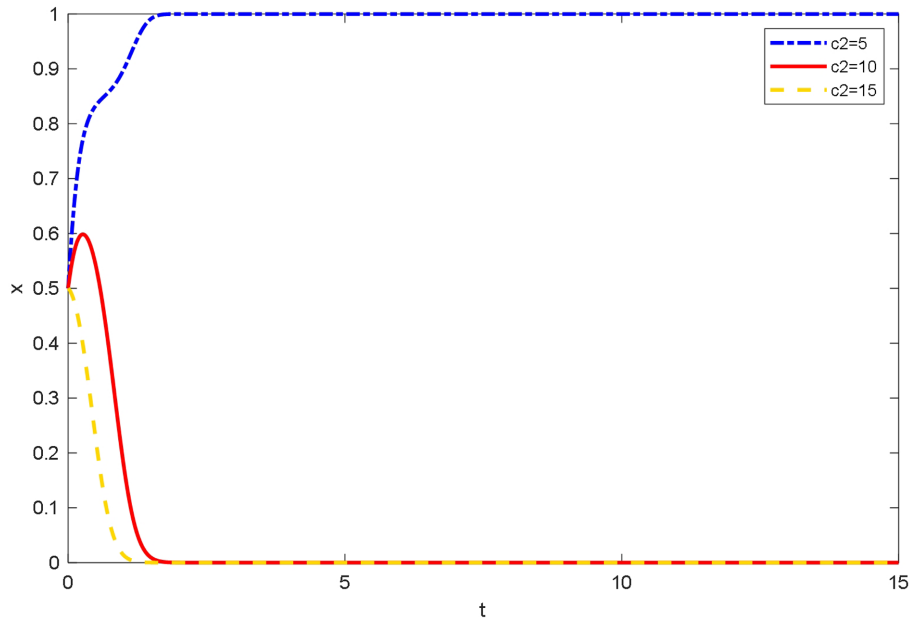

FIGURE 6
Evolutionary trajectory of doctors' strategy selection under different time costs.

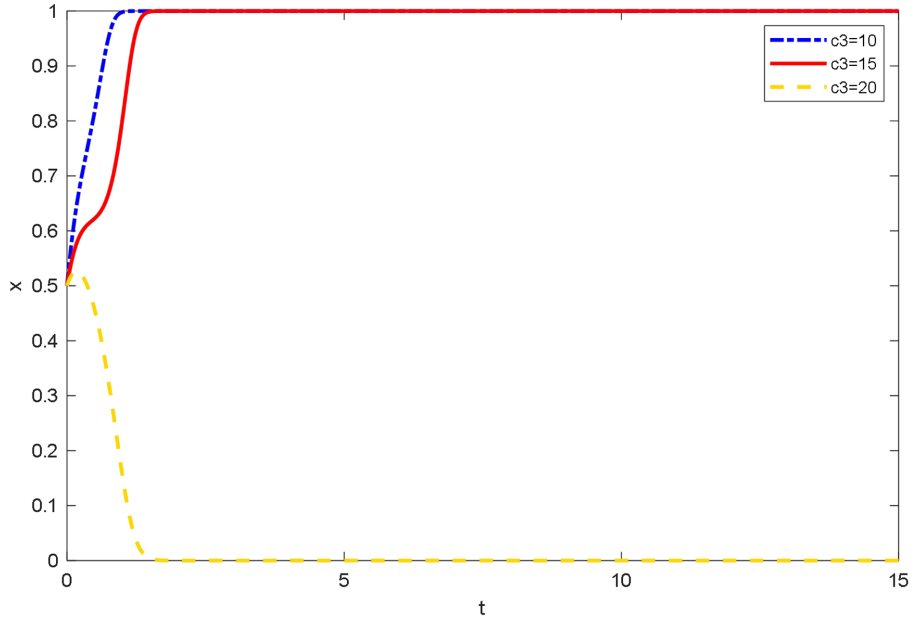

FIGURE 7
Evolutionary trajectory of doctors' strategy selection under different reputation loss.

conditions can be solved by simple diagnosis and treatment. Especially, patients can reduce the costs of useless consultations by using OHP, and OHP can solve the problems of difficult and expensive medical treatment.

Patients tend choosing not to use OHP initially when the online healthcare costs are moderate. This is because at the beginning, people's awareness of paying for knowledge was not strong. However, with time, people's health and consumption concepts have improved. The concept of obtaining high-quality healthcare services by paying lower medical expenses than that of hospitals has gradually become popular among patients. Eventually, patients elect to use OHP.

When online healthcare costs are high, patients tend to not trust the platforms and doctors even though OHP has been rapidly promoted and patients have gradually accepted this medical method due to the convenience. Many factors make patients doubt the professionalism of doctors and the reliability of platforms. When OHP cannot help patients save the cost of seeing a doctor, patients tend not to use OHP.

Case analysis: An example of spring rain doctor platform

Spring Rain Doctor, a developing platform for nearly 8 years since 2011, is the first Internet enterprise in China to try online healthcare. More than 300 public hospitals have settled on the platform. By the end of August 2020, the platform has 630,000 Chinese practicing doctors from all departments. The cumulative number of users of the platform is 130 million, and its daily consulting times exceed 300,000. It is the world's largest mobile doctor–patient communication platform. Doctors' communication with patients is conducted through the website, pictures, mobile phones, and even video format. In addition, doctors could observe timely feedback and service assessments of patients (Chen et al., 2020).

According to Artery Network data, Table 2 shows the proportion of platform users in each region. Guangdong has the largest number of users, accounting for 11.2%, far more than other regions; followed by Shandong, accounting for 7.16%. The reason for this phenomenon may be that Guangdong is a young city, and people are more interested in new things and are willing to try new medical methods. Moreover, the *per capita* income in the region is relatively high, and people's time and opportunity costs are huge. If users can consult online at any time and save the time and cost of going to the hospital, they will be more willing to pay for consultation on the platform. As shown in Table 3, eight of the top ten provinces with the number of users of the Spring Rain Doctor platform are among the top ten provinces by population in 2018. It can be inferred that the population of Spring Rain doctors is evenly distributed across the country, and the population of platform users is not restricted by region. This shows that various regions have the problem of a lack of medical resources. Different regions have different problems. For example, developed regions have more medical resources, but the number of patients is large, and it is difficult to see a doctor. In rural areas, medical resources are scarce, and it is expensive for patients to see a doctor.

TABLE 2 Proportion of users in each province.

Province	The proportion of users in each province (%)
Guangdong	11.2
Shandong	7.16
Hebei	6.05
Jiangsu	5.85
Sichuan	5.45
Zhejiang	4.94
Henan	4.94
Liaoning	4.54
Heilongjiang	4.04
Hubei	3.43

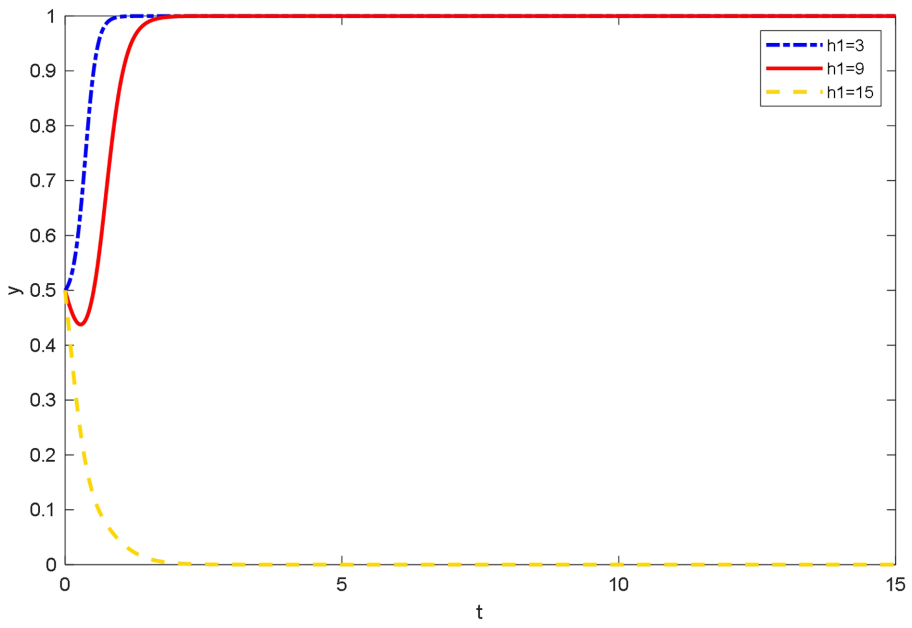

FIGURE 8
Evolutionary trajectory of patient's strategy selection under different online healthcare costs.

Online healthcare services are one of the "standard configurations" of various mobile medical enterprises. This is also one of the most competitive areas. However, only the most reliable medical resources are the most powerful competitive forces. In response, Dr. Wang Jianguo, Vice President of Spring Rain Doctor, released the "Online Diagnosis and Treatment Ability Report" at the meeting. Spring Rain Doctor solves more than 330,000 health problems daily, with an average response time of about 3 min. The source of doctors covers all provinces (autonomous regions, municipalities directly under the Central Government) except Hong Kong, Macao, and Taiwan. Most doctors belong to the 25–45 years age group: senior doctors account for 24%, and other doctors are 38%. In terms of doctor qualifications, Spring Rain Doctor has a strict inspection mechanism. First, it requires four cards, namely, doctor's qualification certificate, a practicing qualification certificate, an ID card, and a bank card showing their real-name information. Then, staff will confirm the doctor's work by phone or offline to determine if the doctor is indeed a working doctor. Simultaneously, the most active and largest group of Spring Rain Doctor comes from the upper first-class hospitals. Figure 9 shows the number of online doctors from the upper first-class hospitals based on the data provided by Artery Network: there are 4,680 doctors, accounting for 62.3% of the total online doctors. This means that the Spring Rain Doctor platform has a large number of high-quality medical resources. In addition, when the doctor serves online, he/she will undergo a strict evaluation mechanism. This shows that the platform's inspection of doctor qualifications is an important factor affecting the platform's online healthcare competitiveness. The findings in Figure 1 are verified.

TABLE 3 The top 10 provinces in population, 2018.

	Province	Population (million)
1	Guangdong	111.69
2	Shandong	100.05
3	Henan	95.59
4	Sichuan	83.02
5	Jiangsu	80.29
6	Hebei	75.19
7	Hunan	68.60
8	Anhui	62.54
9	Hubei	59.02
10	Zhejiang	56.57

On the protection of privacy information, the General Office of the State Administration for Market Regulation, the Secretariat of the Cyberspace Administration of China, Ministry of Industry and Information Technology of the People's Republic of China, and the General Office of the Ministry of Public Security jointly issued the Method for Determining the Illegal Collection and Use of Personal Information by mobile apps on December 30, 2019. Spring Rain Doctor and 10 other apps were reported for illegally collecting and using personal information because they did not clarify to the users to apply for all privacy rights. Users ask for the privacy of their diseases on the Spring Rain Doctor platform to avoid being discovered by acquaintances. After that, the Spring Rain Doctor app launched a privacy policy. Therefore, the protection of the platform's information is an important factor for patients choice of using OHP. If the platform violates the privacy of patient users, it will result in the loss of a large number of users. Thus, the findings in Figure 2 are verified.

In 2016, Spring Rain Doctor, as the largest online consultation platform in the country, sets up the online consultation service function for hardware manufacturers, APPs, websites, WeChat accounts, etc. who have this demand for free. After the opening of

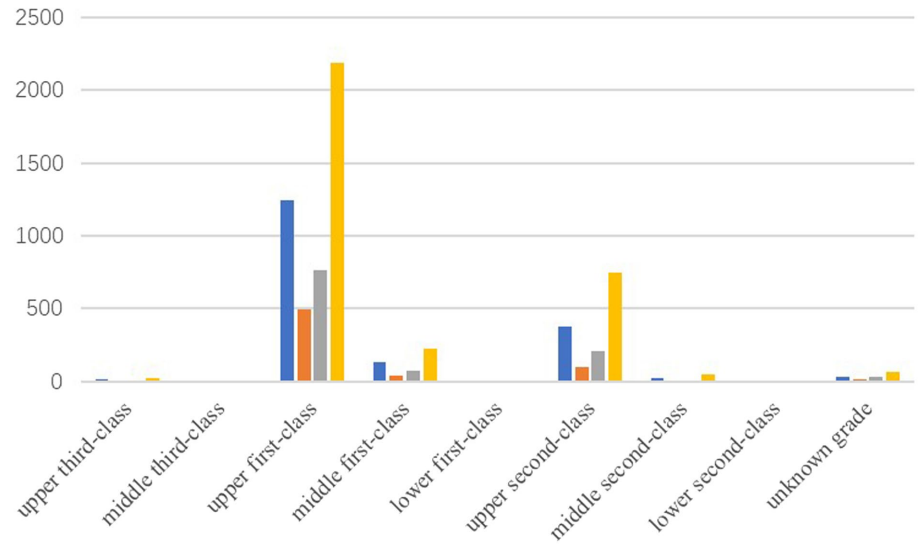

FIGURE 9
Number of online doctors at all levels.

Spring Rain Doctor's online consultation platform, a borderless online consultation portal was used to dig deeper into the platform's online consultation capabilities, strengthen the "foundation" role of this service for mobile healthcare and strive to become the second entrance to health issues of Chinese. With the expansion of Spring Rain Doctor's online healthcare portal, patients can use online healthcare functions more conveniently, and the popularization of its online healthcare functions can be promoted consequently. This shows that Spring Rain Doctor promotes online healthcare as much as possible to increase the probability of patients using OHP. Thus, the findings in Figure 4 are verified.

The doctors were initially interviewed one by one by Spring Rain Doctor's offline team to obtain medical resources. After the brand is being promoted, the number of doctors added through the brand effect exceeded the number of doctors promoted. To obtain a large number of doctor resources, and thus avoid shortage problem of medical resources, Spring Rain Doctor allocates different patients to doctors by layering the needs of users or profiles doctors with different capabilities and services on different platforms. Thus, the doctor and patient can obtain a good match. Simultaneously, to persuade doctors to join, Spring Rain Doctor reduces the registration cost. Spring Rain Doctor's registration and auditing are more user-friendly, especially auditing, supporting everyone to use badges and work permits to replace qualification certificates and some complicated proofs. This reduces the doctor's registration costs and difficulty of usage, while ensuring the authenticity of the doctor's qualifications. This shows that reducing the registration costs of doctors is also a way for the platform to attract doctors to join. Hence, we verified the findings in Figure 5.

Table 4 presents the income of doctors on the Spring Rain Doctor platform as of September 2014 based on the Artery Network data. The doctor's income is divided into two parts. One part is the income obtained by answering users' free consultations, which is paid by the Spring Rain Doctor platform at 1.5 yuan for each reply. The second part is the dynamic pricing of doctors, which is paid by users. Note that since the dynamic pricing part of doctors' income has been changing, the gap between the data and the doctor's actual income may be large. However, it can be seen that the platform attracts more doctors to join through subsidies. This will make the doctors joining the Spring Rain Doctor platform more active and attract a large number of users. In summary, the Spring Rain Doctor platform uses various methods to increase the probability of doctors joining. Thus, the findings in Figure 3 are verified.

TABLE 4 Income of each department on Spring Rain Doctor platform.

Department	Income (million)
Pediatrics	2.48
Otolaryngology	0.56
Obstetrics and Gynecology	2.98
Orthopedics	0.68
Stomatology	0.34
Male Urology	1.56
Cranial Nerve	0.85
Endocrinology	0.45
Internal Medicine	3.84
Dermatology	1.48
Surgery	2.30
Psychology	0.54
Cardiovascular	0.75
Ophthalmology	0.42
Nutritional	0.14
Plastic Surgery	0.40
Chinese Medicine	0.52
Oncology	0.46
Grand Total	20.76

The most important purpose for doctors to join OHP is to increase economic and reputational benefits. Through research, the doctors on the platform of Spring Rain Doctor report that the platform arbitration is biased toward users when disputes occur between doctors and patients. Spring Rain Doctor's doctor evaluation system drop more points than other platforms. It is often the case that doctors did not respond in time and receive bad reviews. These problems have dampened the enthusiasm of doctors. The common point of these problems is that they damage the reputation of doctors. Therefore, the loss of the reputation of doctors is an important factor for doctors to consider joining OHP or not. Thus, the findings in Figure 7 are verified.

Figure 10 shows that the users of Spring Rain Doctor platform are concentrated in the middle of the consumption level. This shows that OHP is more acceptable to the public. However, users below the medium consumption level account for more than 50% of all users. This shows that online healthcare costs are still a key factor for patients to use the Spring Rain Doctor platform. Hence, the findings in Figure 8 are verified.

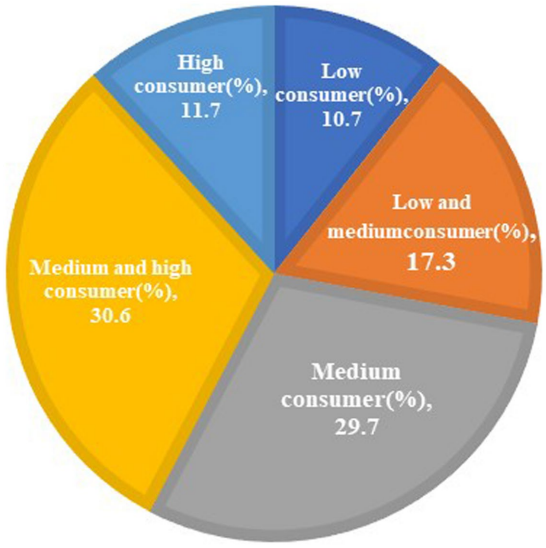

FIGURE 10
Analysis on the consumption ability of Spring Rain Doctor's users.

TABLE 5 Examples of survey questions and interview results.

Question	Result
Do you provide private doctor services?	We can provide the services of a private doctor when we have the time and energy. However, we do not want to take up too much working time.
What is your motivation for online health services?	We can use our free time to increase revenue and reputation.
Have you ever received negative reviews when providing online health services?	The main reason we received bad reviews was that we did not respond in time.
What are your requirements and suggestions for the platform?	Users can clearly explain the complete symptoms at one time during the consultation, thereby saving time.

According to the user survey report of Spring Rain Doctor platform (data from www.woshipm.com), an in-depth interview with doctors is conducted. Examples of survey questions and interview results are shown in Table 5. As shown in Table 5, income and word of mouth are the main motivations for doctors to join OHP, and time cost is the main factor affecting doctors' joining behavior. The findings in Figure 6 are verified.

Based on the above analysis, this article uses the case of Spring Rain Doctor platform to verify the simulation results. This further indicates that the research results are reasonable and have strong practical significance, which is in line with the specific situation of the development of OHP in China.

Discussion

Theoretical implication

We expand and complement the literature on online healthcare. The theoretical implication of this article is as follows.

First, previous studies have explored the factors that affect patients' use of OHP based on the perspectives of PVT (Dong, 2019), social support theory (Tang et al., 2018), PCT (Sun et al., 2022), and UTAUT (Nunes et al., 2019). Some studies have also explored the influencing factors of doctors' participation in OHP based on the perspectives of SDT (Yang et al., 2019c), social capital theory (Lin et al., 2016) and HAPA (Liu and Yu, 2022). However, there is no research that integrates PVT, PCT, and SDT. Based on the above theories, this article incorporates the involved influencing factors into the evolutionary game model, deeply explores the evolutionary mechanism of the behavior of doctors, patients and platforms, further verifies the previous research results, expands the research perspective and theoretical system of online healthcare.

Secondly, previous studies have used evolutionary game theory to explore the behavior of doctors and patients (Chen et al., 2018). Some scholars also constructed an evolutionary game model with users and online health communities as the main participants (Xu et al., 2022). However, no study has constructed an evolutionary game model with doctors, patients and platforms as participants, and explored the adoption conditions and promotion strategies of OHP through the evolutionary game model. This article establishes a tripartite evolutionary game model of doctors, patients and platforms, analyzes the evolutionary stability strategy, and explores the influence of different factors on the evolutionary stability strategy.

Finally, this article combines the theoretical model, numerical simulation and case analysis, and uses the actual case of Spring Rain Doctor to verify the rationality of the model and simulation results. This is of great theoretical significance to the research on OHP application and promotion strategies in China.

Practical implication

This article establishes a game model for the evolution of the players in the online medical field based on the premise of the bounded rationality of the game party. Through the analysis of the three-party evolution game model and the numerical simulation analysis of the evolutionary behavior of doctors, patients, and platforms, we found that the higher the platforms' inspection of doctor qualifications, the more it can strengthen doctor's and patient's trust and promote their participation and use of the platform. Because of the low and medium intensity scrutiny, doctors and patients will choose not to join or use the platform for fear of misdiagnosis. Based on this conclusion, the platform should establish a strict and perfect qualification review mechanism, conduct standardized training, clarify the platform operation standards for doctors, and carry out legal risk education for online healthcare. On the one hand, this can avoid the misdiagnosis of patients, so that patients can get a good consultation experience. Previous studies have proved that the higher the quality of the physician, the higher the levels of patient satisfaction (Wei and Hsu, 2022). On the other hand, the platform can build a brand image and enhance doctors' trust in the platform, which can enable more doctors to participate in OHP. Especially in China, some doctors in second-class hospitals and third-class hospitals have more spare time. The platform can improve the review mechanism to attract these doctors to join, thereby releasing redundant medical resources and reducing the pressure of medical treatment in areas with severe epidemics. Doctors can also gain opportunities for self-improvement, increase reasonable income, and build personal brands. At the same time, the platform can also cover various regions of China more widely.

When the platforms' privacy information protection is moderate or low, doctors and patients tend to choose not to join or use OHP. The greater the protection of the platforms'

information, the more it is able to promote doctors and patients to join and use OHP. Indeed, evidence in the literature indicates patients' hesitation to disclose their personal information online; hence, they switch doctors frequently or switch to an offline hospital visit (Yang et al., 2019b). Thus, the platforms' information protection mechanism is an important factor in doctors' and patients' choice of joining or using OHP. The competent government department should clarify the entry threshold for OHP as soon as possible, improve the information security management system, ensure user information security and privacy, and better play the role of OHP. At the same time, different from previous research conclusions, we believe that privacy information protection not only affects patients' willingness to use, but also affects doctors' participation. We believe that this is because doctors may be harassed by patients due to information leakage, thereby affecting their normal work and life. The platform should improve the security and reliability of the system, and improve the ability to resist hacker attacks. This can not only improve patients' willingness to use OHP, but also encourage doctors to actively participate in OHP by protecting their personal information.

For patients, the richer the medical resources and the higher the quality of the platforms, and the lower the costs of OHP, the more the patients are encouraged to use OHP, thus saving more time and money costs. Previous studies have confirmed that online consultation can provide patients with convenient access to physicians at low cost. Therefore, the platforms should vigorously promote OHP, so that more doctors can actively join in, thereby attracting more patients. OHP can be promoted in many ways, but grassroots doctors are the entrance with the highest conversion rate. Grassroots doctors can connect medical resources and patients to a certain extent, which will be a key part of the cross-border integration of the Internet and the medical industry. The platform should concentrate high-quality resources on grassroots doctors, provide them with certain training opportunities and room to learn, and increase their income.

Meanwhile, the stronger the patients' willingness to use OHP, the more inclined the doctors are to join OHP, thereby obtaining more benefits. This proves that the user traffic of the platform is an important influencing factor for doctors to participate in OHP. According to SDT, doctors are attracted by the economic and social benefits of large numbers of patients (Yang, 2019). Therefore, the core of OHP promotion is the patient. For China, remote cities and township residents are the largest customer groups of OHP. The OHP is just a new form of service in the medical industry. Hence, promoting the popularization of OHP in remote and township residents can reflect the true value of OHP and thus promote the development of the entire mobile medical industry. Therefore, the platforms should increase publicity and advertising in remote cities and rural township residents to attract more medical workers to join the OHP field.

Simultaneously, registration costs, time costs, and reputation loss affect doctors' participation in OHP. Based on PVT, we argue that registration costs can affect physicians' perceived ease of use. The platform should simplify the registration process and make it more user-friendly and convenient. At the same time, if a doctor provides a satisfactory service online, it may simultaneously help him/her gain reputation from both online and offline channels through word of mouth communication (Chen et al., 2020). According to trust theory, doctor's reputation reflects the quality of doctor's service and will have an impact on patient's choice (Gong et al., 2021). Therefore, the loss of a doctor's reputation will harm the doctor's enthusiasm to participate in OHP. Different from previous research conclusions, this paper believes that the reputation loss of doctors comes not only from the negative comments of patients, but also from the unreasonable reputation evaluation mechanism of the platform. Meanwhile, when doctors decide to offer online counseling services in their free time, the number of consultations and extra devoted time is considered negative factors affecting doctors' initiatives (Chen et al., 2020). Without proper stimulating motivators, joining in OHP is stressful for doctors because they have heavy work in hospitals (Yang et al., 2019c). The platform should optimize the function of operation process and add online and offline status for doctors in the graphical consultation interface, so that patients will not give bad reviews to doctors because of the long waiting time. Specifically, the platform should add functions such as message withdrawal, message copying, sending small videos, voice-to-text, and service end countdown, increase the number of remaining conversations in the dialog boxes of both parties and the reply status of the other party, and reduce the upper limit of the number of conversations within the service time limit. We suggest that platforms should use technology to improve the communication efficiency between doctors and patients, reduce the reputation loss and time cost of doctors, and make rational use of limited and valuable medical resources.

Limitations and future research

Although we found some implications of OHP promotion, much work is still needed in the future. For example, we can study the behavior of OHP subjects from the perspective of government regulation and whether free consultation will affect the enthusiasm of doctors. In the future, the government must be included into the scope of OHP subjects to further study the promotion of OHP.

Futhermore, this article does not consider the lags of earnings and returns, as well as the issue of organizational externalities. Future research should consider time as a factor and include the influencing factors of organizational externalities.

Moreover, with the development of Internet digitalization, cutting-edge technologies such as big data, artificial intelligence, blockchain, cloud computing and 5G have unique advantages in the field of digital information. The integration of online healthcare and cutting-edge technology is an inevitable trend. Online healthcare based on emerging technologies not only improves the efficiency of diagnosis and treatment, but also brings a series of risks such as data privacy and accountability. Therefore, future research can combine the characteristics of digital

technology to discuss the promotion strategy and safeguard measures of online healthcare.

Conclusion

In this article, through the establishment of an evolutionary game model of OHP stakeholders, we found that the platforms' qualification inspection of doctors, investment in information protection, initial probabilities of doctors joining and patients using the platform, doctors' registration and time costs and reputation loss, and patients' online healthcare costs all impact the three parties' strategic choices. The three stakeholders (i.e., doctor, patient, and platform) influence each other's behavior. Therefore, the platforms should pay attention to doctor qualification and information protection, improve the platform function and patient evaluation mechanism, and set reasonable prices for online healthcare treatment. Simultaneously, the government should increase supervision, regulate the behavior of the platform, clarify the distribution of responsibility for online healthcare legal issues, and promote the healthy development of OHP. This has significant implications for preventing the spread of COVID-19.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent from the patients/participants or patients/participants legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

Author contributions

LZ: conceptualization, methodology, writing. DL: software. WL: data curation. ZX: conceptualization, software. All authors have read and agreed to the published version of the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Accuracy of steps measured by smartphones-based WeRun compared with ActiGraph-GT3X accelerometer in free-living conditions

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Objectives: The purpose of this study was to evaluate the accuracy and reliability of steps tracked by smartphone-based WeChat app compared with Actigraph-GT3X accelerometer in free-living conditions.

Design: A cross-sectional study and repeated measures.

Methods: A total of 103 employees in the Pudong New Area of Shanghai, China, participated in this study. The participants wore an ActiGraph-GT3X accelerometer during the period of August to September 2019 (Time 1), December 2019 (Time 2) and September 2020 (Time 3). Each time, they wore the ActiGraph-GT3X accelerometer continuously for 7 days to assess their 7-day step counts. The smartphone-based WeRun step counts were collected in the corresponding period when subjects wore accelerometers. The subjects were invited to complete basic demographic characteristics questionnaires and to perform physical examination to obtain health-related results such as height, body weight, body fat percentage, waist circumference, hip circumference, and blood pressure.

Results: Based on 103 participants' 21 days of data, we found that the Spearman correlation coefficient between them was 0.733 ($P < 0.01$). The average number of WeRun steps measured by smartphones was 8,975 (4,059) per day, which was higher than those measured by accelerometers (8,462 ± 3,486 per day, $P < 0.01$). Demographic characteristics and different conditions can affect the consistency of measurements. The consistency was higher in those who were male, older, master's degree and above educated, and traveled by walking. Steps measured by smartphone and accelerometer in working days and August showed stronger correlation than other working conditions and time. Mean absolute percent error (MAPE) for step counts ranged from 0.5 to 15.9%. The test-retest reliability coefficients of WeRun steps ranged from 0.392 to 0.646. A multiple regression analysis adjusted for age, gender, and MVPA/step counts measured during Time 1 showed that body

composition (body weight, BMI, body fat percentage, waist circumference, and hip circumference) was correlated with moderate-to-vigorous intensity physical activity, but it was not correlated with WeRun step counts.

Conclusions: The smartphone-based WeChat app can be used to assess physical activity step counts and is a reliable tool for measuring steps in free-living conditions. However, WeRun step counts' utilization is potentially limited in predicting body composition.

KEYWORDS

ActiGraph-GT3X accelerometer steps, health-related outcomes, WeChat steps, free-living conditions, moderate-to-vigorous intensity physical activity

Introduction

The physical activity guidelines issued by the Bull et al. (1) recommend that adults aged between 18 and 64 years engage in at least 150 min of moderate-to-vigorous aerobic physical activity per week (2, 3). However, more than 1.4 billion people failed to meet this standard, considered as physically inactive. Physical inactivity has become the fourth leading risk factor for human mortality after high blood pressure, tobacco use, and high blood sugar, resulting in more than 5 million deaths worldwide and an economic burden of at least USD 67.5 billion (2, 3).

The ability to measure physical activity scientifically, effectively, and accurately is an essential precondition for health epidemiology and intervention research (4). There are several ways to determine physical activity, including objective methods such as accelerometer, pedometer, and portable metabolic systems, as well as subjective recall questionnaires, such as the International Physical Activity Questionnaire (5) and physical activity logs (5).

As one of the most commonly used accurate measurement tools for measuring physical activity (6), the ActiGraph-GT3X accelerometer can measure steps, sedentary time, and time spent in moderate-to-vigorous intensity physical activity (7). It has been used as a gold standard to evaluate the validity of other measurements of physical activity levels (8). However, accelerometers are difficult to be widely used by the general public to measure steps because they are expensive and require technical expertise, specialized hardware, and cannot be worn for a long time, and the measurement results cannot provide immediate feedback (9).

Walking is one of the most popular types of moderate intensity physical activity. It has substantial importance to decrease chronic disease (such as obesity and CVD) and reduce medical expenditures (10). Step counts taken in daily life are a basic parameter of physical activity evaluation (11). Moreover, steps measured by devices are objective and intuitive, and using this measurement indicator to evaluate the standard of physical activity is quite suitable for the public to understand. Steps are widely accepted by researchers, practitioners, and the general public for assessing, tracking, and communicating the amount of physical activity (12–14).

WeChat, which was researched and developed by Tencent, is the most popular multi-purpose social networking platform in China, with about 1.1 billion monthly active users in 2018 (15). WeRun is an official account with step-counting function embedded in the WeChat app. After following WeRun, customers can obtain the step counts they take at any time measured by built-in accelerometer of their smartphones and share the step counts over the cloud through a secure server (16). WeRun in WeChat app is promising and cost-effective in step measuring, because it allows users to access their data anytime, anywhere (17). Christoph et al. (18) pointed out that short and intermittent bouts of activity may cause inaccuracies in the smartphone-counted steps, thus limiting the validity of smartphones in unconstrained conditions. The previous studies provided useful reference to the validity of devices used to measure physical activity, but they have several limitations: first, the reliability of some research was assessed under laboratory conditions but not free-living environments (19–21). In addition, these studies were based on cross-sectional data collection and the credibility of these findings needs further longitudinal research (22, 23). Physical activity in a short period of time cannot fully represent the long-term physical activity levels. It is well known that physical activity is not constant (24). Present studies have found that some factors can influence physical activity levels, including gender, age, seasons, and travel modes. For instance, active modes of transportation, such as walking, cycling, and public transportation, are associated with more steps and energy expenditure than personal motor vehicle travel (25, 26). These factors may affect the accuracy of the WeChat-counted steps.

Abbreviations: MVPA, moderate-to-vigorous intensity physical activity; BMI, body mass index.

Therefore, our objectives for this study were to (1) verify the consistency of the smartphone-based WeRun steps and the Actigraph-GT3X accelerometer-counted steps of the same subjects under different characteristics and conditions (travel modes, seasons, and weekday/weekend) through measurements of seven consecutive days at multiple time points (2) examine the test-retest reliability of the WeRun steps and (3) compare the predictive value of WeRun steps and moderate-to-vigorous intensity physical activity (MVPA) measured by the ActiGraph-GT3X accelerometer for health-related outcomes.

Methods

Sample size

The total sample of the study was determined by using a single population formula by assuming a 5% level of significance, 0.3 margin error and taking 35% proportion of physical inactivity. Considering a 20% non-response rate, the final sample size was 100.

$$N = \frac{P\ (1 - P)\ Z^2{}_{1-\alpha/2}}{d^2}$$

Participants

In this study, 103 participants were included from eight workplaces in the Pudong New Area of Shanghai, China. The inclusion criteria were as follows: (a) healthy adults without physical disabilities or diseases that impede movement; (b) own and regularly use a smartphone that they are willing to use to register a WeChat account and follow the WeRun official account; and (c) voluntary participation. The exclusion criteria were the following: (a) employees with heart or mental illness who are not suitable for exercise (based on self-report); (b) pregnant women; and (c) employees who intend to resign from their current workplace within 1 year. Eligible participants were provided with detailed information about the purpose and procedures of the study, and signed their informed consent. All study procedures were approved by the Shanghai Municipal Center for Disease Control and Prevention Ethical Review Committee (ChiCTR1900023813).

Measurements

A cross-sectional study and repeated measures was conducted. ActiGraph-GT3X accelerometers were worn during the period of August to September 2019 (Time 1), December 2019 (Time 2), and September 2020 (Time 3), each time for 7 days (five workdays and two weekends). Smartphone-based WeChat application-counted steps of the participants in the corresponding time period were collected. Daily step counts were measured by WeRun, which is a social fitness plugin built in WeChat (informed consent of subjects). The ActiGraph-GT3X accelerometer was used to measure the physical activity of the subjects for seven consecutive days, including step counts and levels of moderate-to-vigorous physical activity. The original data of the accelerometers was collected at frequency of 30 Hz. Before the test, the accelerometer was initialized; the correct way of wearing the accelerometer and matters needing attention were introduced; and informed consent was signed.

Specific requirements for wearing it are as follows: (a) the accelerometers are fixed at the waist and positioned on another axillary line at the iliac crest level of the right or left hip (equipped with a flexible and adjustable elastic belt); (b) time of wearing: the accelerometer should be worn for seven consecutive days except during sleeping, bathing, or swimming. The accelerometers recorded activity during the day, and were removed at night. If the number of days is <3 days a week or the time of wearing is <8 h a day, the data is invalid. The ActiGraph-GT3X accelerometer data were extracted at an interval of 60 s.

The participants followed the official account of WeRun and completed registration on the WeChat online platform. They checked-in on the online official account of WeChat. The WeRun platform can obtain the daily data of the participants' WeRun step counts. The days with <1,000 steps were considered as invalid wearing days, and steps were truncated at 30,000 steps/day. In addition, each time the accelerometer was issued, participants were asked to fill out a questionnaire and undergo a physical examination. The data were collected by trained research assistants. The content of the questionnaire mainly included demographic characteristics (birth year, gender, age, marital status, education level, years of work, and travel modes used in the last week). Physical examination comprised height, weight, body fat percentage, waist circumference, hip circumference, systolic blood pressure, and diastolic blood pressure. This study assumed that the height of the participants did not change during the study. The participants' height was only measured once during inclusion in the study. Height was measured to the nearest 0.1 cm, and body weight was measured to the nearest 0.1 kg. Participants were required to be barefoot when measured for height. Height and weight were measured using the TCS-150 electric scale and Omron HBF-214 Body Composition Monitor Scale, respectively, and body fat percentage was measured using the reliable and valid Omron HBF-214 Body Composition Monitor Scale (Omron based on bioelectrical impedance technology is frequently used to measure body composition) (27). Blood pressure was measured by an electronic sphygmomanometer (Citizen, Model PW332) after the participants remaining relaxed for 2 min. The body mass index (BMI) was calculated by dividing an individual's weight in kilograms by the square of their height in meters (kg/m^2).

Data analysis

ActiLife 6.1.4 is a specialized software for ActiGraph-GT3X accelerometer data processing. The test data of step counts were downloaded to a computer at 60 s intervals and moderate intensity physical activity and vigorous intensity physical activity were downloaded at 10 s intervals (6, 28) through ActiLife 6.1.4, then added them up to MVPA [Based on cut points (29)]. WeRun imports step count data to Microsoft Excel® 2019 from a smartphone's built in accelerometer, and during the study participants share their daily steps *via* a cloud-based secure server. The data were subsequently analyzed in IBM SPSS version 25.0 and SAS version 9.4. The descriptive statistics of the basic demographic characteristics were expressed in terms of proportion (%) and Mean (SD). Bland-Altman plot was used to examine the agreement on step counts measured by smartphone-based WeRun and accelerometer (steps/day). The Shapiro–Wilk test was used to test the normality of continuous variables, and the Spearman correlation coefficient was calculated to determine the relationship between the number of WeRun steps/day and the number of accelerometer steps/day. Mean absolute percentage error (MAPE, [estimated values–measured values]/measured values × 100%) and paired samples *t*-test were calculated to quantify the differences between the smartphone-based WeRun and accelerometer (the criterion measures) at the individual level. Pearson correlation analysis was conducted to calculate the intra class correlation that can be defined as the degree of consistency among three periods. Multivariate regression analysis was used to determine the correlation between health-related outcomes (body weight, BMI, body fat percentage, waist circumference, hip circumference, and blood pressure) and moderate-to-vigorous intensity physical activity and WeRun step counts (adjusted for age, sex, and MVPA or step counts measured by Time 1). MVPA, as well as Step counts measured by WeChat app and accelerometers, were acquired during each period and the three measures were used to calculate the coefficient of association, paired samples *t*-test and regression analysis. $P < 0.05$ was considered statistically significant.

Results

Demographic characteristics of the participants

The demographic characteristics of the participants are shown in Table 1. A total of 103 employees participated the study with mean age of 39.4 ± 10.4 years, nearly two thirds of the participants were female, more than 75% had a college junior degree or higher, and more than four in five were married. At baseline, less than half of the participants were classified as normal weight, 41.7% overweight and 14.6% obese based on BMI risk classification specific to Asian populations. Based on body fat percentage and blood pressure, more than 50% were classified at higher risk.

TABLE 1 Participants characteristics at baseline.

Variables	*n* (%)/mean (SD)
Gender	
Male	34 (33.1)
Female	69 (66.9)
Age (year)	
≤35	40 (38.8)
35–45	33 (32.1)
>45	30 (29.1)
Marital status	
Single/divorced/widowed	19 (18.5)
Married	84 (81.5)
Working year	
≤5	44 (42.7)
5–15	34 (33.1)
>15	25 (24.2)
Education	
High school graduate or below	16 (25.2)
Junior college and Undergraduate	61 (59.3)
Master degree or above	16 (15.5)
Body weight	62.7 (11.0)
Body Mass Index (Kg/m^2)	
Low risk (<23)	42 (40.8)
Increased risk (23–27.4)	43 (41.7)
High risk (≥27.5)	15 (14.6)
Body fat percentage	
Lower risk (≤20% for men and ≤ 30% for women)	35 (34.0)
Higher risk (> 20% for men and > 30% for women)	67 (65.0)
Waist circumference (cm)	80.7 (9.3)
Hip circumference (cm)	95.2 (6.6)
Blood pressure	
Lower risk (SBP<120 mmHg and DBP<80 mmHg)	50 (48.5)
Higher risk (SBP ≥120 mmHg or DBP 80 ≥mmHg)	52 (50.5)
Moderate-to-vigorous intensity physical activity (MVPA) (min/day)	37 (23)

Influencing factors of the correlation coefficient

Figure 1 shows the scatter plot of the average daily steps measured by the ActiGraph-GT3X accelerometer and the WeChat app. It can be seen from the scatter plot that there was a significant positive correlation between the ActiGraph-GT3X accelerometer and WeChat app. Similarly, correlation

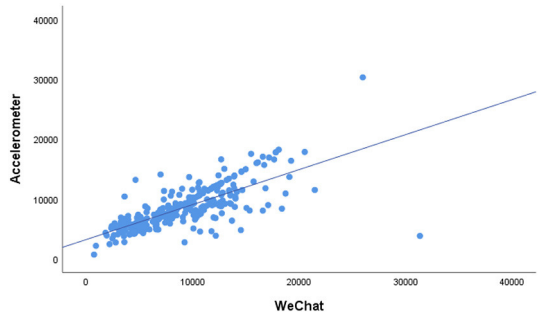

FIGURE 1
Scatter plot of the accelerometer and WeRun steps/day.

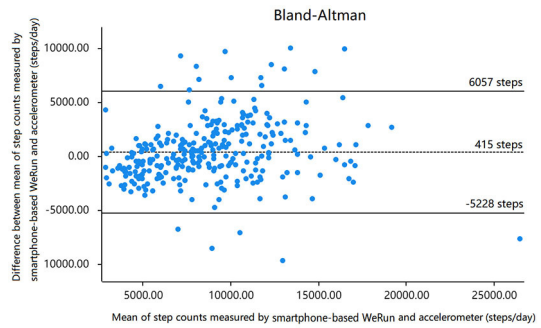

FIGURE 2
Agreement on step counts measured by smartphone-based WeRun and accelerometer (steps/day).

between WeRun and accelerometer was found in Bland-Altman (Figure 2). As shown in Table 2, the average step counts per day measured by the WeChat app and ActiGraph-GT3X accelerometer were 8,974 (4,203) and 8,462 (3,486), respectively. The overall correlation coefficient between the accelerometer and WeRun was 0.733 ($P < 0.01$).

The correlation coefficient is different for different demographic characteristics and different conditions. There was a stronger consistency in males ($r = 0.827$, $P < 0.001$) and people who were over 45 years old ($r = 0.799$, $P < 0.001$). The correlation was the weakest (0.770) among college and bachelor's degree graduates compared with those with high school or below (0.835) certifications and master's degree or above (0.859). The correlation between working years from 5 to 15 years was the strongest (0.937). Participants who travel by personal motor vehicle showed the weakest correlation, at just 0.548. The correlation coefficient on weekdays (0.835) was higher than that on weekends (0.752). The correlation between the accelerometer steps and the WeRun steps was also affected by time, with August at 0.998, September at 0.762 and December at 0.778. Mean absolute percent error (MAPE) for step counts ranged from 0.5% to 15.9%. The magnitude of MAPE was highest for December (Table 2).

Reliability estimate

For test-retest reliability, the intraclass correlation coefficients ranged from 0.392 to 0.646. The details are shown in Table 3. WeRun steps measured in Time 1 and Time 2 ($r = 0.646$) have higher retest reliability than Time 1 and Time 3 ($r = 0.478$), Time 2 and Time 3 ($r = 0.392$).

Regression analyses of moderate-to-vigorous intensity physical activity and smartphone-based step counts with health-related outcome

MVPA was measured by the ActiGraph-GT3X accelerometer. Table 4 presents the results of multiple regression analysis that we used to examine the predictive relationships among WeRun steps and MVPA with health-related outcomes (weight, BMI, body fat proportion, etc.). Health-related outcomes were considered the dependent variables and WeRun steps/MVPA were considered the independent variable. We controlled for the effects of gender, age, and WeRun steps/MVPA at baseline. Body composition showed a significant negative association with high levels of MVPA. The results suggest that each additional minute of moderate-to-vigorous intensity physical activity can reduce body weight by 0.14 kg, BMI by 0.053, body fat percentage by 0.053, waist circumference by 0.119 cm, and hip circumference by 0.090 cm. However, no significant relationships between WeRun step counts and health-related outcomes (body weight, BMI, body fat percentage, waist circumference, hip circumference, waist–hip ratio, and blood pressure) were observed ($P > 0.05$).

Discussion

The results of this study indicated that the step counts estimated by the smartphone-based WeChat application were generally consistent with the step counts obtained by the ActiGraph-GT3X accelerometer, with a correlation coefficient of 0.733 ($P < 0.01$). Steps measured by the WeRun app were higher by 513 steps per day than those measured by the ActiGraph-GT3X accelerometer ($P < 0.01$). To our knowledge, this is the first longitudinal study on the accuracy of the smartphone-based WeChat app step counts for collecting different demographic characteristics under different conditions. Our study results are consistent with those of Victor et al. (30) and Janaine et al. (22). The results show that WeRun steps measured

TABLE 2 Influencing factors of the correlation between WeRun step counts and ActiGraph-GT3X accelerometer step counts.

Variables		WeRun steps/ mean (SD)	Accelerometer steps/ mean (SD)	*r*	MAPE (%)
	General	8,975 (4,059)	8,462 (3,486)	0.733**	6.1**
Gender	Male	10,343 (3,250)	9,290 (2,703)	0.827**	11.3**
	Female	8,472 (3,619)	8,071 (2,763)	0.787**	5.0
Age (year)	≦35	8,668 (3,431)	8,219 (2,890)	0.735**	5.5
	35–45	10,077 (5325)	9,108 (4,060)	0.782**	10.6*
	>45	8359 (4,302)	8073 (3354)	0.799**	3.5
Education	High school and below	11,897 (4,174)	10,727 (3,261)	0.835**	10.9**
	Junior college and Undergraduate	7,790 (2,838)	7,511 (2,221)	0.770**	3.7
	Master degree or above	9,368 (2,478)	8,404 (1,701)	0.859**	11.5*
Working year	≦5	8,136 (2,835)	8,098 (2,362)	0.789**	0.5
	5–15	10,416 (4,076)	9,310 (3,661)	0.937**	11.9**
	>15	8,891 (3,681)	7,948 (2,794)	0.780**	11.7**
Travel mode	Walking	10,247 (1,128)	9,237 (859)	0.932**	10.9**
	Bicycle	9,489 (1,298)	9,714 (837)	0.857**	2.3
	Public transportation	8,364 (463)	7,959 (316)	0.927**	5.1
	Personal motor vehicle	8,400 (761)	7,713 (475)	0.548*	8.9
Working status	Weekend	7,792 (3,647)	7,434 (2,820)	0.752**	4.8
	Weekday	9,636 (3,880)	8,844 (3,104)	0.835**	9.0**
Month	August	9,373 (5,831)	9,620 (5,887)	0.998**	2.6
	September	8,182 (5,835)	7,759 (4,111)	0.762**	5.5**
	December	6,455 (4,494)	7,674 (3,947)	0.778**	15.9**

*$P < 0.05$, **$P < 0.01$ (two-tailed). In both cases (* and **), the correlation and paired samples t-test was statistically significant.

by smartphone are highly correlated with accelerometer-measured steps. However, WeRun overestimated steps generally, and whether WeRun steps can be used to evaluate the steps precisely is affected by some factors, such as gender, age, education, working years, working status and seasons, etc. (31). However, these findings are contrary to those of some studies, such as Höchsmann et al. (18) and Piccinini et al. (13). These latter studies argued that smartphone-based apps were unreliable for measuring step counts. However, it should be noted that the wearing time and measuring environment could cause differences among studies. Those studies' data were collected in specific conditions (running machine, playground, corridor, etc.) and not in a free-living environment. Moreover, participants' wearing time was no more than 8 h per day, and some individuals just wore the accelerometer for several minutes every time. These were possible reasons for the apparent discrepancies between our findings and those of the aforementioned studies (32). Our study found that the step count correlation between the smartphone-based WeChat application and the ActiGraph-GT3X accelerometers was not constant under different users' characteristics and conditions. We found that gender, age, modes of travel, working status, and other factors can affect the consistency and accuracy of the WeChat app and the Actigraph-GT3X accelerometer.

With the popularity of smartphone-based WeRun step counts in research and practice, accuracy and precision are critical, especially under diverse conditions. According to our findings, the correlation coefficient is higher in males than females (0.827 vs. 0.787, respectively). The number of WeRun steps of males was more than that of females and the consistency was stronger in males, which may be due to wearing time and wearing position. For example, females took fewer steps than men regardless of age, a finding that may be partly due to differences in mobile phone carrying habits and locations. Females' apparels, especially dresses, rarely have pockets for smartphones. Most females have the habit of carrying their mobile phones in their bags when they go out. The positioning of devices for monitoring steps will affect the accuracy of the devices (33, 34). The correlation was stronger when mobile phones were placed closer to the body during longer daytime activities (32, 33). With the increase of age, the correlation between the WeRun steps and the accelerometer steps gradually increased. It may be related to changes in lifestyles and intensity of their physical activity with age (35).

TABLE 3 Reliability of the WeRun steps.

Evaluation index		WeRun steps (Time 1)	WeRun steps (Time 2)	WeRun steps (Time 3)
WeRun steps (Time 1)	ICC	1		
WeRun steps (Time 2)	ICC	0.646**	1	
WeRun steps (Time 3)	ICC	0.478**	0.392**	1

**$P < 0.01$ (two-tailed).
ICC, Intraclass correlation coefficient.

TABLE 4 Multiple regression analysis of health-related outcomes and WeRun step counts/MVPA.

Variables	WeRun steps	MVPA
	B (95% CI)	B (95% CI)
Weight (Kg)	−2.563 (−7.196–2.071)	−0.14 (−0.246 −0.035)*
BMI	−1.251 (−2.924–0.422)	−0.053 (−0.091−0.014)*
Body fat percentage	−1.206 (−3.174–0.762)	−0.053 (−0.099 −0.007)*
Waistline (cm)	−1.598 (−4.820–4.500)	−0.119 (−0.211 −0.026)*
Hipline (cm)	−2.886 (−6.025–0.54)	−0.090 (−0.162 −0.017)*
Waist-hip ratio	0.009 (−0.16–0.034)	<0.001 (−0.001–<0.001)
SBP (mmHg)	−3.121 (−10.313–4.070)	0.003 (−0.169–0.176)
DBP (mmHg)	−0.158 (−5.388–5.072)	−0.004 (−0.125–0.118)

*$P < 0.05$ (the regression coefficient was statistically significant).

In addition to the characteristics of the subjects, different conditions may also affect consistency. Compared with working days, the number of steps were lower and the correlation coefficient was weaker than weekends. It may be that the time of carrying smartphones and wearing the ActiGraph-GT3X accelerometer was different between weekdays and weekends, thus causing the correlation between the ActiGraph-GT3X accelerometer and the WeChat app on weekends to be lower than that on weekdays (36). For the different travel modes, the consistency of walking was best, and personal motor vehicle had particularly weak correlation due to the location of the mobile phones (37).This is due to step-counting principle of built-in accelerometer of smartphone, which is affected by the location of the phone. Therefore, it was not accurate and precise to evaluate WeRun steps when traveling by a personal motor vehicle.

The test-retest reliability coefficients of the WeRun steps ranged from 0.392 to 0.646. WeRun steps measured in Time 1 and Time 2 ($r = 0.646$) have higher retest reliability than Time 1 and Time 3 ($r = 0.478$), Time 2 and Time 3 ($r = 0.392$). This may be that several-month intervals for the test-retest reliability were selected in this study. Besides, previous studies documented that walking behavior is affected by the COVID-19 and weather (16, 38). This study was conducted in summer and winter, and the weather effects (e.g., rain, wind) during the data-collected would limit people's travel to a certain extent (36). The third point in time for data collection occurred after the COVID-19, and walking behavior can be highly variable (16). Therefore, objective factors such as time and epidemic situation may hinder the reliability of WeRun steps.

Steps measured by ActiGraph-GT3X accelerometer and smartphone are consistent, but there are differences in the predictive value of body composition. Multivariate regression analysis controlling age, gender, and MVPA/WeRun steps at baseline showed that moderate-to-vigorous intensity physical activity can affect body composition, such as weight, BMI, body fat percentage, waist circumference, hip circumference, and waist–hip ratio ($P < 0.05$), but the WeRun step counts could not. This may because the ActiGraph-GT3X accelerometer has the function of distinguishing the intensity of physical activity, whereas WeRun step counts do not. It might be due to a measurement gap during exercising or other vigorous activities performed without the smartphone (39). Besides, smartphones with a built-in accelerometer can only track steps according to a user's movement and cannot monitor the user's type and quality of movements performed, such as jogging and walking, even though jogging consumes more energy than walking (40). As a result, there is no statistical significance in the correlation between body composition and the WeRun step counts. Although the step measurements are similar between the WeChat app and the accelerometer, WeRun steps cannot replace the role of the accelerometer in predicting body composition. The accelerometer not only tracks the number of steps but also monitors different intensities of physical activity and their duration, thus providing a more direct and clear assessment of energy expenditure. The results of a meta-analysis by Hamer et al. suggested that moderate-to-vigorous intensity physical activity is more effective in improving body composition than low-intensity physical activity (41). However, WeRun-measured step counts have a good prospect in long-term monitoring and supporting a beneficial change in the trend of the population's physical activity.

As economic and technological advances increase the focus on health, devices that track physical activity, such as pedometers, are steadily improving in accuracy and precision. However, owing to the impacts of price, battery life, comfort, applicability, water resistance, and other factors, the use of step-recording equipment by the public is limited (42). WeChat, which is one of the most popular social apps in China, has a feature to track the number of steps. However, the smartphone-based WeChat app cannot assess the duration and intensity of physical activities. In fact, how to improve the accuracy of step counts is still a very important challenge. Smartphones with a built-in accelerometer and GPS-positioning function are popular in the general public and a good tool to collect daily steps without affecting people's lifestyles, which has great prospects in personal health management. WeChat-counted

steps combined with self-conditioning can enhance physical activity management.

Strengths and limitations

This study has several strengths. One of the strengths is that all data were collected under free-living conditions. Participants maintained their daily routines, which is difficult to replicate in controlled environments. Another strength is that the same participants were measured at multiple time points. A third strength is that it analyzed the influence of different conditions and demographic characteristics on consistency. Furthermore, health-related outcomes were measured, and the verification of WeRun step counts was examined more comprehensively, which makes the results more reliable.

One limitation of this study is that the sample size was not large. Second, there was no record of the time for which the participants wore the ActiGraph-GT3X accelerometer or carried smartphones in a day. Third, the use of the ActiGraph-GT3X accelerometer as the gold standard (43) could be seen as a limitation, but it is the reference tool for assessing physical activity in real life for 21 days and has well-established validity (44). Fourth, the long and unequal interval between the second and third measurement may affect the results of the study. Finally, according to the research results of Mitesh et al., there is a difference in the step measurement between the Android and iOS operating systems of smartphones (45), and there is a lack of investigations on step count accuracies measured by different smartphone brands, models, and operating systems.

Conclusion

Under free-living conditions, the steps tracked by the WeChat smartphone app are highly correlated with the number of steps monitored by the ActiGraph-GT3X accelerometer, which is a reliable tool for measuring steps in daily life. However, different demographic characteristics (e.g., age, gender, education) and conditions can influence the accuracy of the WeChat app. The steps measured by the WeChat app may not replace the role of the moderate-to-vigorous intensity physical activity measured by the ActiGraph-GT3X accelerometer in predicting body composition.

Data availability statement

The datasets presented in this article are available from the corresponding author on reasonable request.

Ethics statement

The studies involving human participants were reviewed and approved by the Shanghai Municipal Center for Disease Control and Prevention Ethical Review Committee (ChiCTR900023813). The patients/participants provided their written informed consent to participate in this study.

Author contributions

YJ, TL, JW, and YS conceptualized the idea. YJ, TL, and MC obtained funding. QYao and SS conducted data analysis. QYao drafted the paper. All authors participated in reviews, interpretation of analysis results, and critical revision of the paper. All authors approved the final version for submission.

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Conflict of interest

YS was employed by Winning Ringnex Technology (Shanghai) Co., Ltd.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Effect of mobile health reminders on tuberculosis treatment outcomes in Shanghai, China: A prospective cohort study

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Background: Poor adherence increases the risk of unfavorable outcomes for tuberculosis (TB) patients. Mobile health (mHealth) reminders become promising approaches to support TB patients' treatment. But their effects on TB treatment outcomes remain controversial. In this prospective cohort study, we evaluated the effect of the reminder application (app) and the smart pillbox on TB treatment outcomes compared with the standard care in Shanghai, China.

Methods: We recruited new pulmonary TB (PTB) patients diagnosed between April and November 2019 who were aged 18 or above, treated with the first-line regimen (2HREZ/4HR), and registered at Songjiang CDC (Shanghai). All eligible patients were invited to choose the standard care, the reminder app, or the smart pillbox to support their treatment. Cox proportional hazard model was fitted to assess the effect of mHealth reminders on treatment success.

Results: 260 of 324 eligible patients enrolled with 88 using standard care, 82 the reminder app, and 90 the smart pillbox, followed for a total of 77,430days. 175 (67.3%) participants were male. The median age was 32 (interquartile range [IQR] 25 to 50) years. A total of 44,785 doses were scheduled for 172 patients in the mHealth reminder groups during the study period. 44,604 (99.6%) doses were taken with 39,280 (87.7%) monitored by the mHealth reminders. A significant time-dependent downward linear trend was observed in the monthly proportion of dose intake (p <0.001). 247 (95%) patients were successfully treated. The median treatment duration of successfully treated patients in the standard care group was 360 (IQR 283–369) days, significantly longer than those in the reminder app group (296, IQR 204–365, days) and the smart pillbox group (280, IQR 198–365, days) (both p <0.01). Using the reminder app and the smart pillbox was associated with 1.58 times and 1.63 times increase in the possibility of treatment success compared with the standard care, respectively (both p <0.01).

Conclusion: The reminder app and the smart pillbox interventions were acceptable and improved the treatment outcomes compared with the standard care under the programmatic setting in Shanghai, China. More high-level evidence is expected to confirm the effect of mHealth reminders on TB treatment outcomes.

KEYWORDS

digital health, mobile application, medication monitor, tuberculosis, treatment outcome

Introduction

Tuberculosis (TB) remains one of the leading causes of death worldwide (1). The treatment success rate for TB patients treated with first-line regimens was steadily around 85% in recent years, globally (1). However, the standard first-line regimen requires people to take 2 to 4 medicines daily for at least 6 months (2). Poor adherence to anti-TB chemotherapy increases the risks of morbidity, mortality, drug resistance and results in unfavorable outcomes (3). The World Health Organization (WHO) has recommended directly observed therapy (DOT) for decades to promote adherence to TB treatment. DOT significantly increased the rates of treatment success, adherence, sputum smear conversion and lowered the rate of development of drug resistance when compared with self-administered therapy (SAT) (4). But it's labor-intensive for both patients and healthcare providers (5), which makes it unfeasible to cover all patients in high TB burden countries.

China accounted for 8.5% of the 9.9 million estimated incident TB cases in 2020, ranking second in the world (1). Although the TB prevalence has been halved due to the implementation of the DOTS strategy from 1990 to 2010 (6), treatment adherence interventions are still challenging. A systematic review revealed that 52% of TB patients were on SAT, and 28% were observed by family members (7). In Shanghai, TB patients are managed by doctors from community health centers (CHC) (8). Due to the limit of health care resources, they usually train a family member to conduct DOT and check off the medication calendar every day. They visit patients regularly to evaluate their adherence and offer medical support. Therefore, it is hard for them to discover the non-adherence and take essential interventions in time. The increase of migrants and the aging population makes patient management more challenging since they often live alone and no qualified observers could be sought, indicating the urgent need for innovative adherence interventions to complement DOT.

WHO recently encouraged using digital health technologies such as short message service (SMS), video-supported treatment (VOT), and medication event monitoring systems (MEMS) to help TB patients complete treatment (2, 9). In China, an electronic medication monitor (EMM) without real-time data transmission has been used in 138 counties in three provinces (10). A cluster-randomized trial proved that the EMM improved medication adherence in TB patients while SMS did not (11). But the effect of the EMM and SMS on TB treatment outcomes remains controversial (10, 12–15). Additionally, the EMM cannot provide real-time medication adherence data which may impede timely intervention from healthcare providers.

With the rapid popularization of mobile technology, mobile health (mHealth) interventions such as reminder apps and devices with access to mobile phone networks become promising approaches to improve treatment adherence (16–18). We implemented a mHealth reminder system for TB that integrated the reminder application (app), the smart pillbox, and the management app/website to support TB patients' treatment in Songjiang, Shanghai since 2018.

In this prospective cohort study, we aimed to evaluate the real-world effect of two mHealth reminders, i.e., the reminder app and the smart pillbox, on TB treatment outcomes compared with the standard care in Shanghai, China.

Materials and methods

Study setting and population

Shanghai is a 24-million-population metropolitan in China with a high proportion of internal migrants and an aging population. Internal migrants are those who migrate from their hometown to Shanghai, without a Shanghai household registration status. In Songjiang District, internal migrants accounted for 60% of the population in 2019, and 29% of residents aged 60 and above (19). TB patients were diagnosed in designated TB hospitals as per the provincial TB control program described before (20). Drug-susceptible TB patients were usually given the standard first-line regimen (2HREZ/4HR, isoniazid, rifampin, ethambutol, and pyrazinamide for 2 months, followed by isoniazid and rifampin for 4 months) at the beginning of treatment, and ordered to visit the TB hospital monthly to get medicine and conduct monitoring. Attending doctors evaluated the clinical efficacy at the end of the sixth month based on radiological and bacteriological data. The duration of anti-TB therapy was commonly extended month by month if the clinical efficacy was not favorable as the judgment of doctors. The treatment duration was typically no more than 1 year and the outcome was determined at the end of treatment by doctors. All pulmonary TB (PTB) patients living in Songjiang were mandatorily registered at Songjiang District Center for Diseases Control and Prevention (CDC) *via* a provincial TB management information system (TBMIS). Sixteen CHCs in Songjiang were in charge of the management of anti-TB treatment and also the care for TB patients under the supervision of Songjiang CDC. Residents, as well as migrants with Shanghai Residency Card, were reimbursed for the out-of-pocket expense (i.e., uncovered by medical insurance) of anti-TB drugs and essential examinations (e.g., chest X-ray, sputum bacteriological tests, blood biochemistry) at about 3,000 RMB ($474) on average.

Study design

We conducted a prospective cohort study with the standard care group, the reminder app group, and the smart pillbox group in Songjiang, Shanghai. Newly diagnosed PTB patients between April and November 2019 were consecutively recruited if they were aged 18 or above, treated with the first-line regimen (2HREZ/4HR), and registered at Songjiang CDC. Patients with nontuberculous mycobacterial disease, rifampicin-resistant TB, HIV/AIDS, malignant tumors, renal failure, liver cirrhosis, mental diseases, and communication disorders were excluded. All sixteen CHCs in Songjiang participated in this study. All eligible patients were invited to participate and voluntarily choose one group to support their treatment. The use of the smart pillbox was completely free of charge. Patients choosing the reminder app group required that they or one of their family members owned smartphones with an internet connection paid for by themselves.

The mHealth reminder system

The mHealth reminder system was developed by Beijing SINOVO POWER Technology Company (China) with in-depth customization

by Shanghai Municipal CDC (Figure 1). The system provided two reminders for patients (i.e., the reminder app and the smart pillbox) and one management app as well as the management website for CHC doctors and CDC staff. Both of the apps were in Chinese and compatible with Android and iOS. TB patients could choose to use either of the two reminders but joint use was not allowed.

The smart pillbox was equipped with a 2G subscriber identity module card (SIM card) to connect to the internet, a chargeable battery to support 1-month use, and three LED lights with one beeper to indicate the work status and send reminders. It could contain four bottles of first-line drugs, which was the 1-month quantity (size: 18.5 cm × 12.5 cm × 6.5 cm). The pillbox could set at most three reminders a day using the management app or website. It beeped with the LED lights flashing at the scheduled time to remind patients to take medicine. If not opened, It would keep beeping and flashing for 1 min every 10 min in the following 30 min. Once opened, it stopped beeping and flashing and sent a signal to the server instantly to confirm the drug intake. If opened within 1 h before the scheduled time, a confirmation signal would be sent to the server and this reminder would not take effect. It would also remind patients if it was not closed properly or the battery was low. Its work status was transported to the server in real-time so that the CHC doctors could be informed and provide in-time help.

The reminder app could also set at most three reminders a day using the management app or website. It pushed drug intake alerts at the scheduled time every day and the patients tapped on the "confirm" button if they had taken the prescribed drugs. The alert would not be sent if patients had confirmed intake within 1 h before the scheduled time. It also provided functions of the drug intake calendar review, healthcare visit prompts, side effect reports, health education materials, patient forum, and communication with CHC doctors.

The management app pushed alerts late in the day (usually at 3 p.m.) if the patient had never opened the pillbox or confirmed drug intake in the app so that CHC doctors could take additional interventions. They could also check the real-time adherence reports, collect the management records, and conduct data analysis using the management app or by logging in to the management website to assist their supervision.

Study procedures

Once PTB patients were diagnosed at the TB hospitals and registered at Songjiang CDC, the CHC doctors from the community where the patients lived would be informed instantly through the TBMIS and were required to meet the patients within 3 days to build the relationship and screen patients who met the enrolment criteria. The eligible patient was invited by CHC doctors to choose one study group to participate in. Enrolled patients were asked to complete a questionnaire about demographic information and followed for the whole treatment. The CHC doctors routinely appointed a family member as the treatment observer, who was trained to remind the patients to take daily medicine and visit the TB hospital monthly. Patients who lived alone were under self-administered treatment. The CHC doctors visited patients every 10 days during intensive phases and once a month during continuous phases to evaluate their adherence by checking medication calendars, medical records, and residual pills. They also offered medical support including instructions about adverse drug reactions, infection control, nutrition, and psychological problems. Patients were encouraged to contact CHC doctors at any time for help. CDC staff had no impact on the individual interventions.

Standard care group

Patients in the standard care group were offered the standard care, which was a mix of family member observed treatment and self-administered treatment. The treatment observers conducted DOT and checked off the medication calendar every day. As for patients without observers, they took medicine and made records by themselves. The CHC doctors checked the medication calendar at every home visit and took essential interventions to improve adherence.

Reminder app and smart pillbox groups

Patients in the reminder app and smart pillbox groups were trained to install and use the mHealth reminders by the CHC doctors

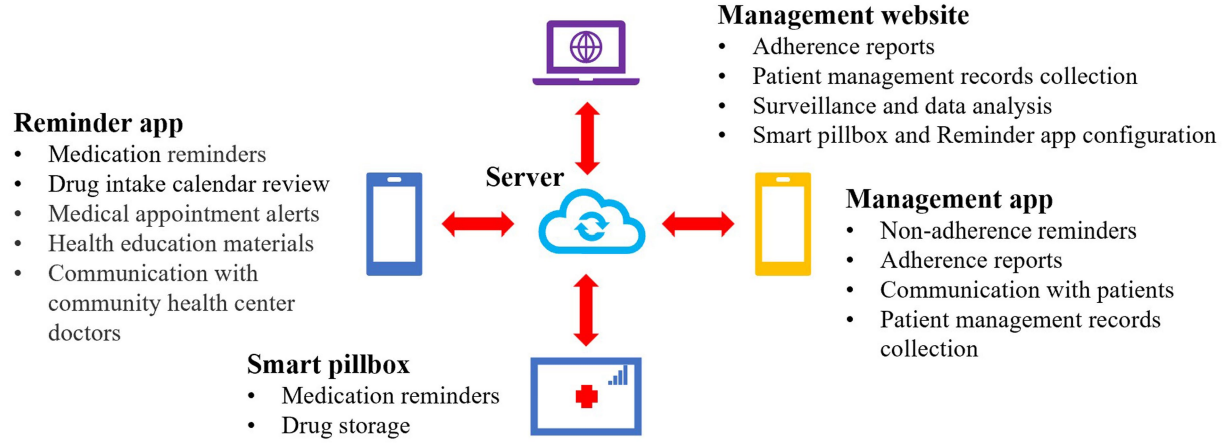

FIGURE 1
Schematic diagram for the mHealth reminder system. mHealth: mobile health.

after enrolling. The doctors set at least one drug intake reminder according to the patient's prescriptions. Patients in the reminder app group were taught to tap on the "confirm" button after they had taken the drugs. Patients in the smart pillbox group were taught to store anti-TB medicine in the pillbox and take every dose from it. The CHC doctors would take interventions such as a phone call or a home visit to remind patients to take medicine and deal with medical or technical emergencies if they received intake missing alerts. They also retrained patients at every home visit if necessary.

Data collection and statistical analysis

We collected demographic information using the questionnaire completed by the participants after enrollment. Clinical characteristics including the treatment outcomes were recorded by the TB hospital staff in the TBMIS and were extracted for analysis. Treatment outcomes followed the WHO definition (21). Treatment success was defined as the sum of cured and treatment completed. Treatment duration was defined as the time from the initial to the end of the anti-TB chemotherapy. Enrolled patients were followed until treatment outcomes occurred. Recurrence was determined by retrieval from TBMIS. Extrapulmonary TB (EPTB) was defined as TB involving organs other than the lungs. The majority of EPTB in the current study were tuberculous pleuritis. A bacteriologically confirmed case was defined as a PTB case whose biological specimen was positive smear microscopy, culture, or Xpert MTB/RIF.

Dose intake data for the patients in the reminder app and smart pillbox groups were extracted from the mHealth reminder system. The system labeled each scheduled dose during the treatment as "monitored by the reminders," "recorded by the CHC doctors," or "missed." Once the pillbox was opened or the confirmation was made through the app, this dose was considered "monitored by the reminders." If the CHC doctors confirmed that the patients had taken the dose but the system failed to record the data (either because of the system dysfunction or the patients' failure to obey the procedure), they manually labeled this dose as "recorded by the CHC doctors." Otherwise, the dose was labeled as "missed."

Data analyses were on the intention-to-treat population. We compared categorical baseline characteristics and treatment outcomes between groups using Pearson's Chi-squared test or Fisher's exact test, as appropriate. Continuous characteristics were analyzed using Wilcoxon rank-sum test or Kruskal-Wallis rank-sum test followed by Dunn's *post hoc* test for pairwise comparison. Dose intake data analysis was performed using the Cochran-Armitage trend test. We used Kaplan–Meier survival analysis to estimate the probability of treatment success and used the log-rank test to perform comparisons across study groups. We assessed the effect of mHealth reminders on treatment success using the Cox proportional hazard model. Unadjusted hazard ratios (HR) were calculated from univariate analysis. Adjusted hazard ratios were estimated by multivariate analysis. Factors in univariate analysis with a value of p less than 0.20 and other potentially associated ones entered the multivariate model. Power calculation for the comparison of survival curves under the Cox proportional hazard model was conducted using the "powerCT.default0" function of R package "powerSurvEpi."

Analysis was performed using R® software (4.1.2). A value of p less than 0.05 was considered significant.

Ethical approval

The study was approved by the Ethical Review Committee at Shanghai Municipal Center for Disease Control and Prevention (2019-14). All enrolled patients provided written consent before inclusion in the study.

Results

Characteristics of the participants

From April 1 to November 30, 2019, 353 newly diagnosed PTB patients were registered at Songjiang CDC and 329 (93.2%) were successfully screened. Among 324 eligible patients, 260 (80.2%) enrolled with 88 in the standard care group, 82 in the reminder app group, and 90 in the smart pillbox group (Figure 2). The median training time was 20 [interquartile range (IQR) 10–30] and 10 (IQR 10–30) minutes for the reminder app group and the smart pillbox group, respectively ($p = 0.002$, Wilcoxon rank-sum test). 7 (8.5%) patients in the reminder app group and 6 (6.7%) in the smart pillbox group dropped out and continued treatment under the standard care. They were followed and retained in the initial study groups for the intention-to-treat analysis. 260 enrolled patients were followed for a total of 77,430 days (2,581 months) until treatment outcomes occurred, with no lost-to-follow-up.

Overall, 175 (67.3%) participants were male. The median age was 32 (IQR 25 to 50) years and differed significantly among the three groups ($p < 0.001$, Kruskal-Wallis test). Compared with the standard care group, the smart pillbox group was older ($p = 0.005$, Dunn's test) and the reminder app group was younger ($p < 0.001$, Dunn's test). The majority were migrants, married, students or employed, insured, covered by the reimbursement policy, and bacteriologically confirmed, with significant differences among the three groups (all $p < 0.05$; Table 1).

Dose intake in the mHealth reminder groups

A total of 44,785 doses were scheduled for 172 patients in the mHealth reminder groups during the study period. 44,604 (99.6%) doses were taken with 39,280 (87.7%) monitored by the mHealth reminders and 5,324 (11.9%) recorded by the CHC doctors after intervention and confirmation. Additionally, the proportion of dose intake monitored by the reminder app and the smart pillbox was 89.5 and 86.0%, respectively ($p < 0.001$). Both had a significant time-dependent downward linear trend ($p < 0.001$, Cochran-Armitage trend test, compared with month 1), ranging from 94.2 to 65.7% and from 91.6 to 59.0%, respectively (Figure 3).

Error bars were 95% CIs. The line indicated the monthly scheduled doses for all the patients.

Effect of mHealth reminders on tuberculosis treatment outcomes

247 (95%) patients were successfully treated and 5 (2.0%) relapsed within 1 year. The treatment success rate ranged from 93.3% in the smart pillbox group to 96.6% in the standard care group, varying

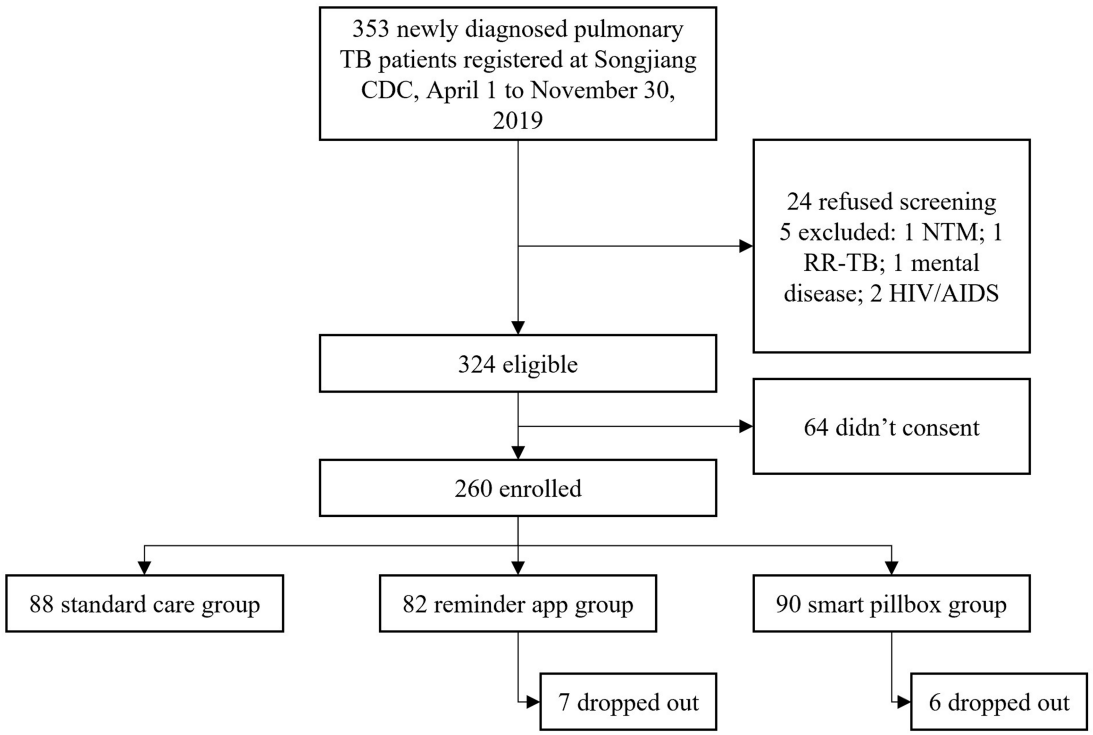

FIGURE 2
Flow chart. TB, tuberculosis; CDC, Center for Diseases Control and Prevention; NTM, nontuberculous mycobacterial disease; RR-TB, rifampicin-resistant tuberculosis.

insignificantly between the three groups. The recurrence rate also differed insignificantly (Table 2).

However, we found that the treatment duration of successfully treated patients in the standard care group (median 360, IQR 283–369, mean 322, days) was significantly longer than those in the reminder app group (median 296, IQR 204–365, mean 286, days) and the smart pillbox group (median 280, IQR 198–365, mean 283, days) (both $p < 0.01$, Dunn's test, Figure 4). The Kaplan–Meier estimates also showed that the treatment success occurred sooner in the reminder app and smart pillbox groups than in the standard care group ($p = 0.02$ and 0.03, respectively, Log-rank test adjusted by Bonferroni-Holm method, Figure 5).

In the multivariate analysis, using the reminder app to support anti-TB treatment was associated with a 1.58 times increase in the possibility of treatment success compared with the standard care (adjusted HR = 1.58, 95%CI 1.12–2.22, $p < 0.01$). Similarly, the smart pillbox was associated with a 1.63 times increase (adjusted HR = 1.63, 95%CI 1.16–2.30, $p < 0.01$). In addition, bacteriologically confirmed and extrapulmonary TB were independently associated with decreased possibility of treatment success ($p < 0.05$, Table 3). The power for the comparison of survival curves under the Cox proportional hazards model was 0.84 (the reminder app group vs. standard care group), and 0.89 (the smart pillbox group vs. standard care group), respectively.

Discussion

In this prospective cohort study, we observed that both the reminder app and the smart pillbox increased the possibility of treatment success compared with the standard care under the programmatic setting in a high TB burden country (adjusted HR = 1.58 and 1.63, respectively, both $p < 0.01$). Although the treatment success rates differed insignificantly between the three groups, patients using mHealth reminders acquired treatment success much sooner than those under standard care did (both $p < 0.05$). Besides, more than 92% of participants in the mHealth reminder groups completed study periods. The dose intake rates were extremely high in two mHealth reminder groups with more than 85% of doses monitored by the reminders. Our findings suggest the acceptability of the reminder app and the smart pillbox and also the effectiveness on the TB treatment outcomes in Shanghai, China.

Smartphone apps have been widely used (22) to support the treatment of chronic diseases, such as hypertension (23) and diabetes (24). However, the apps providing drug intake reminders, follow-up alerts, and side effects monitoring to support active TB patients' treatment are limited (25) and most assessed the effect on adherence instead of the treatment outcomes. In Shenzhen, China, a comprehensive app that mainly focused on video-observed therapy was reportedly easy-to-use and significantly increased patient adherence (26). Li et al. reported that a similar reminder app improved TB patients' revisit examination adherence in Tianjin, China (27). Essentially, the reminder app used in the current study offered an SMS-like intervention as described by WHO (9). The effect of SMS on TB treatment adherence and success was controversial in the trial settings (4, 28). But in our cohort, the reminder app was associated with a 1.58 times increase in the possibility of treatment success under the programmatic setting. This might result from the additional interactive services such as the patient forum, and instant communication with CHC doctors.

10.3389/fpubh.2023.923319

TABLE 1 Baseline characteristics of patients enrolled in the study.

Characteristic	Overall (*n* =260)	Standard care (*n* =88)	Reminder app (*n* =82)	Smart pillbox (*n* =90)	*p*-value[a]
Sex					0.761
Female	85 (32.7%)	28 (31.8%)	25 (30.5%)	32 (35.6%)	
Male	175 (67.3%)	60 (68.2%)	57 (69.5%)	58 (64.4%)	
Age, years					
Median (IQR)	32 (25, 50)	30 (26, 53)	26 (24, 33)	44 (31, 65)	<0.001
18–29	114 (43.8%)	42 (47.7%)	52 (63.4%)	20 (22.2%)	<0.001
30–44	65 (25.0%)	16 (18.2%)	22 (26.8%)	27 (30.0%)	
45–59	33 (12.7%)	14 (15.9%)	4 (4.9%)	15 (16.7%)	
>=60	48 (18.5%)	16 (18.2%)	4 (4.9%)	28 (31.1%)	
Migrant					<0.001
No	86 (33.1%)	21 (23.9%)	16 (19.5%)	49 (54.4%)	
Yes	174 (66.9%)	67 (76.1%)	66 (80.5%)	41 (45.6%)	
Completed high school					0.224
No	106 (40.8%)	34 (38.6%)	29 (35.4%)	43 (47.8%)	
Yes	154 (59.2%)	54 (61.4%)	53 (64.6%)	47 (52.2%)	
Marital status					<0.001
Married	158 (60.8%)	56 (63.6%)	34 (41.5%)	68 (75.6%)	
Single	102 (39.2%)	32 (36.4%)	48 (58.5%)	22 (24.4%)	
Occupation					0.006
Student or employed	197 (75.8%)	70 (79.5%)	69 (84.1%)	58 (64.4%)	
Unemployed or retired	63 (24.2%)	18 (20.5%)	13 (15.9%)	32 (35.6%)	
Insured					<0.001
No	89 (34.2%)	40 (45.5%)	39 (47.6%)	10 (11.1%)	
Yes	171 (65.8%)	48 (54.5%)	43 (52.4%)	80 (88.9%)	
Reimbursement policy covered					<0.001
No	114 (43.8%)	52 (59.1%)	45 (54.9%)	17 (18.9%)	
Yes	146 (56.2%)	36 (40.9%)	37 (45.1%)	73 (81.1%)	
Number of family members	2 (1, 3)	1 (0, 2.25)	2 (1, 3)	2 (1, 3)	0.014
Family income last year (CNY ¥)	100,000 (60,000, 150,000)	100,000 (52,000, 180,000)	90,000 (60,000, 138,750)	100,000 (60,000, 157,500)	0.576
Hypertension					0.049
No	235 (90.4%)	81 (92.0%)	78 (95.1%)	76 (84.4%)	
Yes	25 (9.6%)	7 (8.0%)	4 (4.9%)	14 (15.6%)	
Type 2 diabetes					0.610
No	248 (95.4%)	85 (96.6%)	79 (96.3%)	84 (93.3%)	
Yes	12 (4.6%)	3 (3.4%)	3 (3.7%)	6 (6.7%)	
Cavity					0.631
No	224 (86.2%)	74 (84.1%)	70 (85.4%)	80 (88.9%)	
Yes	36 (13.8%)	14 (15.9%)	12 (14.6%)	10 (11.1%)	
Combined with EPTB					0.090
No	222 (85.4%)	75 (85.2%)	65 (79.3%)	82 (91.1%)	
Yes	38 (14.6%)	13 (14.8%)	17 (20.7%)	8 (8.9%)	
Bacteriologically confirmed					0.002
No	102 (39.2%)	37 (42.0%)	42 (51.2%)	23 (25.6%)	
Yes	158 (60.8%)	51 (58.0%)	40 (48.8%)	67 (74.4%)	

Data are *n* (%) or median (IQR).

EPTB, extrapulmonary TB. [a]*p*-values were for comparison between three groups using Pearson's Chi-squared test, Fisher's exact test, or Kruskal-Wallis rank-sum test.

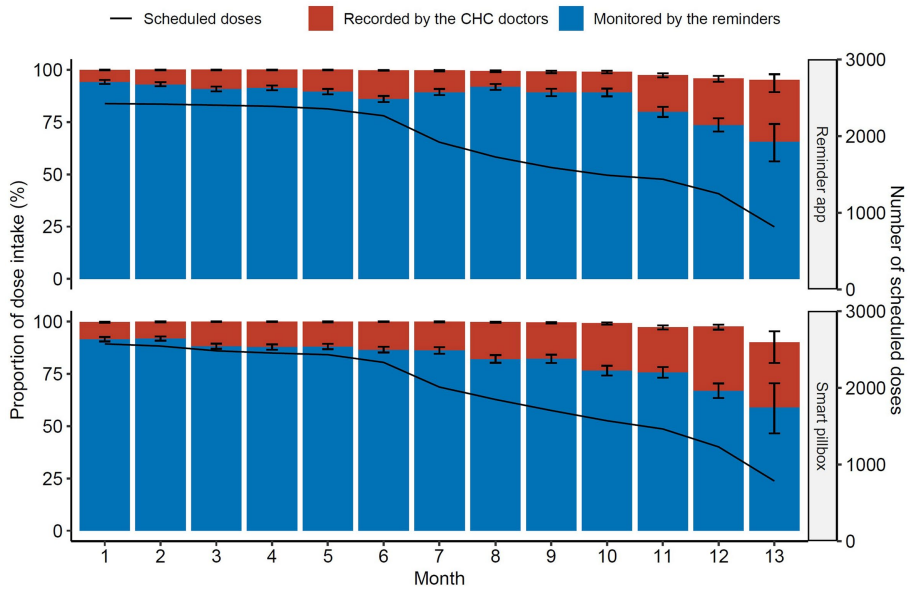

FIGURE 3
Proportions of dose intake through treatment. The black solid line indicated the monthly number of the scheduled doses. CHC, community health center.

TABLE 2 Treatment outcomes of patients in the study.

Outcomes	Overall (*n* =260)	Standard care (*n* =88)	Reminder app (*n* =82)	Smart pillbox (*n* =90)	*p*-value[a]
Follow-up time (person-months)	2,581	949	785	847	
Treatment success					0.599
No	13 (5.0%)	3 (3.4%)	4 (4.9%)	6 (6.7%)	
Yes	247 (95.0%)	85 (96.6%)	78 (95.1%)	84 (93.3%)	
Treatment outcomes					0.022
Treatment complete	176 (67.7%)	66 (75.0%)	62 (75.6%)	48 (53.3%)	
Cured	71 (27.3%)	19 (21.6%)	16 (19.5%)	36 (40.0%)	
Died	4 (1.5%)	1 (1.1%)	1 (1.2%)	2 (2.2%)	
Transferred out	8 (3.1%)	2 (2.3%)	3 (3.7%)	3 (3.3%)	
Treatment failed	1 (0.4%)	0 (0.0%)	0 (0.0%)	1 (1.1%)	
Recurrence					0.330
No	242 (98.0%)	83 (97.6%)	78 (100.0%)	81 (96.4%)	
Yes	5 (2.0%)	2 (2.4%)	0 (0.0%)	3 (3.6%)	

Data are *n* (%).[a]*p*-values were for comparison between three groups using Pearson's Chi-squared test or Fisher's exact test.

In China, an EMM that did not provide real-time data was proved to be beneficial to improving TB patients' adherence in a randomized trial (11). Moreover, a recent ecological study suggested that it also improved the treatment outcomes under programmatic conditions (10). In our cohort, we observed a similar result that the smart pillbox was associated with a 1.63 times increase in the possibility of treatment success under the programmatic setting. This was also consistent with other real-time EMM studies in Morocco (17) and South Africa (29). Real-time data transport is the foundation to enable instant interaction between patients and healthcare providers. China has a strong and widely covered national telecommunication network, which makes it feasible to scale up the application of real-time EMMs to provide better care for TB patients.

In our cohort, all of the treatment success rates across the three groups surpassed 90%. Meanwhile, the treatment duration was extremely long compared with the six-month standard regimen. Although the 2HREZ/4HR regimen was universally adopted at the start of treatment for new drug-susceptible TB patients in Shanghai, it was very common to extend the continuous phase of anti-TB therapy if the treatment effect was not satisfying (30). We observed

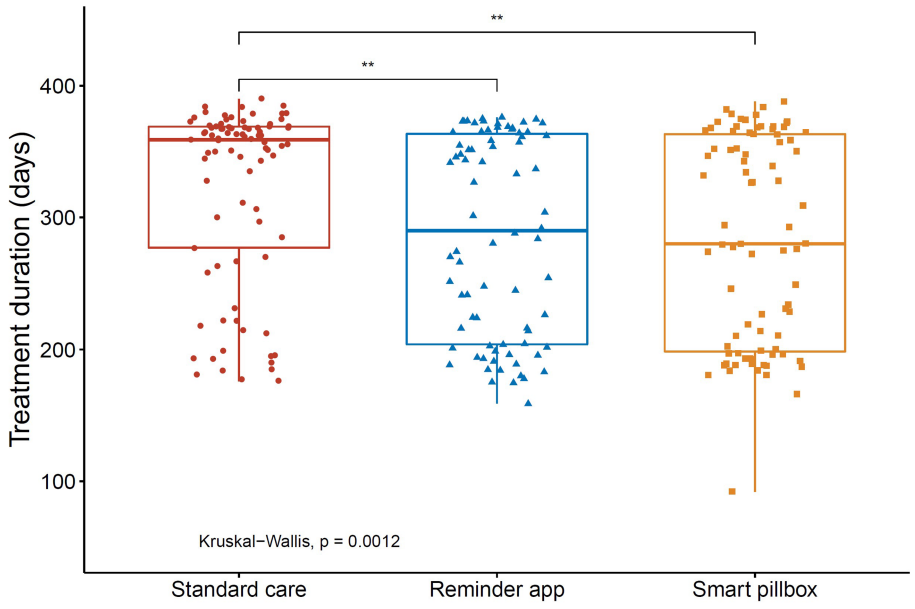

FIGURE 4
Treatment duration for successfully treated patients in the study. **p<0.01. Treatment duration was defined as the time from the initial to the end of the anti-TB chemotherapy.

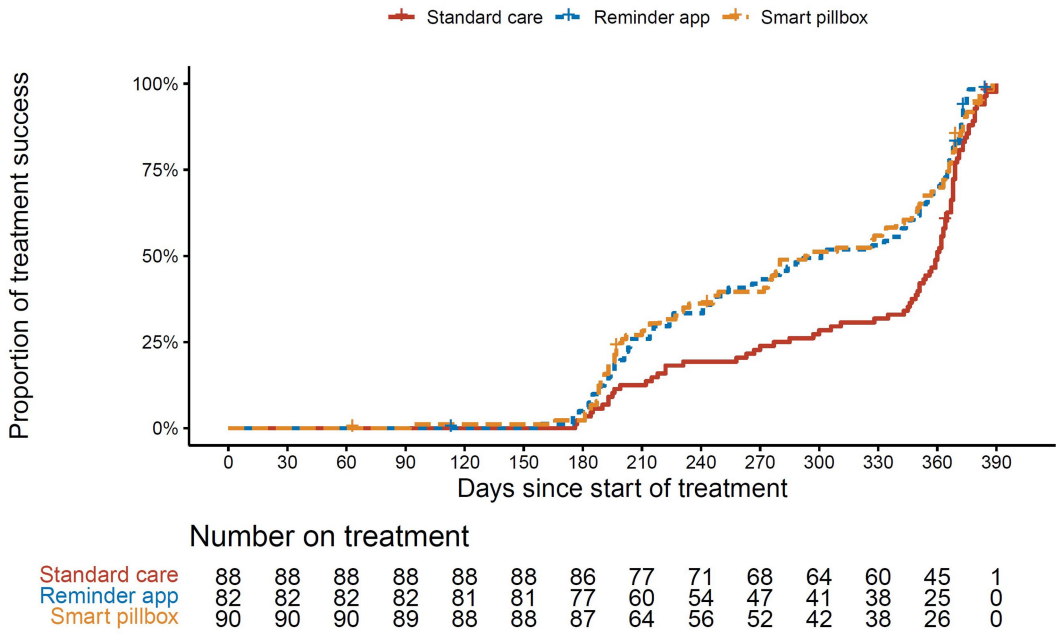

FIGURE 5
Kaplan–Meier survival estimates for treatment success.

that the median treatment duration of successfully treated patients in two mHealth reminder groups was significantly less than that in the standard care group (both $p < 0.05$), which indicated that the patients acquired treatment success much sooner and had a lower drug burden. Therefore, we used the Cox proportional hazard model to take into account the treatment duration and adjust other potentially associated factors.

The overall proportions of dose intake monitored by the reminder app (89.5%) and the smart pillbox (86.0%) in our study were slightly higher than the results from the studies using similar interventions in Tianjin, China (84.8%) (27) and Morocco (81.3%) (17). However, the decreasing trend over the months was similar. This might indicate the need to provide more care for patients while the treatment duration was extended.

10.3389/fpubh.2023.923319

TABLE 3 Univariate and multivariate analysis of factors associated with treatment success.

Characteristic	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	*p*-value	Hazard ratio (95% CI)[a]	*p*-value
Sex				
Female	1.00	–	1.00	–
Male	0.95 (0.73, 1.24)	0.710	0.89 (0.67, 1.17)	0.4
Age, years				
18–29	1.00	–	1.00	–
30–44	0.69 (0.51, 0.95)	0.023	0.62 (0.44, 0.88)	0.007
45–59	0.98 (0.66, 1.47)	0.936	0.94 (0.61, 1.44)	0.8
>=60	0.87 (0.61, 1.24)	0.437	0.91 (0.59, 1.40)	0.7
Migrant				
No	1.00	–		
Yes	1.09 (0.83, 1.43)	0.542		
Completed high school				
No	1.00	–		
Yes	0.90 (0.70, 1.16)	0.428		
Marital status				
Married	1.00	–		
Single	1.16 (0.90, 1.50)	0.261		
Occupation				
Student or employed	1.00	–		
Unemployed or retired	1.04 (0.77, 1.40)	0.788		
Insured				
No	1.00	–		
Yes	1.00 (0.77, 1.29)	0.975		
Reimbursement policy covered				
No	1.00	–	1.00	–
Yes	1.16 (0.90, 1.49)	0.263	1.10 (0.82, 1.48)	0.5
Number of family members	0.96 (0.88, 1.05)	0.347		
Bacteriologically confirmed				
No	1.00	–	1.00	–
Yes	0.82 (0.63, 1.06)	0.128	0.75 (0.57, 0.99)	0.044
Cavity				
No	1.00	–	1.00	–
Yes	0.71 (0.49, 1.03)	0.069	0.68 (0.46, 1.00)	0.050
Combined with EPTB				
No	1.00	–	1.00	–
Yes	0.61 (0.43, 0.87)	0.006	0.51 (0.35, 0.74)	<0.001
Type 2 diabetes				
No	1.00	–	1.00	–
Yes	1.05 (0.58, 1.93)	0.863	1.02 (0.54, 1.91)	>0.9
Group				
Standard care	1.00	–	1.00	–
Reminder app	1.50 (1.10, 2.06)	0.010	1.58 (1.12, 2.22)	0.009
Smart pillbox	1.42 (1.05, 1.93)	0.023	1.63 (1.16, 2.30)	0.005

[a]Adjusted for potentially confounding factors of sex, age, reimbursement policy coverage, bacteriological confirmation, cavity, combined with EPTB, and type 2 diabetes comorbidity.
EPTB, extrapulmonary TB.

WHO has suggested that the treatment adherence interventions be selected based on the individual patient's needs (2). In this study, the mHealth reminder system offered two interventions and participants chose the study group voluntarily. We found the patients in the smart pillbox group were significantly older than those in the reminder app group. Although the smart pillbox is almost maintenance-free except for recharging, young people are familiar with using smartphone apps and have more outdoor activities, they might feel uncomfortable carrying the pillbox with them. It is worth mentioning that the mHealth reminder system is open-ended and can be connected to more reminders such as the bracelet (31) and the smaller pillbox in the future to meet more patients' needs.

To our knowledge, this was the first study to assess the effectiveness of the reminder app and the smart pillbox that was integrated into one system on TB treatment outcomes globally. There were still several limitations in our study. Firstly, the observational study design reflected the real-world situation and provided suggestions for the integration of mHealth reminders into the TB program, but made it impossible to randomize the participants at enrollment. Although the multivariate model has been adopted to adjust potential confounders, the difference in treatment outcomes could still be partially attributed to imbalanced factors. In the future, randomized clinical trials (RCTs) (32, 33) are needed to provide a stricter evaluation of the effectiveness. Secondly, to make the treatment outcomes comparable between study groups, we excluded previously treated and rifampicin-resistant patients from our study as several RCTs (32, 34) did. However, these patients usually have more lengthy treatments and face more problems with treatment adherence (3). Therefore, applying mHealth interventions to them should be cautious before more evidence emerge. Lastly, the drug intake data collected through mHealth reminders was indirect evidence of adherence and there was no verification of the data using methods such as drug urine tests. But one study (35) comparing EMM data and urine tests for traces of TB drugs proved the high correlation between reminders data and adherence.

Conclusion

In conclusion, the reminder app and the smart pillbox interventions were acceptable and improved the treatment outcomes compared with the standard care under the programmatic setting in Shanghai, China. More high-level evidence is expected to confirm the effect of mHealth reminders on TB treatment outcomes.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethical Review Committee at Shanghai Municipal Center for Disease Control and Prevention (2019-14). The patients/participants provided their written informed consent to participate in this study.

Author contributions

ZW and LL participated in the study design, data collecting, and statistical analysis. YL, ZZ, and CN participated in the data collecting and statistical analysis. ZW wrote the first draft of the manuscript. JC, QP, and ZY reviewed and revised the first draft. XS and WZ conceived, designed, and managed the study. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The reviewer QZ declared a shared affiliation with the author ZW to the handling editor at the time of review.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2023.923319/full#supplementary-material

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Glossary

app	application
CDC	Center for Diseases Control and Prevention
CHC	community health center
DOT	directly observed therapy
EMM	electronic medication monitor
EPTB	extrapulmonary TB
IQR	interquartile range
MEMS	medication event monitoring system
mHealth	mobile health
PTB	pulmonary TB
RCT	randomized clinical trial
SAT	self-administered therapy
SIM	subscriber identity module
SMS	short message service
TB	tuberculosis
TBMIS	TB management information system
VOT	video-supported treatment
WHO	World Health Organization

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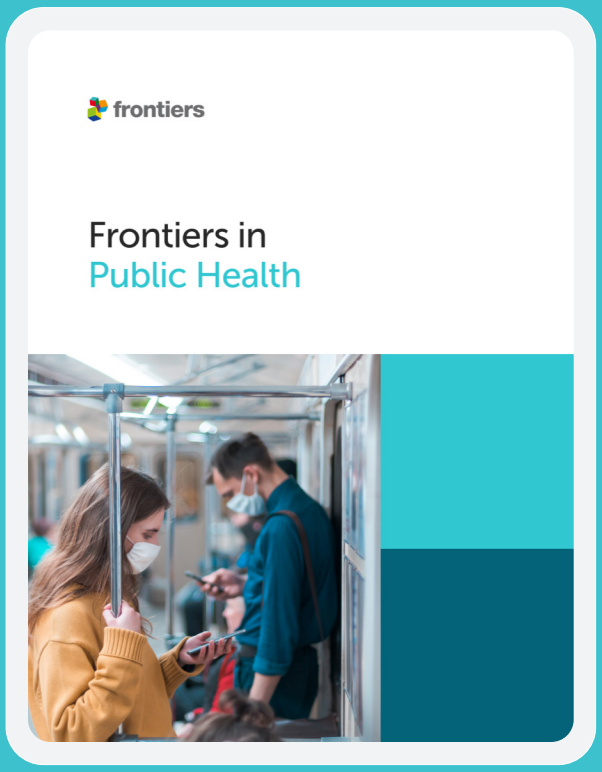

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