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Recent advances in attempts to improve medication adherence – from basic research to clinical practice.

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Table of contents

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Editorial: Recent advances in attempts to improve medication adherence-from basic research to clinical practice

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medication adherence, clinical practice, basic research, Europe, healtcare systems

Editorial on the Research Topic
Recent advances in attempts to improve medication adherence-from basic research to clinical practice

Adequate implementation of evidence-based pharmacotherapies is an obvious precondition for their effectiveness in real-life settings. Indeed, 'Drugs do not work in patients who do not take them', as the well-known quote by C. Everett Koop, US Surgeon General, says (Everett Koop, 1985). Unfortunately, despite more than half a century of dedicated research, corrective and awareness-raising activities, medication adherence still remains far from perfect. Twenty years ago, the World Health Organization released its seminal report on adherence (World Health Organization, 2003), which popularised the memorable number of as many as 50% of patients deviating from their prescribed treatment. Even if it may be assumed that these statistics seriously simplify the problem of non-adherence, there are also good reasons to believe that this proportion was not overestimated. What is worse, current statistics of non-adherence are not much different (Foley et al., 2021).

An analysis of the milestones of medication adherence research and practice (Figure 1) proves that patients' deviations from prescribed treatment are as old as the medicine itself. Hippocrates, the father of medicine, was the first one to make a note of what we now call non-adherence. This phenomenon has since not only caused frustration for thousands of practitioners, but has also been the object of interest for thousands of researchers. As a result, currently conducted searches of scientific literature databases using medication adherence terms return over 100,000 records. What can we learn from that bulk of publications?

One practical lesson is that a magic wand that would solve the puzzle of non-adherence simply does not exist. Taking medications as prescribed is a human behaviour driven by many interlinked factors. Therefore, a single one-size-fits-all solution is unlikely to be found. If so, should we abandon our hope to improve adherence? Some inspiration could be drawn from

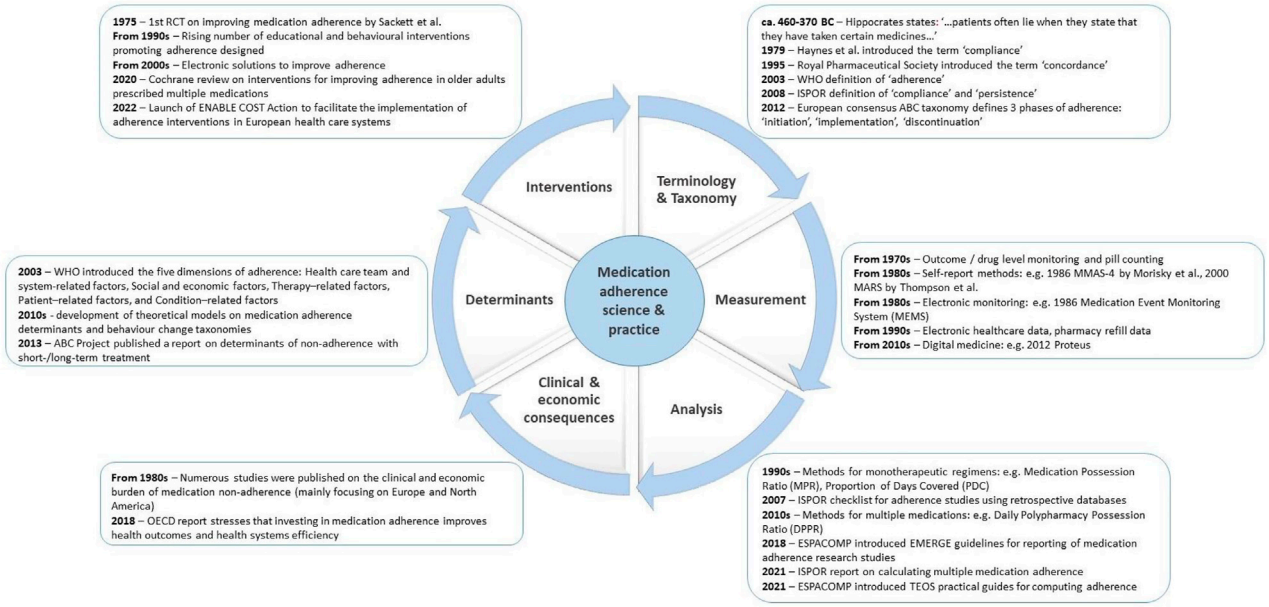

FIGURE 1
Milestones of medication adherence-related science and practice. Notes: ENABLE—European Network to Advance Best practices and technoLogy on medication adherencE" (ENABLE) COST Action, ESPACOMP—International Society for Medication Adherence, ISPOR - International Society for Pharmacoeconomics and Outcomes Research, MARS - Medication Adherence Report Scale, MMAS-4—4-Item Morisky Medication Adherence Scale, OECD—Organization for Economic Cooperation and Development, WHO—World Health Organisation.

road traffic: no single intervention makes it 100% safe, yet several improvements (e.g., airbags, speed limits, *etc.*) proved to work, and their collective application has produced an additive effect in saving drivers and passengers' lives.

Such a perspective created the background for this Research Topic of "Frontiers in Pharmacology". When designing it, we aimed to cover the full spectrum of issues and solutions (Figure 1), which, when brought together, may help improve medication adherence. In response to this call, a wide range of modern approaches and innovative technologies has been described, from new survey instruments (Larsen et al.), to electronic pillboxes (Goetzinger et al.). Tackling adherence in real-life conditions, studies investigated new, unexpected factors affecting adherence: the COVID-19 pandemics (Malo et al.), and war hostilities (Khanyk et al.).

Unlike the other tools that mostly assess the level of adherence, OMAS-37 looked at the causes of non-adherence (Larsen et al.). Exploring various barriers to proper drug taking, it proved to be a valid and reliable instrument which may be a good starting point for further interventions. Another approach has been used by (Kostalova et al.), who measured tacrolimus concentration in kidney transplant recipients. Its intra-patient variability seemed to be an easy-to-use marker of non-adherence to this life-saving therapy. Finally, using tree-based prediction models (Wendl et al.), helped to identify target groups and individuals for adherence interventions in typical chronic conditions of diabetes type 1, type 2 and hyperlipidaemia. Notably, their approach also allowed to predict the economic consequences of interventions.

Two studies of our collection assessed adherence to statins. Interestingly, a Dutch study in diabetes type 2 patients found relatively high levels of adherence (Beernink et al.). Nevertheless, several easy to assess factors, such as higher HbA1c and higher BMI, correlated with lower adherence, and not attaining the LDLc level. Based on an analysis of longitudinal trends of statin use in new users before and during the COVID-19 pandemic, the following four patterns were identified: high adherence (37.2% of subjects); low adherence (35.6%); occasional use (14.9%); and gradual decline (12. 3%) (Malo et al.). A study in Indonesia (Alfian et al.) found the level of self-reported non-adherence to antihypertensive treatment to be 41. 8%. Among other factors, patients' awareness of hypertension and emotional burden due to this condition correlated with non-adherence. These findings can form a solid basis for selecting patients in need of adherence support, and finding appropriate ways to support them, thus tailoring interventions to the relevant determinants.

Perhaps, the best interventions are those targeted at relevant determinants in a way that is acceptable to patients. As illustrated by (Barnestein-Fonseca et al.), individual training significantly improves inhalation technique in older adult COPD patients. However, novel technologies are also well-received: as many as two-thirds of breast cancer survivors declared that they would accept a medication adherence enhancing eHealth technology (electronic pillbox connected to a smartphone application) to improve daily adherence to their adjuvant endocrine therapy [Goetzinger et al.).

In the light of these findings, it is frustrating that European countries give medication adherence management low priority. A pan-European study identified 13 reimbursed medication adherence enhancing interventions (MAEIs) in nine countries only (Ágh et al.). The countries with a higher GDP *per capita* tend to have more reimbursed interventions. Is it because they can afford that? Or just the opposite: maybe due to better care for medication adherence these countries are wealthier? Some inspiration can be

drawn from Ukraine: the country, under the unfavourable conditions of hostilities, tries to do its best to maintain long-term treatment of their citizens (Khanyk et al.), assuming that the human capital is crucial for its existence.

Looking forward, we have to accept the simple fact that medication non-adherence will remain a challenge. The aging of the global society, the rising tide of non-communicable chronic conditions, multimorbidity and associated polypharmacy, as well as new global challenges, such as the COVID-19 pandemic, are likely to create new barriers to medication-taking as prescribed (Kardas et al., 2021; Ágh et al., 2021). In the recent years, as illustrated by publications in this issue, medication non-adherence ceased to be merely a 'patient problem' and is now considered an important indicator of the quality of care within healthcare systems. Therefore, instead of being blamed, patients need to be supported in their therapeutic journeys. To enhance adherence, all stakeholders need to collectively create adherence-enabling environments. MAEIs of proven effectiveness need to be implemented on a much broader scale. Even if one single intervention helps selected patients only, adopting more such solutions in daily care is definitely worth trying. In other words, in lack of a magic wand that could eliminate non-adherence, we need to make the most of available innovations.

Author contributions

PK and TA wrote the first draft. AD, IP, and BW commented on it and provided feedback. All authors agreed with submission of the final 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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References

Ágh, T., van Boven, J. F., Wettermark, B., Menditto, E., Pinnock, H., Tsiligianni, I., et al. (2021). A cross-sectional survey on medication management practices for noncommunicable diseases in europe during the second wave of the COVID-19 pandemic. *Front. Pharmacol.* 12, 685696. doi:10.3389/fphar.2021.685696

Everett Koop, C. (1985). "Improving medication compliance," in *Proceedings of a symposium* (Reston, VA: National Pharmaceutical Council).

Foley, L., Larkin, J., Lombard-Vance, R., Murphy, A. W., Hynes, L., Galvin, E., et al. (2021). Prevalence and predictors of medication non-adherence among people living with multimorbidity: A systematic review and meta-analysis. *BMJ Open* 11 (9), e044987. doi:10.1136/bmjopen-2020-044987

Kardas, P., van Boven, J. F. M., Pinnock, H., Menditto, E., Wettermark, B., Tsiligianni, I., et al. (2021). Disparities in European healthcare system approaches to maintaining continuity of medication for non-communicable diseases during the COVID-19 outbreak. *Lancet Reg. Health Eur.* 4, 100099. doi:10.1016/j.lanepe.2021.100099

World Health Organization (2003). *Adherence to long-term therapies: Evidence for action*. Geneva, Switzerland: World Health Organization. Available at: https://apps.who.int/iris/handle/10665/42682 last (accessed January 2nd, 2023).

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Reimbursed Medication Adherence Enhancing Interventions in European Countries: Results of the EUREcA Study

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Introduction: Current literature lacks detailed understanding of the reimbursement framework of medication adherence enhancing interventions (MAEIs). As part of the ENABLE COST Action, the EUREcA ("EUropen REimbursement strategies for interventions targeting medication Adherence") study aimed to provide an in-depth overview of reimbursed MAEIs currently available in European countries at national and regional levels and to pave the way for further MAEIs to be implemented in the future.

Methods: A web-based, cross-sectional survey was performed across 38 European countries and Israel. The survey questionnaire was developed as a result of an iterative process of discussion informed by a desk review. The survey was performed among invited ENABLE collaborators from June to July 2021. Besides descriptive analysis, association between country income and health care expenditure, and the availability of reimbursed MAEIs were also assessed.

Results: The survey identified 13 reimbursed MAEIs in nine countries: multi-dose drug dispensing (n = 5), medication review (n = 4), smart device (n = 2), mobile application (n = 1), and patient education (n = 1). The median GDP per capita of countries having ≥1 reimbursed MAEI was significantly higher compared to countries having no reimbursed adherence intervention (33,888 EUR vs 16,620 EUR, respectively; p = 0.05).

Conclusions: Our findings highlight that to date only a small number of MAEIs have been reimbursed in European countries. Comprehensive health technology assessment recommendations and multi-stakeholder collaboration could help removing barriers related to the implementation and reimbursement of MAEIs.

Keywords: medication adherence, persistence, intervention, reimbursement, health economics, health policy

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INTRODUCTION

According to the estimation of the World Health Organization (WHO), adherence to long-term pharmacotherapies averages only 50% (WHO, 2003). Medication non-adherence has a serious negative impact on health outcomes and results in increased health care utilization and costs (Breekveldt-Postma et al., 2008; Cutler et al., 2018; Kleinsinger, 2018; Mongkhon et al., 2018; Inotai et al., 2021). It should be also noted that the trend of accelerated aging society in the 21st century increases the burden of multimorbidity and polypharmacy and consequently the likelihood and negative consequences of poor adherence (Midao et al., 2018; Kardas et al., 2021; Kurczewska-Michalak et al., 2021).

Several medication adherence enhancing interventions (MAEIs) - including many innovative technologies (e.g., smart devices, mobile applications) - have been developed in the last decade which may greatly improve suboptimal adherence to therapies and hence, therapeutic outcomes (Salema et al., 2011; Nieuwlaat et al., 2014; Costa et al., 2015; van Driel et al., 2016; Blakey et al., 2018; Godinho et al., 2020; Zijp et al., 2020; Gohil et al., 2021; Whiteley et al., 2021). The need for these technologies became increasingly important during the COVID-19 pandemic (Agh et al., 2021). However, currently MAEIs are mainly used within clinical research settings and little is known about their implementation in routine clinical practice (Zullig et al., 2019; Kostalova et al., 2022).

To our knowledge, there is a gap in the scientific literature with regards to the implementation, health technology assessment (HTA), policy regulation and reimbursement of MAEIs. In 2018, the Organisation for Economic Co-operation and Development (OECD) identified four enablers for improving medication adherence at the system level, such as (i) acknowledge ("to acknowledge that medication non-adherence harms health and increases healthcare costs"), (ii) inform ("to systematically monitor adherence"), (iii) incentivise ("to make changes in financial incentives for providers and patients"), and (iv) steer and support ("adherence begins with a patient and a prescribing clinician and a dispensing pharmacist who should all be supported by other health system stakeholders") (Khan and Socha-Dietrich, 2018). Nevertheless, neither this OECD study (Khan and Socha-Dietrich, 2018) nor other key publications on this topic (Nieuwlaat et al., 2014; WHO, 2014) did provide any recommendation on the implementation and reimbursement of MAEIs. Beside the above listed factors, barriers to implementation may also include the limited evidence on the cost-effectiveness of these interventions (Elliott et al., 2005; Simon-Tuval et al., 2016). Moreover, successful implementation of these innovative technologies in daily practice is further hampered by significant differences between healthcare systems, reimbursement pathways and policy regulations across countries which makes the issue of transferability of MAEIs highly relevant (Khan and Socha-Dietrich, 2018).

To overcome challenges related to implementing MAEIs, on October 2020 the European Network to Advance Best practices and technoLogy on medication adherencE (ENABLE, COST Action 19132) was launched. ENABLE is a 4-years research initiative funded by the European Commission that is expected to catalyze research, policy, and implementation regarding MAEIs across healthcare systems in all European countries and Israel (van Boven et al., 2021). As part of the ENABLE research project, the objectives of this study were to provide an in-depth overview and critical assessment of reimbursed MAEIs in European countries at national and regional levels in order to identify good practice models and to pave the way for further MAEIs to be implemented in the future.

MATERIAL AND METHODS

Study Design

An anonymous, web-based, cross-sectional survey, called the "EUropean REimbursement strategies for interventions targeting medication Adherence" (EUREcA), was performed across 38 European countries (i.e., Albania, Austria, Belgium, Bosnia and Herzegovina, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxemburg, Malta, Moldova, Montenegro, the Netherlands, North Macedonia, Norway, Poland, Portugal, Romania, Serbia, Slovakia, Slovenia, Spain, Sweden, Switzerland, Turkey, and the United Kingdom) and Israel. The target population of the survey was limited to members of ENABLE including academics with medical or pharmaceutical backgrounds, healthcare providers and health economists. Ethical issues for this study were governed by the Ethical Committee of the Medical University of Lodz, Poland. According to the policy of that Commission, non-experimental studies are not a subject to ethical approval procedure, and hence, such an approval was not needed. Each participant was requested to provide a written, online recorded informed consent before completing the survey. No personal data was stored in relation to this survey. The study was reported according to the Checklist for Reporting Results of Internet E-Surveys (CHERRIES) (Eysenbach, 2004).

Questionnaire Development

The primary outcome of the survey was a better understanding on the available reimbursed MAEIs across European countries. In relation to the aim of this study, MAEI was defined as "any structured intervention aiming to help patients to make optimal use of their pharmacotherapy". Interventions of interest could be reimbursed/financed by public funds, pharma companies, patient organizations or any other organizations implemented at national and regional levels targeting any kind of pharmacotherapy (regardless of health condition). The survey questionnaire was developed as a result of an iterative process of discussion and consensus among the authors informed by a desk review. The draft questionnaire was validated by four external adherence experts with respect to the face validity and the technical functionality of the online

questionnaire. Finally, the questionnaire contained one question on informed consent, three questions on demographic data, nine questions per intervention, allowing for maximum three reimbursed MAEIs per respondent per country, one question on data regarding reimbursed MAEIs planned to be introduced in the next 24 months and one question on any other relevant information. The majority of questions were closed, multiple-choice questions or "yes"/"no" questions; there were only two open-ended questions. A copy of the survey questionnaire can be seen in **Supplementary Figure S1**.

Data Collection

The EUREcA survey was posted on SurveyMonkey.com (www.survey-monkey.com) on 15th of June 2021. The survey was not open for the general public. A unique link to access the web-based survey was sent by email to ENABLE members (n = 85). At the beginning of the survey, before giving informed consent, all participants were informed about the objectives of the survey, the use and storage of the data and the length of time of the survey. The online questionnaire was distributed over 23 pages. The average time required to complete the survey was estimated to be 20 min. The survey was open until 20th of July 2021; reminders were sent weekly to all invited ENABLE collaborators. No incentives were offered to participants for completing the survey. Online surveying system settings were set to prevent multiple entries from the same individual IP address.

Data Analysis

As the first step of data synthesis, a completeness check was conducted to ensure that adequate responses were received. Only data on interventions with complete set of information (i.e., answers were provided to all questions) were included in the analysis. In case of more than one respondent from a country, survey results were sent to the ENABLE country representatives for clarifications and data validation.

Data on the identified reimbursed MAEIs were presented in a descriptive way. Mann-Whitney U test was used to assess the differences in country income (i.e., real gross domestic product [GDP] per capita in 2019 EUR) (Eurostat, 2022) and health care expenditure data (i.e., health care expenditure per capita in 2019 EUR) (OECD, 2020) between countries reporting ≥1 vs no reimbursed MAEI. In all statistical analyses, the significance level was set at 0.05. Statistical analyses were performed using R software (The R Foundation for Statistical Computing, Vienna, Austria; version 4.1.2).

RESULTS

Survey Participants

Fifty-four participants (survey response rate = 64%) covering all 39 ENABLE countries (1, 2, and three respondents from 26, 11, and two countries, respectively) completed the survey (**Table 1**). Sixty-seven percent (n = 36) of respondents had academic background (i.e., medical or pharmaceutical sciences) and 76% (n = 41) of participants had more than 10 years of work experience.

Reimbursed Medication Adherence Enhancing Interventions

The survey identified 13 reimbursed MAEIs from nine countries (**Figure 1**). Interventions were categorized by the following types: multi-dose drug dispensing (MDD) (n = 5), medication review (n = 4), smart device (n = 2), mobile application (n = 1), and patient education (n = 1). We did not identify any MAEI planned to be reimbursed in the next 24 months in the evaluated countries. Characteristics of the analyzed MAEIs are summarized in **Table 2**.

MDD services were implemented and reimbursed primarily in Northern and Western European countries (i.e., Belgium, Denmark, Finland, Norway, and the United Kingdom). In all countries MDD services were reimbursed by public health insurance predominantly to older people who take multiple medicines either at home or in nursing homes.

Based on our results, medication review was reimbursed in 4 European countries (i.e., Hungary, Slovenia, Spain, and the United Kingdom). In all but one of these countries this service was provided by primary care centers; in the United Kingdom community pharmacies were responsible for medication review. The identified medication review services were reimbursed by public health insurance primarily for patients with chronic disorders. In Slovenia, two types of medication reviews were available. The "type 3" medication review (PCNE, 2016) performed in primary care centers was reimbursed since 2016, while the "type 2a" medication review (PCNE, 2016) provided by community pharmacies was not reimbursed. In Hungary, from 2018 as part of the "Three Generations for Health Program" consortiums of primary care centers could get reimbursement for providing medication review type services; however, the program was closed at the end of 2021.

Experts from Finland and the Netherlands reported that in their countries there were reimbursed adherence enhancing smart devices. Popit Sense® is a smart device for monitoring pill-taking. The device monitors through sensors when pills are taken. Data on pill consumption are sent to Popit Pill Reminder Application® on a smartphone. This smart device was reimbursed by a pharma company in Finland for patients with rheumatoid arthritis. Another example is the Enerzair® smart inhaler which is a drug-device combination (devices integrated with a drug and dispensed at the same time). The device is connected with a mobile application for self-monitoring. This smart inhaler was reimbursed by the national health insurance in the Netherlands for the maintenance treatment of asthma/COPD in adult patients.

In our survey we identified only one reimbursed mobile health application for enhancing medication adherence. MindFrame® is a mobile health solution that supports the treatment of individuals suffering from schizophrenia in Denmark. This application helps patients to play a more active role in their

TABLE 1 | General characteristics of survey participants.

Country	Number of Survey Participants	Primary Field of Work (Work Experience in years) of Each Survey Participant
Albania	1	Academia (0–9 years)
Austria	1	Clinical /Healthcare (10–19 years)
Belgium	1	Commercial company /Industry (20–29 years)
Bosnia and Herzegovina	2	Academia (10–19 years)
		Government /Health Administration /Health Authority (10–19years)
Bulgaria	2	Academia (0–9 years)
		Academia (≥30 years)
Croatia	2	Academia (10–19 years)
		Clinical /Healthcare (0–9 years)
Cyprus	1	Health Insurance /Regulatory Agency (20–29 years)
Czech Republic	1	Academia (≥30 years)
Denmark	1	Academia (20–29 years)
Estonia	2	Health Insurance /Regulatory Agency (10–19 years)
		Academia (20–29 years)
Finland	1	Academia (0–9 years)
France	1	Commercial company /Industry (0–9 years)
Germany	1	Academia (10–19 years)
Greece	1	Academia (0–9 years)
Hungary	2	Clinical /Healthcare (10–19 years)
		Other: Research /Education not Academia (0–9 years)
Iceland	2	Clinical /Healthcare (10–19 years)
		Clinical /Healthcare (10–19 years)
Ireland	2	Commercial company /Industry (0–9 years)
		Academia (≥30 years)
Israel	1	Academia (0–9 years)
Italy	1	Academia (10–19 years)
Latvia	1	Clinical /Healthcare (20–29 years)
Lithuania	2	Academia (20–29 years)
		Academia (10–19 years)
Luxembourg	1	Academia (0–9 years)
Malta	1	Academia (≥30 years)
Moldova	1	Academia (10–19 years)
Montenegro	2	Academia (20–29 years)
		Clinical /Healthcare (0–9 years)
Netherlands	1	Academia (10–19 years)
North Macedonia	1	Academia (10–19 years)
Norway	1	Academia (20–29 years)
Poland	1	Academia (20–29 years)
Portugal	3	Academia (≥30 years)
		Academia (20–29 years)
		Academia (0–9 years)
Romania	1	Academia (20–29 years)
Serbia	1	Academia (10–19 years)
Slovakia	1	Academia (20–29 years)
Slovenia	1	Clinical /Healthcare (20–29 years)
Spain	3	Other: Research /Education not Academia (≥30 years)
		Academia (10–19 years)
		Academia (0–9 years)
Sweden	1	Academia (20–29 years)
Switzerland	2	Academia (≥30 years)
		Academia (20–29 years)
Turkey	1	Academia (10–19 years)
United Kingdom	2	Other: Clinical Academia (≥30 years)
		Clinical /Healthcare (20–29 years)

treatment and allows mental health professionals to monitor patients remotely.

Last but not least, we identified one reimbursed patient education program as well. The "Be Educated and Empowered Patient" (BEEP) is an education program for organ transplanted patients launched by the Hungarian Transplant Federation. The program was reimbursed from various funds of pharma companies and state grants. This program primarily aims to improve the health literacy level and health behaviour of newly transplanted patients and thus it only has an indirect effect on medication adherence.

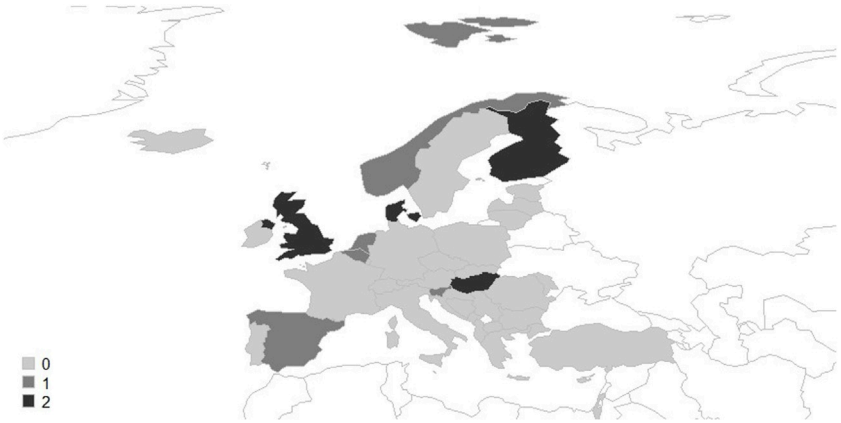

FIGURE 1 | Number of reimbursed medication adherence enhancing interventions across European countries.

TABLE 2 | Characteristics of identified reimbursed medication adherence enhancing interventions.

Type of Intervention	Country	Year of Introduction	Level of Intervention	Target Population	Who Pays the Reimbursement?	Who Gets the Reimbursement?
Multi-dose drug dispensing	Belgium	2012	National	Elderly patients	Public insurance /Public healthcare system /Government	Pharmacy
	Denmark	2001	National	Elderly patients		
	Finland	2006	National	Reimbursed only for patients ≥75 years of age and using ≥6 drugs suitable for drug dispensing		
	Norway	Early 2010s	National	Elderly patients		
	United Kingdom	2014	National	Elderly patients, or those otherwise struggling to cope with their medication		
Medication review	Hungary	2019	National	40–65 years old patients with chronic disorders	Public insurance /Public healthcare system /Government	Primary care (GP)
	Slovenia	2016	National	Patients with drug related problems; identified and referred by a GP		Primary care (clinical pharmacist)
	Spain	2012	Regional	Patients with chronic diseases and polypharmacy		Primary care, Hospital and Pharmacy
	United Kingdom	Years ago	National	Patients on long-term medication		Pharmacy and Hospital
Smart device	Finland	2019	National	Patients on rheumatoid arthritis medication	Pharma company	IT company
	Netherlands	2020	National	Patients with asthma/COPD	Public insurance /Public healthcare system /Government and Pharma company	Pharmacy
Mobile application	Denmark	No information	National	Patients with mental disorder	No information	No information
Patient education	Hungary	2016	National	Newly transplanted patients	Patient organization	Healthcare providers

COPD, chronic obstructive pulmonary disease; GP, general practitioner; IT, information technology.

Association Between Country Economy and the Availability of Reimbursed Medication Adherence Enhancing Interventions

We found a significant difference between the median real GDP per capita (p = 0.05) for countries having ≥1 (33,880 EUR) compared to no reimbursed (16,620 EUR) MAEI (**Figure 2**). In case of median health care expenditure per capita the difference was statistically not significant (countries with ≥1 vs no reimbursed MAEI: 3,154 EUR vs 1,788 EUR, respectively; p = 0.06).

DISCUSSION

To our knowledge, this is the first study to provide an in-depth overview on reimbursed MAEIs across Europe. From the evaluated 39 countries, there were only nine countries in

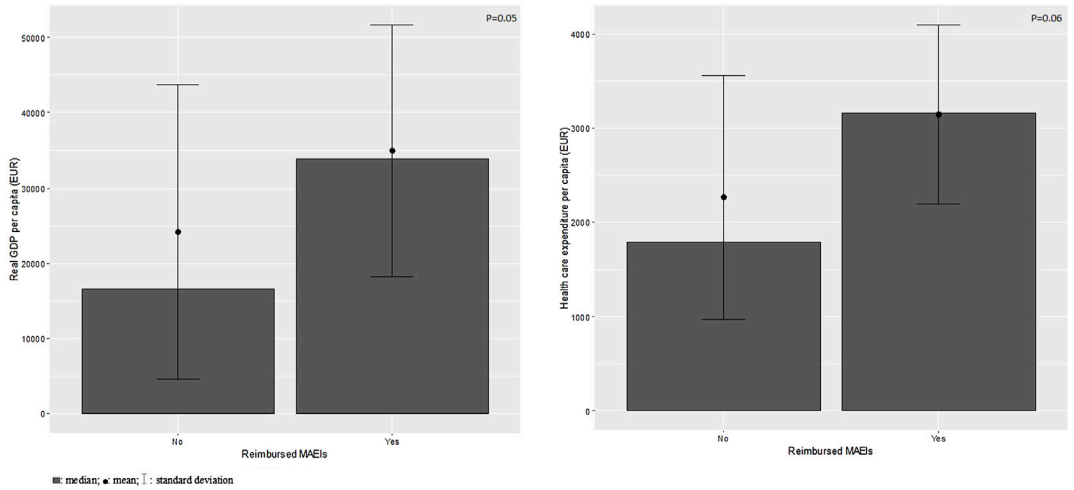

FIGURE 2 | Association between country income and health care expenditure, and the availability of reimbursed medication adherence enhancing interventions across European countries. GDP: gross domestic product; MAEI: medication adherence enhancing intervention.

which we could identify reimbursed adherence interventions. Our findings confirm that despite of the considerable economic and clinical burdens of medication non-adherence, MAEIs remain on a low priority on the health policy agenda of funding bodies. In the European Union, almost 200,000 people die each year because of non-adherence and the direct and indirect costs of poor adherence were estimated to be 80–125 billion EUR annually (European Commission, 2011). However, these losses could be reduced by implementing MAEIs in the everyday clinical practice.

At present, there is no uniform terminology for MAEIs which made it difficult to identify reimbursed adherence interventions. In our survey, MAEI was defined by the authors as a result of discussion and consensus as "any structured intervention aiming to help patients to make optimal use of their pharmacotherapy". However, it might be that respondents interpreted this definition differently when determining whether an intervention affects medication adherence or not. One uniform, common accepted, standard definition for MAEI would be highly warranted to be able to define interventions improving adherence more precisely; particularly in the view of the wide range of various types of educational (e.g., group/individual education provided by physicians, pharmacists, nurses, allied health professionals) and behavioural (e.g., calendar/diary, reminder chart/ medication list, large print labels, packaging change, multi-compartment pillbox/calendar pack/compliance aid, adherence monitoring, reminders) interventions developed recently (Cross et al., 2020).

In total, 13 reimbursed MAEIs were included in our analysis from which MDD and medication review were the most common. In general, as part of MDD, medicines such as tablets, capsules and pills are repackaged with a special equipment automatically into unit-dose bags according to the time of administration, then these bags are dispensed by the community pharmacy to the patient. Unit-dose bags are labelled with the patient's identification data, the drug name, and time of administration (Sinnemaki et al., 2013; Rechel, 2018). Although several Northern and Western European countries embraced MDD to improve medication adherence, evidence on its cost implications is still limited (Rechel, 2018). Herborg et al. (Herborg et al., 2008) conducted a HTA for MDD in Denmark, but this analysis did not cover all HTA aspects. Their study was limited to stakeholders' perspectives and perceptions on the implementation, operation, consequences, and future potential of MDD in the primary care; however, cost-effectiveness of MDD was not evaluated. This HTA concluded that MDD can be effective to improve the medication adherence of chronic patients in the Danish primary care, but there might be organizational obstacles (e.g., resistance from nurses and doctors). Medication review as defined by the Pharmaceutical Care Network Europe (PCNE) is "a structured evaluation of a patient's medicines with the aim of optimizing medicines use and improving health outcomes" (PCNE, 2016). The medication review consultations between doctors, nurses or pharmacists and patients in primary care centers or community pharmacies help to increase patients' knowledge and understanding of their pharmacotherapy and provide an opportunity to detect any drug-related problems. Regarding medication review, a recent meta-analysis found that even on a short-term period, this service has an effect on most drug-related outcomes (e.g., the number of drug changes, the number of drug-related problems, medication adherence); however, similar to MDD the available information does not allow to draw clear conclusions about its economic impact (Huiskes et al., 2017).

Other types of MAEIs such as e-health technologies (e.g., smart devices, mobile applications) or patient education programs were reimbursed only in limited number of European countries. Nevertheless, several e-health interventions have been developed in the past few years (Ma et al., 2022) which could provide an opportunity to improve medication adherence with minimal effort from health care

providers whose time and resources are limited (Pouls et al., 2021).

Based on these findings we can conclude that although several studies have demonstrated that MAEIs may improve clinical outcomes (Salema et al., 2011; Nieuwlaat et al., 2014; van Driel et al., 2016; Blakey et al., 2018; Godinho et al., 2020; Zijp et al., 2020; Gohil et al., 2021; Whiteley et al., 2021), existing evidence on the economic aspects of MAEIs is of poor quality (Elliott et al., 2005). Heterogeneity in the results of economic evaluations within different intervention types is significant due to disparity in the nature of interventions, investigated outcomes, the measures of non-adherence used and time horizons of studies, which makes comparing findings challenging. It should be also noted, that different type of MAEIs may require different type of economic evaluations. For example, in case of service-based interventions (e.g., pharmacy services) multiple phases of the implementation process have to be taken into consideration (i.e., installation phase: preparation of the service provider to deliver the service, initial implementation phase: to pilot the service in a small number of patients, and full operation phase: the full implementation of the service in routine care) (Perraudin et al., 2019), in comparison to e-health technologies (e.g., smart devices) which can be evaluated in a conventional cost-effectiveness analysis. Besides clinical and economic impacts, the consideration of other factors, including social (e.g., access for vulnerable population groups, caregiver burden), and patient related factors (e.g., responsiveness to patients' individual needs) during the critical evaluation of MAEIs may also facilitate decision making while allocating scarce resources. Additionally, the thorough HTA of an e-health intervention may require further specific aspects, e.g., software update and data privacy (Moshi et al., 2018). Lack of published evidence on the HTA and reimbursement pathways of MAEIs from other regions (e.g., North America, Asia) did not allow the comparison between regions. Using structured and explicit approaches for health policy decisions involving multiple value criteria during the HTA of MAEIs could help to identify the most effective interventions based on the best available evidence. Detailed recommendations on the value criteria and economic evaluations would help removing barriers relating to the HTA of MAEIs.

The majority (77%) of the identified MAEIs were reimbursed from public health care funds; however, improving medication adherence is a common goal of all stakeholders in the health care system (i.e., policy makers, pharma industry, health care providers, pharmacists, patients and caregivers). A close cooperation of key stakeholders related to the reimbursement of MAEIs could add a surplus value to the implementation by bridging the gap between clinical research and clinical practice.

We found a statistically significant association between country income (i.e., real GDP per capita, $p = 0.05$) and the availability of reimbursed MAEIs, and a not significant trend in case of health care expenditure. This result raises the possibility that not only the awareness of decision makers on medication non-adherence, but country income might also influence the implementation and reimbursement of MAEIs. Evidence suggests that MAEIs are usually not embedded in a broader understanding of the reasons for suboptimal adherence (Clyne and McLachlan, 2015). Further studies are needed to raise stakeholders' awareness on medication non-adherence to overcome this challenge.

Our results should be considered in the light of certain limitations. First, participants' answers to the survey may be biased by their subjectivity, background and work experience. The survey was completed by ENABLE members and in some countries, information was based on the answers of only one participant. The majority of respondents had academic background (i.e., medical or pharmaceutical sciences) and they might not have sufficient information on e.g. specific MAEIs reimbursed by pharma companies to patients with certain diseases only. Furthermore, it should be noted that the lack of a common definition for MAEIs might also bias the identification of reimbursed interventions. Although our survey might not provide a complete picture on the reimbursement landscape of MAEIs in Europe, it does provide a useful starting point for discussion and may also help to determine where further research is needed. Finally, our survey questionnaire with many closed questions allowed us to capture very specific information on MAEIs. To minimize the potential risks of the self-developed questionnaire, external experts were asked to assess its validity and technical functionality.

In conclusion, to date only a small number of MAEIs have been reimbursed across Europe. Discussions about MAEIs is hampered by the lack of a common terminology. Besides the clinical studies, more research effort should be devoted to better understand the effect of MAEIs on economic outcomes. Specific HTA process guidelines involving multiple value indicators and consequently the comprehensive assessment of MAEIs would help to identify the most effective and cost-effective adherence programs. A close cooperation of key stakeholders related to the reimbursement of MAEIs could set new benchmark to manage medication non-adherence.

EUROPEAN NETWORK TO ADVANCE BEST PRACTICES AND TECHNOLOGY ON MEDICATION ADHERENCE (ENABLE)

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DATA AVAILABILITY STATEMENT

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

AUTHOR CONTRIBUTIONS

All authors contributed to conception and design of the study. TA, MH, KG and PK developed the first draft of the survey

questionnaire. TA and PK aggregated responses to the survey and organized the database. TA performed the statistical analysis. TA wrote the first draft of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2022.892240/full#supplementary-material

REFERENCES

Ágh, T., van Boven, J. F., Wettermark, B., Menditto, E., Pinnock, H., Tsiligianni, I., et al. (2021). A Cross-Sectional Survey on Medication Management Practices for Noncommunicable Diseases in Europe during the Second Wave of the COVID-19 Pandemic. *Front. Pharmacol.* 12, 685696. doi:10.3389/fphar.2021.685696

Blakey, J. D., Bender, B. G., Dima, A. L., Weinman, J., Safioti, G., and Costello, R. W. (2018). Digital Technologies and Adherence in Respiratory Diseases: the Road Ahead. *Eur. Respir. J.* 52 (5), 1801147. doi:10.1183/13993003.01147-2018

Breekveldt-Postma, N. S., Penning-van Beest, F. J., Siiskonen, S. J., Falvey, H., Vincze, G., Klungel, O. H., et al. (2008). The Effect of Discontinuation of Antihypertensives on the Risk of Acute Myocardial Infarction and Stroke. *Curr. Med. Res. Opin.* 24 (1), 121–127. doi:10.1185/030079908x253843

Clyne, W., and McLachlan, S. (2015). A Mixed-Methods Study of the Implementation of Medication Adherence Policy Solutions: How Do European Countries Compare? *Patient Prefer Adherence* 9, 1505–1515. doi:10.2147/PPA.S85408

Costa, E., Giardini, A., Savin, M., Menditto, E., Lehane, E., Laosa, O., et al. (2015). Interventional Tools to Improve Medication Adherence: Review of Literature. *Patient Prefer Adherence* 9, 1303–1314. doi:10.2147/PPA.S87551

Cross, A. J., Elliott, R. A., Petrie, K., Kuruvilla, L., and George, J. (2020). Interventions for Improving Medication-Taking Ability and Adherence in Older Adults Prescribed Multiple Medications. *Cochrane Database Syst. Rev.* 5, CD012419. doi:10.1002/14651858.CD012419.pub2

Cutler, R. L., Fernandez-Llimos, F., Frommer, M., Benrimoj, C., and Garcia-Cardenas, V. (2018). Economic Impact of Medication Non-adherence by Disease Groups: a Systematic Review. *BMJ Open* 8 (1), e016982. doi:10.1136/bmjopen-2017-016982

Elliott, R. A., Barber, N., and Horne, R. (2005). Cost-effectiveness of Adherence-Enhancing Interventions: a Quality Assessment of the Evidence. *Ann. Pharmacother.* 39 (3), 508–515. doi:10.1345/aph.1E398

European Commission.(2011). MEDI-VOICE. MEDI-VOICE Report Summary. Project ID: 17893.

Eurostat (2022). Real GDP Per Capita [SDG_08_10]. Available at: https://ec.europa.eu/eurostat/web/products-datasets/-/sdg_08_10 (Accessed January 10, 2022).

Eysenbach, G. (2004). Improving the Quality of Web Surveys: the Checklist for Reporting Results of Internet E-Surveys (CHERRIES). *J. Med. Internet Res.* 6 (3), e34. doi:10.2196/jmir.6.3.e34

Godinho, M. A., Jonnagaddala, J., Gudi, N., Islam, R., Narasimhan, P., and Liaw, S. T. (2020). mHealth for Integrated People-Centred Health Services in the Western Pacific: A Systematic Review. *Int. J. Med. Inf.* 142, 104259. doi:10.1016/j.ijmedinf.2020.104259

Gohil, S., Majd, Z., Sheneman, J. C., and Abughosh, S. M. (2021). Interventions to Improve Medication Adherence in Inflammatory Bowel Disease: a Systematic Review. *Patient Educ. Couns.* S0738-3991 (21), 00676–685. doi:10.1016/j.pec.2021.10.017

Herborg, H., Haugbølle, L. S., and Lee, A. (2008). Automated Dose Dispensing in Danish Primary Health Care - a Technology under Construction. *Pharm. Pract. (Granada)* 6 (2), 103–112. doi:10.4321/s1886-36552008000200008

Huiskes, V. J., Burger, D. M., van den Ende, C. H., and van den Bemt, B. J. (2017). Effectiveness of Medication Review: a Systematic Review and Meta-Analysis of Randomized Controlled Trials. *BMC Fam. Pract.* 18 (1), 5. doi:10.1186/s12875-016-0577-x

Inotai, A., Ágh, T., Maris, R., Erdősi, D., Kovács, S., Kaló, Z., et al. (2021). Systematic Review of Real-World Studies Evaluating the Impact of Medication Non-adherence to Endocrine Therapies on Hard Clinical Endpoints in Patients with Non-metastatic Breast Cancer. *Cancer Treat. Rev.* 100, 102264. doi:10.1016/j.ctrv.2021.102264

Kardas, P., Urbański, F., Lichwierowicz, A., Chudzyńska, E., Kardas, G., and Czech, M. (2021). Prevalence and Age Structure of Polypharmacy in Poland: Results of the Analysis of the National Real-World Database of 38 Million Citizens. *Front. Pharmacol.* 12, 655364. doi:10.3389/fphar.2021.655364

Khan, R., and Socha-Dietrich, K. (2018). Investing in Medication Adherence Improves Health Outcomes and Health System Efficiency. *OECD Health Work. Pap.* 105, 39. doi:10.1787/8178962c-en

Kleinsinger, F. (2018). The Unmet Challenge of Medication Nonadherence. *Perm. J.* 22, 18–033. doi:10.7812/TPP/18-033

Kostalova, B., Ribaut, J., Dobbels, F., Gerull, S., Mala-Ladova, K., Zullig, L. L., et al. (2022). Medication Adherence Interventions in Transplantation Lack Information on How to Implement Findings from Randomized Controlled Trials in Real-World Settings: A Systematic Review. *Transpl. Rev. Orl.* 36, 100671. doi:10.1016/j.trre.2021.100671

Kurczewska-Michalak, M., Lewek, P., Jankowska-Polańska, B., Giardini, A., Granata, N., Maffoni, M., et al. (2021). Polypharmacy Management in the Older Adults: A Scoping Review of Available Interventions. *Front. Pharmacol.* 12, 734045. doi:10.3389/fphar.2021.734045

Ma, Y., Zhao, C., Zhao, Y., Lu, J., Jiang, H., Cao, Y., et al. (2022). Telemedicine Application in Patients with Chronic Disease: a Systematic Review and Meta-Analysis. *BMC Med. Inf. Decis. Mak.* 22 (1), 105. doi:10.1186/s12911-022-01845-2

Midão, L., Giardini, A., Menditto, E., Kardas, P., and Costa, E. (2018). Polypharmacy Prevalence Among Older Adults Based on the Survey of Health, Ageing and Retirement in Europe. *Arch. Gerontol. Geriatr.* 78, 213–220. doi:10.1016/j.archger.2018.06.018

Mongkhon, P., Ashcroft, D. M., Scholfield, C. N., and Kongkaew, C. (2018). Hospital Admissions Associated with Medication Non-adherence: a Systematic Review of Prospective Observational Studies. *BMJ Qual. Saf.* 27 (11), 902–914. doi:10.1136/bmjqs-2017-007453

Moshi, M. R., Tooher, R., and Merlin, T. (2018). Suitability of Current Evaluation Frameworks for Use in the Health Technology Assessment of Mobile Medical Applications: a Systematic Review. *Int. J. Technol. Assess. Health Care* 34 (5), 464–475. doi:10.1017/S026646231800051X

Nieuwlaat, R., Wilczynski, N., Navarro, T., Hobson, N., Jeffery, R., Keepanasseril, A., et al. (2014). Interventions for Enhancing Medication Adherence. *Cochrane Database Syst. Rev.* 2014 (11), CD000011. doi:10.1002/14651858.CD000011.pub4

Organisation for Economic Co-operation and Development (OECD) (2020). *Health at a Glance: Europe 2020: State of Health in the EU Cycle*. Paris: OECD Publishing doi:10.1787/82129230-en (Accessed January 10, 2022)

Perraudin, C., Locca, J. F., Rossier, C., Bugnon, O., and Schneider, M. P. (2019). Implementation of an Interprofessional Medication Adherence Program for Chronic Patients in Community Pharmacies: How Much Does it Cost for the Provider? *BMC Health Serv. Res.* 19 (1), 15. doi:10.1186/s12913-018-3851-x

Pharmaceutical Network Europe (PCNE) (2016). Position Paper on the PCNE Definition of Medication Review 2016. Available at: http://www.pcne.org/upload/files/149_Position_Paper_on_PCNE_ Medication_Review_final.pdf (Accessed January 10, 2022).

Pouls, B. P. H., Vriezekolk, J. E., Bekker, C. L., Linn, A. J., van Onzenoort, H. A. W., Vervloet, M., et al. (2021). Effect of Interactive eHealth Interventions on Improving Medication Adherence in Adults with Long-Term Medication: Systematic Review. *J. Med. Internet Res.* 23 (1), e18901. doi:10.2196/18901

Rechel, B. (2018)., 24. 3–6.Hub-And-Spoke Dispensing Models for Community Pharmacies in Europe*Eurohealth*4

Salema, N. E., Elliott, R. A., and Glazebrook, C. (2011). A Systematic Review of Adherence-Enhancing Interventions in Adolescents Taking Long-Term Medicines. *J. Adolesc. Health* 49 (5), 455–466. doi:10.1016/j.jadohealth.2011.02.010

Simon-Tuval, T., Neumann, P. J., and Greenberg, D. (2016). Cost-effectiveness of Adherence-Enhancing Interventions: a Systematic Review. *Expert Rev. Pharmacoecon Outcomes Res.* 16 (1), 67–84. doi:10.1586/14737167.2016.1138858

Sinnemäki, J., Sihvo, S., Isojärvi, J., Blom, M., Airaksinen, M., and Mäntylä, A. (2013). Automated Dose Dispensing Service for Primary Healthcare Patients: a Systematic Review. *Syst. Rev.* 2, 1. doi:10.1186/2046-4053-2-1

van Boven, J. F., Tsiligianni, I., Potočnjak, I., Mihajlović, J., Dima, A. L., Nabergoj Makovec, U., et al. (2021). European Network to Advance Best Practices and Technology on Medication Adherence: Mission Statement. *Front. Pharmacol.* 12, 748702. doi:10.3389/fphar.2021.748702

van Driel, M. L., Morledge, M. D., Ulep, R., Shaffer, J. P., Davies, P., and Deichmann, R. (2016). Interventions to Improve Adherence to Lipid-Lowering Medication. *Cochrane Database Syst. Rev.* 12 (12), CD004371. doi:10.1002/14651858.CD004371.pub4

Whiteley, L. B., Olsen, E. M., Haubrick, K. K., Odoom, E., Tarantino, N., and Brown, L. K. (2021). A Review of Interventions to Enhance HIV Medication Adherence. *Curr. HIV/AIDS Rep.* 18 (5), 443–457. doi:10.1007/s11904-021-00568-9

World Health Organization (WHO) (2003). *Adherence to Long-Term Therapies: Evidence for Action*. Switzerland: World Health Organization.

World Health Organization (WHO) (2014). *Assessing Chronic Disease Management in European Health Systems Concepts and Approaches*. Switzerland: World Health Organization.

Zijp, T. R., Touw, D. J., and van Boven, J. F. M. (2020). User Acceptability and Technical Robustness Evaluation of a Novel Smart Pill Bottle Prototype Designed to Support Medication Adherence. *Patient Prefer Adherence* 14, 625–634. doi:10.2147/PPA.S240443

Zullig, L. L., Deschodt, M., Liska, J., Bosworth, H. B., and De Geest, S. (2019). Moving from the Trial to the Real World: Improving Medication Adherence Using Insights of Implementation Science. *Annu. Rev. Pharmacol. Toxicol.* 59, 423–445. doi:10.1146/annurev-pharmtox-010818-021348

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Adherence to Statin Therapy and Attainment of LDL Cholesterol Targets in an Outpatient Population of Type 2 Diabetes Patients: Analysis in the DIAbetes and LifEstyle Cohort Twente (DIALECT)

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Objective: To assess adherence to statin therapy and its association with sociodemographic data, medical characteristics, LDLc levels, and LDLc target attainment in real-world T2D patients treated in secondary care.

Research Design and Methods: Cross-sectional analyses were performed on baseline data of 393 patients in the DIAbetes and LifEstyle Cohort Twente (DIALECT). The medication possession ratio (MPR), calculated with pharmacy dispensing data, was used to determine adherence to statins for an intended period of 24 months. Statins were included in the analyses if they were used for at least six consecutive months with at least three dispenses. Adherence was defined as an MPR ≥80%. Associations with adherence were assessed using descriptive statistics and binary logistic regression.

Results: Overall, 80% of the patients had a statin prescription and of those, 89% were adherent. The proportion of patients who reached LDLc targets of ≤2.5 mmol/L and <1.8 mmol/L differed significantly between the adherent, nonadherent and non-statin group (90% vs. 74% vs. 46%; $p < 0.01$ and 56% vs. 26% vs. 6%; $p < 0.01$, respectively). Serum LDLc levels were lower in the adherent versus the nonadherent and non-statin group (1.76 ± 0.60 vs. 2.23 ± 0.90 vs. 2.71 ± 0.67 mmol/L; $p < 0.01$). Higher HbA1c levels were independently associated with nonadherence (OR: 1.05, 95% CI 1.01–1.08; $p < 0.01$). Mediation adherence (OR: 2.88, 95% CI 1.04–7.97; $p = 0.041$) and lower BMI (OR: 0.88, 95% CI 0.81–0.96; $p < 0.01$) were independently associated with attaining the LDLc target of ≤2.5 mmol/L.

Conclusion: In patients with T2D treated in secondary care, statin adherence was relatively high and was associated with significantly lower LDLc levels. It is important to identify nonadherence as it appeared an important determinant of failure to reach LDLc targets. The finding that many patients who failed to attain LDLc targets did not receive statin treatment offers an opportunity to improve diabetes care.

Keywords: diabet mellitus type 2, statin (HMG-CoA reductase inhibitor), medication adherance, medication possesion ratio, LDL—cholesterol, cholesterol, lipid lowering medication, LDL cholesterol targets

INTRODUCTION

Type 2 diabetes (T2D) is associated with an increased risk for cardiovascular complications (Emerging Risk Factors Collaboration Sarwar et al., 2012; Rana et al., 2016). Prevention of cardiovascular complications by treatment of dyslipidaemia is therefore one of the main goals of diabetes care. Indeed, lowering of low-density lipoprotein cholesterol (LDLc) in T2D consistently reduces cardiovascular events (Colhoun et al., 2004; De Vries et al., 2012; De Vries et al., 2014; Burggraaf and Castro Cabezas, 2017). Given the strong association between LDLc and cardiovascular outcomes, diabetes guidelines provide treatment recommendations in order to reach specific LDLc targets (Piepoli et al., 2016; Kwaliteitsinstituut voor de Gezondheidszorg CBO, Nederlands Huisartsen Genootschap, 2020). Nevertheless, a recent Dutch study in the Diabetes and LifEstyle Cohort Twente (DIALECT) showed that the LDLc target of ≤2.5 mmol/L was not achieved by approximately 25% of this real-world cohort of patients with long-standing complicated T2D (Gant et al., 2018).

To improve long-term clinical outcomes, it is important to identify causes for failure of reaching LDLc treatment targets, especially in those with a very high cardiovascular risk profile. Notably, patient adherence to lipid-lowering drugs is a key factor to take into account. Previous studies have shown high rates of nonadherence to statin therapy (17.8–79.2%) (Hope et al., 2019). However, the majority of these studies did not assess the association of adherence with LDLc levels and LDLc target attainment, and some of these studies did assess adherence using patient self-report questionnaires, which might have resulted in over- or under-reporting (Perreault et al., 2009; Stuurman-Bieze et al., 2013; Wallach-Kildemoes et al., 2013; Halava et al., 2014; Farsaei et al., 2015). We aim to assess adherence to statin therapy using pharmacy dispensing data and its association with sociodemographic data, medical characteristics, LDLc levels and LDLc target attainment in a group of 393 real-world patients with complicated T2D.

MATERIALS AND METHODS

Study Design and Setting

This study was performed in the DIAbetes and LifEstyle Cohort Twente-1 (DIALECT-1) cohort (Gant et al., 2017). DIALECT is an observational prospective cohort study performed in the Ziekenhuis Groep Twente Hospital (Almelo and Hengelo, Netherlands) and designed to investigate the effect of lifestyle and dietary habits and pharmacological treatment on outcomes in patients with complicated T2D treated in secondary care. The primary aim of DIALECT is to identify targets for the improvement of treatment quality by a systematic assessment of both pharmacological and nutritional management. Patients in the DIALECT-1 population were recruited between September 2009 and January 2016 (n = 450). Our study was performed according to the guidelines of good clinical practice and the declaration of Helsinki. Written informed consent was obtained from all patients before participation. The study has been approved by the local institutional review boards (Medisch Ethische Toetsingscommissie Reg. Nos., NL57219.044.16 and 1009.68020) and is registered in Netherlands Trial Register (NTR trial code 5855).

Participants

The study population consisted of patients with T2D aged ≥18 years treated in the outpatient clinic as part of routine secondary care. In Netherlands, criteria for referral from primary to secondary health care are inability to achieve adequate glycaemic control [defined as failure to achieve the HbA1c target, which is usually ≤7% (53 mmol/mol)] with oral antidiabetics or a standard insulin regimen, macroalbuminuria and/or estimated glomerular filtration rate ≤60 ml/min, or multiple cardiovascular complications (Gant et al., 2018). Patients on renal replacement therapy or patients with insufficient knowledge of the Dutch language were excluded from participation.

Eligible patients were selected from the electronic patient file and contacted by phone, as described in detail previously (Gant et al., 2017). Of the original 450 patients included in DIALECT-1, 15 patients were excluded at a later stage because it turned out their actual diagnosis was type 1 diabetes (n = 9) or LADA (n = 2). Other reasons were dialysis before inclusion (n = 1) or because patients were included in the database twice (n = 2). Of these 435 patients, 393 patients were eligible for the current study. We excluded patients who did not have a baseline LDL laboratory value (n = 9), those with no informed consent for collecting pharmacy data (n = 17), those from whom no pharmacy data were available (n = 13), and those intolerant to statins due to side-effects (n = 3). Characteristics of excluded patients did not differ materially from those who were eligible for the current study (**Supplementary Table S1**).

Baseline Demographics and Clinical Variables

At the outpatient clinic, baseline sociodemographic characteristics, medical history, lifestyle behaviours, and

current medications were recorded. Anthropometric dimensions were measured using standard procedures. Non-fasting blood tests were taken at baseline visit to determine serum LDLc, total cholesterol, and HbA1c. Further details concerning baseline demographics and clinical variables have been described previously (Gant et al., 2017).

Measurement of Adherence to Statins

For this study, pharmacy dispensing data were used to determine medication adherence. All the patients included in this study were re-approached in 2016 and 2017 in order to obtain new informed consent for collecting pharmacy data. Pharmacies were subsequently approached to provide the complete medication dispensing history of the patient from the baseline date of DIALECT-1 up to that day. As for the loss of patients, all the patients included in this study are under long-term treatment in our hospital. For patients who were referred to primary care or for patients who moved to another location, we had access to their contact details, which allowed us to approach them to provide consent for collecting pharmacy data. Analysis of the medication dispensing history was performed for an intended period of 24 months starting from the baseline visit. Using the pharmacy dispensing data, we calculated the number of tablets every patient obtained for each individual chronic medication during the intended 24-months follow-up. For each chronic medication, the first dispensing date after baseline and corresponding data about the number of tablets and dose were noted. The end date was defined as the date of the day before the last collection. Statins were included in the analyses if they were used for at least six consecutive months with at least three dispenses.

Adherence was subsequently determined by calculating the medication possession ratio (MPR), an adequate and well-accepted proxy for medication adherence by using pharmacy dispensing data (Steiner and Prochazka, 1997). The MPR is the proportion of time that prescribed medication is actually available for the patient and is defined as the ratio between the sum of days' supply for all fills in a certain period and the number of days in that period. Good adherence was defined as an MPR ≥80% (Anghel et al., 2019). By default, 26 of the included patients were provided an automated medication dispensing system (Baxter Healthcare Corporation, Deerfield, LI, United States). These patients had an MPR of 100%. Changes to another statin or dosage during the follow-up period were carefully documented in the database. Left over medication after a change to another statin or dosage was subtracted from the total number of pills and accordingly, left over medication was not included in analyses.

Cholesterol Targets

We assessed the association of medication adherence with two common LDLc targets. The primary treatment target for LDLc was ≤2.5 mmol/L, in line with the Dutch guidelines for cardiovascular risk management in T2D (Kwaliteitsinstituut voor de Gezondheidszorg CBO, Nederlands Huisartsen Genootschap, 2020). In addition, we studied associations with the LDLc target of <1.8 mmol/L for patients with a very high risk of CVDs (97% of our population) that is advocated in the European guideline for CVD prevention (Piepoli et al., 20162016). Finally, we assessed associations with serum LDLc and total cholesterol levels.

Other Clinical Outcomes

In addition to associations of adherence with cholesterol outcomes, we assessed associations with other intermediate clinical characteristics (e.g., diabetes duration, HbA1c, and blood pressure), and microvascular and macrovascular complications. Details concerning the intermediate clinical characteristics and definitions of microvascular and macrovascular complications have been described previously (Gant et al., 2017).

Statin Type and Intensity

Associations of adherence with statin type (simvastatin, atorvastatin, rosuvastatin, fluvastatin, and pravastatin) and intensity were also tested. Three statin treatment intensities were defined: "medium intensity" statin treatment was defined as simvastatin 20–40 mg/day, atorvastatin 10–20 mg/day, rosuvastatin 5 mg/day, or pravastatin 40–80 mg/day (Helfand et al., 2006). Lower and higher prescribed dosages were defined as "low-intensity" and "high-intensity" statin treatment, respectively.

Statistical Analysis

All statistical analyses were performed using IBM SPSS for Windows (version 24.0; IBM Corp., Armonk, NY, United States). Normally distributed data are presented as mean ± SDs. Skewed variables are presented as median [interquartile ranges (IQRs)]. Dichotomous variables are presented as number (percentages). A two tailed p value < 0.05 was considered statistically significant. Normality of data was assessed using the Kolmogorov-Smirnov and Shapiro-Wilk tests of normality and by visually inspecting the frequency histograms of each variable. Post Hoc Tukey's range tests were performed to assess if any of the three groups were statistically significantly different from each other. Significant differences determined by the Tukey's range test are indicated by an asterisk (*). If all groups differed statistically significantly from each other, the asterisk was omitted.

The population was divided into two groups according to their adherence based on pharmacy dispensing data (MPR ≥80% or MPR <80%) and a third group consisting of patients without statin prescription. Differences between the adherent, nonadherent and non-statin group in sociodemographic data, medical characteristics, LDLc levels, and LDLc target attainment (≤2.5 mmol/L and <1.8 mmol/L) were tested using the one-way analysis of variance for normally distributed variables, Kruskal-Wallis for skewed variables, and the χ^2 test for dichotomous variables. Determinants of nonadherence and determinants of attaining the LDLc target of ≤2.5 mmol/L were studied using binary logistic regression analysis based on complete cases. Potential confounders were selected based on relevant differences in characteristics in the baseline table, biological plausibility and previous literature.

TABLE 1 | Baseline characteristics by overall adherence in the DIALECT-1 population.

	Total population	Adherent	Nonadherent	No statin	*p*
Patients	393	280 (89.2)	34 (10.8)	79 (20.1)	
MPR (%)	99.5 (92.4–101.3)	99.9 (95.3–101.8)	60.9 (38.3–70.2)	N/A	<0.01*
Refills	8 (3–10)	8 (3–11)	7 (3–10)	N/A	0.10
Age, years	62.7 ± 9.1	63.1 ± 8.5	62.8 ± 10.7	61.3 ± 10.2	0.30
Male sex	230 (58.5)	168 (60.0)	20 (58.8)	42 (53.2)	0.55
Diabetes duration, years	11 [7–18]	12 [7–19]	9 [5–15]	9 [4–14]	<0.01*
BMI, kg/m^2[a]	33.0 ± 6.2	33.2 ± 6.2	31.2 ± 6.8	32.9 ± 6.0	0.19
Smoking status					
Current	68 (17.3)	48 (17.1)	6 (17.6)	14 (17.7)	0.99
Former	209 (53.2)	153 (54.6)	19 (55.9)	37 (46.8)	0.45
Never	116 (29.5)	79 (28.2)	9 (26.5)	28 (35.4)	0.43
HbA1c, % (mmol/mol)[a]	7.4 ± 3,2 (57.0 ± 11.5)	7.4 ± 3.0 (57.0 ± 9.8)	7.8 ± 3.7 (61.5 ± 16.9)*	7.2 ± 3.4 (55.3 ± 13.7)*	0.031*
Serum cholesterol, mmol/L[a]	3.97 ± 0.90	3.72 ± 0.77	4.25 ± 1.00	4.72 ± 0.86	<0.01*
LDL cholesterol, mmol/L	1.99 ± 0.75	1.76 ± 0.60	2.23 ± 0.90	2.71 ± 0.67	<0.01*
LDL cholesterol ≤2.5 mmol/L	313 (79.6)	252 (90.0)	25 (73.5)	36 (45.6)	<0.01*
LDL cholesterol <1.8 mmol/L	172 (43.8)	158 (56.4)	9 (26.5)	5 (6.3)	<0.01*
Systolic BP, mmHg[a]	139 ± 16	139 ± 16	139 ± 15	141 ± 15	0.58
Diastolic BP, mmHg[a]	76 ± 9	75 ± 9*	76 ± 8	78 ± 9*	0.017*
Microvascular complications	271 (69.0)	202 (72.1)	25 (73.5)	44 (55.7)	0.017*
Neuropathy	140 (35.6)	104 (37.1)	10 (29.4)	26 (32.9)	0.58
Retinopathy[a]	92 (23.4)	71 (25.4)	10 (29.4)	11 (13.9)	0.09
DKD	158 (40.2)	121 (43.2)	15 (44.1)	22 (27.8)	0.049*
Macrovascular complications	142 (36.1)	109 (38.9)	15 (44.1)	18 (22.8)	0.018*
Insulin use	246 (62.6)	183 (65.4)	22 (64.7)	41 (51.9)	0.09
Antihypertensive drug use	323 (82.2)	243 (86.8)	26 (76.5)	54 (68.4)	<0.01*

Data are presented as n *(%), mean ± SD, or median (interquartile range) for nominal, normally distributed, and nonnormally distributed data, respectively.*
Abbreviations: MPR, Medication Possession Ratio; LDL, Low-Density Lipoprotein; DKD, Diabetic kidney disease.
[a]*Missing values for BMI* (n = 2), *HbA1c* (n = 2), *serum cholesterol* (n = 3), *systolic blood pressure* (n = 2), *diastolic blood pressure* (n = 2), *retinopathy* (n = 2), *DKD* (n = 2).
**Statistically significant difference between the groups* (p *value < 0.05).*

RESULTS

Descriptive Data

The mean age was 63 ± 9 years (**Table 1**), median diabetes duration was 11 (7–18) years, mean HbA1c was 57 ± 12 mmol/mol (7.4 ± 3.2%), and the mean BMI was 33 ± 6 kg/m^2, reflecting a population with advanced T2D.

Medication Adherence

Of our total study population, 314 out of 393 (80%) patients had a statin prescription and of these, 280 (89%) were found to be adherent (**Table 1**). MPR rates for adherent and nonadherent patients were approximately 100% (95–102%) and 61% (38–70%), respectively. The adherent, nonadherent, and non-statin groups had a similar age, sex distribution, and BMI.

Medication Adherence and Cholesterol Levels

The proportion of patients who reached the LDLc target of ≤2.5 mmol/L differed significantly between the adherent, nonadherent and non-statin groups (90% vs. 74% vs. 46%, respectively; $p < 0.01$) (**Figure 1**). The same applied to attainment of the LDLc target of <1.8 mmol/L (56% vs. 26.5% vs. 6%; $p < 0.01$). Accordingly, serum LDLc levels were significantly different between the adherent, nonadherent and non-statin groups (1.76 ± 0.60 vs. 2.23 ± 0.90 vs. 2.71 ± 0.67 mmol/L; $p < 0.01$) (**Table 1**). The same was true for to total cholesterol levels (3.72 ± 0.77 vs. 4.25 ± 1.00 vs. 4.72 ± 0.86 mmol/L; $p < 0.01$).

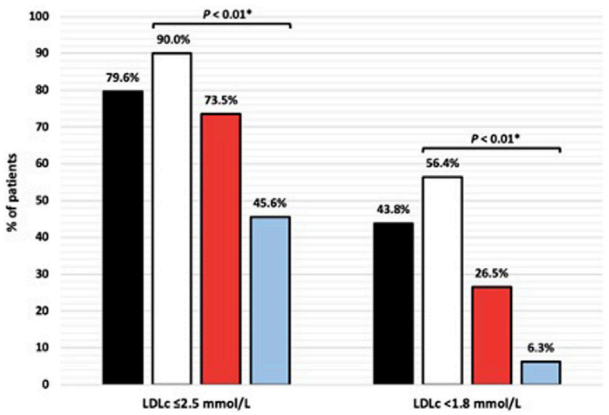

FIGURE 1 | Attainment of LDL cholesterol (LDLc) targets by adherence. Black bars, total population; white bars, adherent; red bars, nonadherent; blue bars, no statin. *$p < 0.05$ indicates significant differences between adherent, nonadherent and non-statin groups.

TABLE 2 | Statin subtype prescription and treatment intensity.

	Total population	Adherent	Nonadherent	*p*
Subtype				
Overall	314	280 (89.2)	34 (10.8)	
Simvastatin	155 (49.4)	132 (85.2)	23 (14.8)	0.024*
Atorvastatin	63 (20.1)	58 (92.1)	5 (7.9)	0.41
Rosuvastatin	72 (22.9)	67 (93.1)	5 (6.9)	0.23
Pravastatin	20 (6.4)	19 (95.0)	1 (5.0)	0.39
Fluvastatin	3 (1.0)	3 (100)	0 (0)	0.54
Treatment intensity				
Low	23 (7.3)	22 (95.7)	1 (4.3)	0.30
Medium	209 (66.6)	183 (87.6)	26 (12.4)	0.20
High	81 (25.8)	74 (91.4)	7 (8.6)	0.46

Data are presented as n *(%).*

**Statistically significant difference between the groups (*p *value < 0.05).*

Medication Adherence and Other Cardiovascular Risk Factors

Diabetes duration did not differ between adherent and nonadherent patients [12 (7–19) vs. 9 (5–15) years; $p = 0.067$], but was significantly higher in adherent patients compared with patients without statin prescription [12 (7–19) vs. 9 (4–14) years; $p < 0.01$)] (**Table 1**). HbA1c levels were significantly higher in nonadherent patients compared with adherent patients [61.5 ± 16.9 (7.8 ± 3.7%) vs. 57.0 ± 9.8 mmol/mol (7.4 ± 3.0%); $p = 0.031$]. No significant differences were found between systolic and diastolic blood pressure levels in the two groups using statins. However, diastolic blood pressure was significantly higher in patients without statin prescription compared with adherent patients (78 ± 9 vs. 75 ± 9 mmHg; $p < 0.01$). The proportion of patients with an insulin or antihypertensive drug prescription did not differ between adherent and nonadherent patients, but antihypertensive drug use was significantly lower in patients without statin prescription compared with adherent patients (68% vs. 87%; $p < 0.01$).

Medication Adherence and Diabetes Complications

The prevalence of microvascular and macrovascular complications did not differ between adherent and nonadherent patients (72% vs. 74%; $p = 0.87$ and 39% vs. 44%; $p = 0.56$, respectively) (**Table 1**). However, the prevalence of these complications was significantly lower in patients without statin prescription compared with adherent and nonadherent patients (56%; $p = 0.017$ and 23%; $p = 0.018$). Within the individual components of microvascular complications, the prevalence of diabetic kidney disease was significantly lower in patients without statin prescription compared with adherent and nonadherent patients (28% vs. 43% vs. 44%, respectively; $p = 0.049$).

Medication Adherence and Type and Intensity of Statin Therapy

Regarding statin prescriptions, the most common compound was simvastatin (49%) (**Table 2**). In the nonadherent group, the proportion of patients who had a prescription of simvastatin was significantly higher compared with adherent patients (68% vs. 47%, $p = 0.024$). No significant associations were found between adherence and other statin subtypes or treatment intensity.

Determinants of Nonadherence

Multivariate binary logistic regression (**Table 3**) indicated that higher HbA1c levels (OR: 1.05, 95% CI 1.01–1.08 per 1 mmol/mol increment in HbA1c; $p < 0.01$) were independently associated with nonadherence. No significant associations were found for diabetes duration, BMI, microvascular complications, macrovascular complications, insulin prescription, antihypertensive drug prescription, and statin prescription.

Determinants of Attaining the LDLc Target of ≤2.5 mmol/L

Multivariate binary logistic regression (**Table 4**) indicated that medication adherence (OR: 2.88, 95% CI 1.04–7.97; $p = 0.041$), lower BMI (OR: 0.88, 95% CI 0.81–0.96 per 1 kg/m^2 decrement in BMI; $p < 0.01$), and pravastatin prescription (OR: 11.53, 95% CI 3.69–36.01; $p < 0.01$) were independently associated with attaining the LDLc target of ≤2.5 mmol/L. No significant associations were found for diabetes duration, HbA1c, microvascular complications, macrovascular complications, insulin prescription, antihypertensive drug prescription, and prescription of other statin subtypes.

DISCUSSION

Main Results

In this report, we present the assessment of adherence to statins in a real-life population with T2D patients managed in routine secondary care using pharmacy dispensing data. To our knowledge, this is one of the first studies to report adherence in the real-world setting by calculating the MPR using pharmacy dispensing data and report the association of adherence with sociodemographic data, medical characteristics, LDLc levels, and LDLc target attainment in T2D patients. Generally, statin adherence levels were relatively high compared with those seen in other studies (17.8–79.2%) (Hope et al., 2019), and adherence was associated with lower LDLc levels. In addition, LDLc targets were reached less frequently in nonadherent patients. This highlights the importance of identifying nonadherence, as it appears to be an important determinant of failure to reach LDLc targets. Despite extensive evidence of the effectiveness of lipid-lowering drugs, the share of non-statin users in our study was high (20.1%). The finding that many patients who failed to attain LDLc targets did not receive statin treatment offers an opportunity to improve diabetes care.

Related Research

In a recent study by Fang et al. (2021), a cross-sectional analysis of data from adults with diabetes in the United States participating

TABLE 3 | Independent determinants of nonadherence to statins.

Variable	OR (95% CI) univariate	*p* value univariate	OR (95% CI) multivariate	*p* value multivariate
Diabetes duration	0.96 (0.91–1.00)	0.07	0.95 (0.89–1.00)	0.06
High BMI	0.94 (0.88–1.01)	0.07	0.94 (0.88–1.01)	0.10
HbA1c (mmol/mol)	1.04 (1.01–1.07)	0.024	1.05 (1.01–1.08)	<0.01
Microvascular complications	1.07 (0.48–2.40)	0.87	1.22 (0.49–3.01)	0.67
Macrovascular complications	1.24 (0.60–2.54)	0.56	1.83 (0.79–4.21)	0.16
Insulin prescription	0.97 (0.46–2.05)	0.94	1.30 (0.54–3.14)	0.56
Any antihypertensive treatment	0.50 (0.21–1.18)	0.11	2.45 (0.91–6.59)	0.08
Statin prescription				
Simvastatin	Ref.		Ref.	
Atorvastatin	0.50 (0.18–1.37)	0.17	0.42 (0.14–1.26)	0.12
Rosuvastatin	0.43 (0.16–1.18)	0.10	0.52 (0.18–1.51)	0.23
Pravastatin	0.29 (0.04–2.24)	0.23	0.35 (0.04–2.85)	0.32
Fluvastatin	[a]		[a]	

Fully adjusted logistic regression model with nonadherence as study outcome. Abbreviation: OR, odds ratio.
[a]Fluvastatin was prescribed in only three patients, which were all adherent These three patients were omitted for the purpose of analysis.

TABLE 4 | Independent determinants of attaining the LDLc target of ≤2.5 mmol/L.

Variable	OR (95% CI) univariate	*p* value univariate	OR (95% CI) multivariate	*p* value multivariate
Medication adherence	3.24 (1.38–7.63)	<0.01	2.88 (1.04–7.97)	0.041
Diabetes duration	0.97 (0.94–1.00)	0.049	0.99 (0.94–1.05)	0.83
High BMI	0.94 (0.90–0.99)	0.014	0.88 (0.81–0.96)	<0.01
HbA1c (mmol/mol)	1.01 (0.99–1.03)	0.45	1.03 (0.99–1.06)	0.15
Microvascular complications	1.06 (0.62–1.82)	0.82	0.81 (0.33–1.95)	0.63
Macrovascular complications	1.08 (0.65–1.79)	0.78	1.12 (0.49–2.55)	0.80
Insulin prescription	0.67 (0.41–1.11)	0.12	0.65 (0.27–1.55)	0.33
Any antihypertensive treatment	0.69 (0.38–1.26)	0.22	1.19 (0.36–3.93)	0.78
Statin prescription				
Simvastatin	Ref.		Ref.	
Atorvastatin	0.79 (0.30–2.07)	0.63	1.04 (0.36–3.01)	0.94
Rosuvastatin	0.55 (0.20–1.53)	0.25	0.59 (0.18–1.99)	0.40
Pravastatin	6.23 (2.37–16.37)	<0.01	11.53 (3.69–36.01)	<0.01
Fluvastatin	3.74 (0.32–43.21)	0.29	4.11 (0.32–53.60)	0.28

Fully adjusted logistic regression model with LDLc ≤2.5 mmol/L as study outcome.
Abbreviations: BMI, body mass index; OR, odds ratio.

in the National Health and Nutrition Examination Survey (NHANES), national trends in diabetes treatment and risk-factor control from 1999 through 2018 were assessed. They found that the use of statin medication plateaued after 2010 at approximately 56%. Our study confirms and extends this finding by demonstrating that in a health setting with well-established insurance coverage still many patients do not receive statin treatment and that non-adherence to statins is one of the determinants why patients do not reach targets.

As a possible explanation for the high degree of medication adherence in our population, one might speculate that patients treated in secondary care may feel more urgency to adhere to their treatment in comparison to patients treated in primary care. This is supported by comparing our study results with the results of the study of Guglielmi et al. (2017), where nonadherence rates of respectively 39% and 45% after 3 and 6 months were seen in patients treated in primary care.

In terms of urgency, another possible explanation for the high degree of medication adherence in our total population might be that the high prevalence of microvascular and macrovascular complications in the DIALECT population motivates patients to take their medication. However, the degree of diabetes complications does not explain why one patient was adherent and another was not, as the prevalence of microvascular and macrovascular complications did not differ between adherent and nonadherent patients in our study.

Furthermore, the well-organized pharmacy service in Netherlands could be a factor that improves adherence by frequent personalized contact between pharmacy staff and patients and proactive medication deliveries. Of the DIALECT population, 26 patients were using an automated medication dispensing system. Although organized delivery does not guarantee actual medication intake, the overall results as based on the MPR are very much in line with our previous findings regarding medication adherence based on LC-MS/MS analysis of urine samples in the same patients (Beernink et al., 2021).

Our main finding, i.e., that statin adherence was related to LDLc target attainment, is in line with a previous study in 653 patients with T2D treated for dyslipidaemia in a managed care diabetes program (Parris et al., 2005). The percentage of the patients achieving an LDLc target of ≤2.5 mmol/L was lower in that study versus ours (44% vs. 80%). The same applied to the median MPR rates, namely 70% versus 99.5% in our study. The differences in MPR rates could be a possible explanation for the differences in LDLc target attainment. One might speculate that differences in statin subtype prescription could also play a role in explaining the LDLc results. However, the most frequently prescribed compound in the former study was atorvastatin, which is known to be more potent than simvastatin (Law et al., 2003).

Of note, the level of adherence in our study was in the same range as previously reported in a large cohort of coronary heart disease patients that assessed associations of adherence with LDLc, where an overall MPR of 79.8% was found (Chi et al., 2014). In that study, 85.8% reached the 2.5 mmol/L LDLc target and 32.4% had a LDLc value less than 1.8 mmol/L, the latter percentage being considerably lower compared with our study, which might be explained by differences in prevailing guidelines and/or the presence of the additional underlying condition diabetes.

Despite the high medication adherence rates, a previous DIALECT study (Gant et al., 2017) showed low adherence rates to general lifestyle and dietary guidelines. Although medication adherence rates are high, adherence in the broad sense is much worse. In this context, one could also wonder whether the high medication adherence rates we found are specific to statins or are a reflection of overall medication adherence to any type of drug.

Regarding the high rate of non-statin users in our population, a previous DIALECT study (Gant et al., 2018) showed that of the patients without a statin prescription, a third did not have a prescription due to previous side-effects, another third did not have an indication for lipid-lowering therapy and in a third of the patients no reason was recorded for not having a statin prescription in the electronic patient file. Probably, patients in the latter subgroup did not want to use a statin because of previously experienced side-effects or a poor perception of statins. The possibility that a strict indication for lipid-lowering therapy was missed by the physician is unlikely, as the DIALECT population consists of patients with a very high risk of cardiovascular diseases. Furthermore, these patients are treated by a very committed team of nephrologists, pharmacists and specialized nurses, who are all aware of the current treatment guidelines.

Strengths and Limitations

A strength of this study is that it was performed in a real-world population and that patients were unaware that medication adherence would be analysed. Another strength of this study is that, in addition to the majority of other studies on this subject, we assessed associations between adherence and LDLc levels and LDLc target attainment. The eventual provision of medication outside the pharmacy (e.g., during hospitalization) was not taken into account in this study. This could be considered as a limitation. Changes in treatment during the follow-up period were not included in the analyses, which could also be considered a limitation. Changes to another statin or dosage were carefully documented in the database.

The MPR is an adequate and commonly used proxy for medication use in retrospective studies. However, a limitation of assessing medication adherence by calculating the MPR is that patients who filled their prescription only once or did not fill their prescription the first time are not included, since the MPR can only be calculated for patients with at least two dispenses. Because of the secondary care setting and the high medication adherence, the proxy approach is legitimate. Another limitation of the MPR is that collection of medication does not guarantee actual medication intake. Nonetheless, the pharmacy dispensing data aligned with our previous assessment of adherence based on liquid chromatography-tandem mass spectrometry (LC-MS/MS) analysis of urine samples (Beernink et al., 2021). In that study, we found an overall adherence rate of 89.3% to oral antidiabetics, antihypertensives, and statins. However, we should note that the LC-MS/MS method was not appropriate to gain a complete picture of adherence for statins, since it cannot detect simvastatin (i.e., the most widely used statin in Netherlands) (Nederland, Zorginstituut, 2008). A comparison (data not reported) between the LC-MS/MS data and MPR adherence data showed that 91.9% of the patients who were adherent to detectable statins based on LC-MS/MS were also adherent based on the MPR.

Finally, given the study design being observational, causality between adherence and study outcomes cannot be determined.

CONCLUSION

Although nonadherence was only seen in a small proportion of the patients, it is important to recognize nonadherence early because nonadherent patients reach their LDLc targets much less often, putting them at risk for diabetes complications. In these patients, reasons for nonadherence should be explored, discussed, and personalized support should be provided. Additionally, we need to focus on identifying non-statin users at risk for complications and intensifying statin therapy to achieve better LDLc target attainment.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding authors upon reasonable request.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Medisch Ethische Toetsingscommissie Twente. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JB performed statistical analyses and wrote the manuscript. MO supervised the statistical analysis, interpreted the outcome measures, reviewed/edited the manuscript and contributed to the discussion. JvB, HJH, SB, GN, RN, CG, HH, and WK reviewed/edited the

manuscript and contributed to the discussion. GL set up and coordinated the study, performed study procedures, coordinated practical research assistant, reviewed/edited the manuscript, contributed to the discussion, and is the principal investigator of this study. JB is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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SUPPLEMENTARY MATERIAL

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REFERENCES

Anghel, L. A., Farcas, A. M., and Oprean, R. N. (2019). An Overview of the Common Methods Used to Measure Treatment Adherence. *Med. Pharm. Rep.* 92 (2), 117–122. doi:10.15386/mpr-1201

Beernink, J. M., Oosterwijk, M. M., Khunti, K., Gupta, P., Patel, P., van Boven, J. F. M., et al. (2021). Biochemical Urine Testing of Medication Adherence and its Association with Clinical Markers in an Outpatient Population of Type 2 Diabetes Patients: Analysis in the DIAbetes and LifEstyle Cohort Twente (DIALECT). *Diabetes Care* 44 (6), 1419–1425. doi:10.2337/dc20-2533

Burggraaf, B., and Castro Cabezas, M. (2017). Interventions in Type 2 Diabetes Mellitus and Cardiovascular Mortality-An Overview of Clinical Trials. *Eur. J. Intern Med.* 42, 1–15. doi:10.1016/j.ejim.2017.04.017

Chi, M. D., Vansomphone, S. S., Liu, I. L., Cheetham, C., Green, K. R., Scott, R. D., et al. (2014). Adherence to Statins and LDL-Cholesterol Goal Attainment. *Am. J. Manag. Care* 20 (4), e105

Colhoun, H. M., Betteridge, D. J., Durrington, P. N., Hitman, G. A., Neil, H. A., Livingstone, S. J., et al. (2004). Primary Prevention of Cardiovascular Disease with Atorvastatin in Type 2 Diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): Multicentre Randomised Placebo-Controlled Trial. *Lancet* 364 (9435), 685–696. doi:10.1016/S0140-6736(04)16895-5

De Vries, F. M., Denig, P., Pouwels, K. B., Postma, M. J., and Hak, E. (2012). Primary Prevention of Major Cardiovascular and Cerebrovascular Events with Statins in Diabetic Patients: a Meta-Analysis. *Drugs* 72 (18), 2365–2373. doi:10.2165/11638240-000000000-00000

De Vries, F. M., Kolthof, J., Postma, M. J., Denig, P., and Hak, E. (2014). Efficacy of Standard and Intensive Statin Treatment for the Secondary Prevention of Cardiovascular and Cerebrovascular Events in Diabetes Patients: a Meta-Analysis. *PLoS One* 9 (11), e111247. doi:10.1371/journal.pone.0111247

Emerging Risk Factors Collaboration, Sarwar, N., Sarwar, N., Gao, P., Seshasai, S. R., Gobin, R., Kaptoge, S., et al. (2012). Diabetes Mellitus, Fasting Blood Glucose Concentration, and Risk of Vascular Disease: a Collaborative Meta-Analysis of 102 Prospective Studies. *Lancet* 375 (9733), 2215–2222. doi:10.1016/S0140-6736(10)60484-9

Fang, M., Wang, D., Coresh, J., and Selvin, E. (2021). Trends in Diabetes Treatment and Control in U.S. Adults, 1999-2018. *N. Engl. J. Med.* 384 (23), 2219–2228. doi:10.1056/NEJMsa2032271

Farsaei, S., Sabzghabaee, A. M., Amini, M., and Zargarzadeh, A. H. (2015). Adherence to Statin Therapy in Patients with Type 2 Diabetes: An Important Dilemma. *J. Res. Med. Sci.* 20 (2), 109

Gant, C. M., Binnenmars, S. H., Berg, E. V. D., Bakker, S. J. L., Navis, G., and Laverman, G. D. (2017). Integrated Assessment of Pharmacological and Nutritional Cardiovascular Risk Management: Blood Pressure Control in the DIAbetes and LifEstyle Cohort Twente (DIALECT). *Nutrients* 9 (7), 709. doi:10.3390/nu9070709

Gant, C. M., Binnenmars, S. H., Harmelink, M., Soedamah-Muthu, S. S., Bakker, S. J. L., Navis, G., et al. (2018). Real-life Achievement of Lipid-Lowering Treatment Targets in the DIAbetes and LifEstyle Cohort Twente: Systemic Assessment of Pharmacological and Nutritional Factors. *Nutr. Diabetes* 8, 24. doi:10.1038/s41387-018-0028-y

Guglielmi, V., Bellia, A., Pecchioli, S., Della-Morte, D., Parretti, D., Cricelli, I., et al. (2017). Effectiveness of Adherence to Lipid Lowering Therapy on LDL-Cholesterol in Patients with Very High Cardiovascular Risk: A Real-World Evidence Study in Primary Care. *Atherosclerosis* 263, 36–41. doi:10.1016/j.atherosclerosis.2017.05.018

Halava, H., Korhonen, M. J., Huupponen, R., Setoguchi, S., Pentti, J., Kivimäki, M., et al. (2014). Lifestyle Factors as Predictors of Nonadherence to Statin Therapy Among Patients with and without Cardiovascular Comorbidities. *CMAJ* 186 (12), E449–E456. doi:10.1503/cmaj.131807

Helfand, M., Carson, S., and Kelle, C. (2006). *Drug Class Review on HMG-CoA Reductase Inhibitors (Statins): Final Report*. Portland, Oregon: Oregon Health & Science University.

Hope, H. F., Binkley, G. M., Fenton, S., Kitas, G. D., Verstappen, S. M. M., and Symmons, D. P. M. (2019). Systematic Review of the Predictors of Statin Adherence for the Primary Prevention of Cardiovascular Disease. *PLoS One* 14 (1), e0201196. doi:10.1371/journal.pone.0201196

Kwaliteitsinstituut voor de Gezondheidszorg CBO, Nederlands Huisartsen Genootschap (NHG) (2020). Multidisciplinaire Richtlijn Cardiovasculair Risicomanagement (Revision 2019). Available at: https://richtlijnen.nhg.org/standaarden/cardiovasculair-risicomanagement (Accessed August 8, 2020).

Law, M. R., Wald, N. J., and Rudnicka, A. R. (2003). Quantifying Effect of Statins on Low Density Lipoprotein Cholesterol, Ischaemic Heart Disease, and Stroke: Systematic Review and Meta-Analysis. *BMJ* 326 (7404), 1423. doi:10.1136/bmj.326.7404.1423

Nederland, Zorginstituut (2008). *GIPeilingen 2008: Ontwikkelingen genees- en hulpmiddelengebruik the Netherlands*. Available at: https://www.zorginstituutnederland.nl/publicaties/publicatie/2009/09/15/gipeilingen-2008 (Accessed April 28, 2021).

Parris, E. S., Lawrence, D. B., Mohn, L. A., and Long, L. B. (2005). Adherence to Statin Therapy and LDL Cholesterol Goal Attainment by Patients with Diabetes and Dyslipidemia. *Diabetes Care* 28 (3), 595–599. doi:10.2337/diacare.28.3.595

Perreault, S., Dragomir, A., Blais, L., Bérard, A., Lalonde, L., White, M., et al. (2009). Impact of Better Adherence to Statin Agents in the Primary Prevention of Coronary Artery Disease. *Eur. J. Clin. Pharmacol.* 65 (10), 1013–1024. doi:10.1007/s00228-009-0673-0

Piepoli, M. F., Piepoli, M. F., Hoes, A. W., Agewall, S., Albus, C., Brotons, C., et al. (2016). 2016 European Guidelines on Cardiovascular Disease Prevention in Clinical Practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (Constituted by Representatives of 10 Societies and by Invited Experts): Developed with the Special Contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur. J. Prev. Cardiol.* 23 (29), NP1–2381. doi:10.1177/2047487316653709

Rana, J. S., Liu, J. Y., Moffet, H. H., Jaffe, M., and Karter, A. J. (2016). Diabetes and Prior Coronary Heart Disease Are Not Necessarily Risk Equivalent for Future Coronary Heart Disease Events. *J. Gen. Intern Med.* 31 (4), 387–393. doi:10.1007/s11606-015-3556-3

Steiner, J. F., and Prochazka, A. V. (1997). The Assessment of Refill Compliance Using Pharmacy Records: Methods, Validity, and Applications. *J. Clin. Epidemiol.* 50 (1), 105–116. doi:10.1016/s0895-4356(96)00268-5

Stuurman-Bieze, A. G., Hiddink, E. G., van Boven, J. F., and Vegter, S. (2013). Proactive Pharmaceutical Care Interventions Improve Patients' Adherence to Lipid-Lowering Medication. *Ann. Pharmacother.* 47 (11), 1448–1456. doi:10.1177/1060028013501146

Wallach-Kildemoes, H., Andersen, M., Diderichsen, F., and Lange, T. (2013). Adherence to Preventive Statin Therapy According to Socioeconomic Position. *Eur. J. Clin. Pharmacol.* 69 (8), 1553–1563. doi:10.1007/s00228-013-1488-6

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The role of illness perceptions on medication nonadherence among patients with hypertension: A multicenter study in indonesia

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Introduction: Nonadherence to antihypertensive medications is recognized as a significant cause of treatment failure. Therefore, identifying its underlying factors, particularly from the patient's perspective, is essential for developing tailored intervention strategies. The objective of this study was to evaluate the associations between different domains of illness perception and medication nonadherence among patients with hypertension in Indonesia.

Patients and methods: A multicenter cross-sectional study was conducted among patients with hypertension aged 18 years old and older who were using antihypertensive medications in the last 3 months in the community health centers in the three cities in Indonesia. The different domains of illness perception (e.g., consequences, timeline, personal control, treatment control, identity, concerns, comprehension, and emotional response) and medication nonadherence were assessed using a validated Brief Illness Perceptions Questionnaire (BIPQ) and Medication Adherence Report Scale (MARS), respectively. A logistic regression analysis was conducted to evaluate the associations between the different domains of illness perception and medication nonadherence adjusting for confounders. The odds ratios (ORs) and 95% confidence intervals (CIs) were reported.

Results: A total of 440 participants were included, whom 41.8% reported nonadherence to antihypertensive medications. The majority of the participants were females (64.3%) and aged between 60 and 69 years old (39.5%). The treatment control (OR: 0.80, 95% confidence interval: 0.7–10.90), patient's comprehension of hypertension (OR: 0.89, 95% CI: 0.820–0.97), and patient's emotions (OR: 0.93, 95% CI: 0.88–0.99) were significantly associated with medication nonadherence. No significant associations were observed between the other domains of illness perception and medication nonadherence.

Conclusion: Different dimensions of illness perception were associated with non-adherence to antihypertensive medications. Educational interventions should be developed based on patients' perception of their illness.

KEYWORDS

illness perception, medication adherence, antihypertensive medication, LMICs, Indonesia

1 Introduction

Hypertension is a global public health challenge which is known as the major modifiable risk factor for the global burden of cardiovascular disease and all-cause mortality worldwide (Mills et al., 2020). The hypertension prevalence among adults was reported higher in low-income to middle-income countries (LMICs) compared to high-income countries (HICs) (Nielsen et al., 2017). Despite the increasing prevalence, however, its treatment and control remains suboptimal particularly in LMICs (Mills et al., 2020). Although the effectiveness of antihypertensive medication is well documented, less than a 10th of patients with hypertension have their blood pressure controlled (Schutte et al., 2021).

Medication nonadherence is a well-recognized determinant contributing to the uncontrolled blood pressure in patients with hypertension (Burnier and Egan, 2019). Of the 25 studies involving 12,603 patients with hypertension in the previous meta-analysis, 45.2% of the patients were reported nonadherent to antihypertensive medications (Abegaz et al., 2017). Patients may experience different types of nonadherence to antihypertensive medications, that is intentional (a conscious and active decision after balancing the pros and cons of a medication) and unintentional (passive decision due to factors beyond the patient's control) non-adherence (Lowry et al., 2005; Bae et al., 2016). The nonadherence to antihypertensive medications is associated with increased risks of resistant hypertension (Hamrahian, 2020), cerebrovascular and coronary events (Corrao et al., 2011), reduced quality of life (Peacock et al., 2021), and increased healthcare costs (Mennini et al., 2015). Therefore, recent guidelines have highlighted the urgency to address medication nonadherence as a major problem in the management of hypertension (Unger et al., 2020).

The guidelines in Indonesia emphasized the urgency of addressing medication nonadherence during the patient counseling in the clinical practices (Indonesia, 2016a; 2016b). Yet, information of which focus needs more attention to improve medication adherence remains unclear. The previous studies have identified possible factors that are associated with nonadherence to antihypertensive medications in LMICs and HICs, such as gender (Abegaz et al., 2017), socioeconomic-related factors (van der Laan et al., 2017), therapy-related factors (Alfian et al., 2019), healthcare team and system-related factors (van der Laan et al., 2017), and patient-related factors such as medication beliefs (Alfian et al., 2020). Another important factor that contributes to nonadherence of patients with antihypertensive medications is the asymptomatic and lifelong nature of the disease (Sabate, 2003).

The common-sense model of self-regulation showed that an adaptive response to illness relies on the patient's belief or perception (Leventhal et al., 1992). This illness perception may not be validated scientifically or medically but is developed from patient experience, social influences, and interaction with healthcare professionals (Leventhal H, Meyer D, 1980). Therefore, the patient's perception of their illness is a decisive factor that influences their health-seeking behavior (Norfazilah et al., 2013). Patients with hypertension who were aware of their disease being chronic are more likely to take medication in order to control or prevent more severe conditions (Chen et al., 2011). The previous studies conducted in either LMICs and HICs showed that the illness perception plays a significant role on patient's adherence to antihypertensive medications (Ross et al., 2004; Žugelj et al., 2010; Rajpura and Nayak, 2014; Taheri-Kharameh et al., 2016). However, limited study has focused on the different domains of patient's perspective on their diseases and its impact on medication nonadherence particularly in Indonesia, where societal and racial determinants may lead to significant differences from the other countries. This information is needed to develop tailored intervention strategies. Therefore, the objective of this study was to evaluate the associations between different domains of illness perception and medication nonadherence among patients with hypertension in Indonesia.

2 Patients and methods

2.1 Study design, setting, and patient recruitment

We conducted a multicenter cross-sectional survey in Bandung City, Samarinda City, and the Special Region of Yogyakarta in Indonesia from October 2018 to September 2019. We purposively recruited patients from selected community health centers (CHCs) in accordance with the required number of patients diagnosed with hypertension. The CHCs are primary healthcare centers aimed to provide integrated chronic disease management at the subdistrict level and staffed with doctors, dentists, nurses, midwives, and

pharmacists. The patients aged 18 years and older, diagnosed with hypertension for more than 1 year, taking antihypertensive medications in the last 3 months, and literate in the Indonesian language were eligible to participate in this study. We excluded patients with severe mental or physical constraints, pregnant, or in the lactation period. This study was approved by the Health Research Ethics Committee of Universitas Padjadjaran, Indonesia (No. 1137/UN6. KEP/EC/2018) and was performed according to the Declaration of Helsinki. We obtained a written informed consent from all of the patients who participated in this study.

2.2 Measures

2.2.1 Illness perceptions

Patients' perceptions of hypertension were measured using the Brief Illness Perceptions Questionnaire (BIPQ) (Broadbent et al., 2006). The BIPQ is a 9-item self-reported questionnaire developed to rapidly evaluate the cognitive and emotional representation of an illness (Broadbent et al., 2006). The BIPQ includes five subscales for cognitive representation of illness perception (e.g., consequences, timeline, personal control, treatment control, and identity), two subscales on emotional representation of illness perception (e.g., concern and emotions), and two subscales on illness comprehensibility of illness perception (e.g., comprehension and perceived cause of illness). However, the question on perceived cause of illness is an open-ended question that measures the patients' beliefs about the causes of their illness and involves qualitative analysis. Thus, it was omitted in our study. The eight items are rated on a 10-point Likert scale and are evaluated using the following subscales: (1) consequences: perception of consequences of hypertension in daily life; (2) timeline: expectations about the duration of hypertension; (3) personal control: perception of the degree of personal control over hypertension; (4) treatment control: perception of the degree patients can control their hypertension in terms of received treatment; (5) identity: perceived symptoms of hypertension; (6) concern: concern about hypertension; (7) comprehension: understanding of hypertension; and (8) emotional burden: emotional burden due to hypertension. The total score of illness perception was calculated by reverse score for personal control, treatment control, and comprehension and then was added to the score of the other items. Thus, a higher BIPQ total score indicated that the patient perceives the illness as more threatening. The BIPQ demonstrated good psychometric properties, and it has been widely used among patients with different chronic conditions (Broadbent et al., 2015). The Indonesian version of BIPQ also showed to be valid and reliable (Rias et al., 2021). Consultation with experts was conducted to maintain the content validity of the Indonesian version of the BIPQ.

2.2.2 Medication nonadherence

The adherence to antihypertensive medications was measured using the Medication Adherence Report Scale (MARS), which has shown good psychometric indicators and internal reliability (Chan et al., 2020). The MARS contains one item that reflects unintentional non-adherence ("I forget to take my antihypertensive medications") and four items that largely reflect different forms of intentional non-adherence (e.g., "I alter the dose of my antihypertensive medications") in the last 3 months on a 5-point Likert scale ranging from 1 (always), 2 (often), 3 (sometimes), 4 (rarely), to 5 (never). Nonadherence is defined *a priori* as a score of one–three on any of the items to reflect unintentional, intentional, and in part intentional non-adherence (Alfian et al., 2020). Adherence is defined as a score of four or five on all items to allow for missing or changing a dose rarely (Alfian et al., 2020). The MARS has been forward and backward translated and validated to Indonesian version and showed to be valid and reliable (Alfian and Putra, 2017).

2.2.3 Sociodemographic covariates

The sociodemographic factors of patients included gender, age, education level completed (no formal education or elementary school, junior and senior high school, or university), and type of health insurance. The type of health insurance in Indonesia was classified as patients who could not afford to pay the health insurance premium (BPJS-PBI), those who could afford to pay the health insurance premium (BPJS-Non PBI), and those without any health insurance. We used a structured case report form to record the duration of hypertension (in years).

2.3 Data collection

We used a nonprobability purposive sampling technique to recruit patients. The pharmacists on duty screened the patient's eligibility at the CHCs. The pharmacist then asked the researcher or trained research assistant to approach the eligible patient, to briefly describe and discuss the study to the patient, and ask the patient to provide written informed consent. Patients were asked to complete the BIPQ and MARS questionnaires independently. However, in some cases, some elderly patients who have difficulty in reading and writing the answer themselves were interviewed by the trained research assistants.

2.4 Sample size calculation

Nonadherence rates using the MARS questionnaire among Indonesian patients with hypertension based on a previous

TABLE 1 Characteristics of patients (N = 440).

Characteristics	n (%)
Gender	
Male	157 (35.7)
Female	283 (64.3)
Age in years	
≤49	49 (11.1)
50–59	140 (31.8)
60–69	174 (39.5)
≥70	74 (16.8)
Missing	3 (0.7)
Health insurance type	
BPJS-PBI	242 (55.0)
BPJS-Non PBI	184 (41.8)
Without insurance	14 (3.2)
Last education level	
No formal education or elementary school	91 (20.7)
Junior high school	74 (16.8)
Senior high school	206 (46.8)
University	67 (15.2)
Missing	2 (0.5)
Time from diagnosis in years, mean (SD)	
Hypertension, mean (SD)	5.0 (4.2)
Missing	16
Illness perception, mean (SD)	
Consequences	4.4 (3.2)
Missing	1
Timeline	4.8 (3.2)
Missing	1
Personal control	2.8 (2.3)
Missing	1
Treatment control	2.2 (2.0)
Missing	1
Identity	4.3 (2.9)
Missing	1
Concerns	4.7 (3.5)
Missing	1
Comprehension	3.8 (2.7)
Missing	1
Emotional	4.3 (3.5)
Missing	2
MARS score	
Adherent	256 (58.2)
Nonadherent	184 (41.8)

Abbreviations: BPJS-PBI: patients who could not afford to pay the health insurance premium, BPJS-Non PBI: patients who could afford to pay the health insurance premium, MARS: medication adherence report scale, SD: standard deviation.

small-scale study ranged from 40 to 55% (Rahmadani et al., 2018; Alfian et al., 2020). Therefore, a minimum sample size of 180 patients was needed according to the formula for prediction models with a binary outcome (Peduzzi et al., 1996), which included a maximum of nine potential independent variables in the multivariate analysis and assuming a nonadherence proportion of 50%.

TABLE 2 Associations between different domains of illness perception and medication nonadherence.

Illness perception	Nonadherence		
	OR*	95% CI	*p*-value
Treatment control	0.80	0.71–0.90	<0.001
Comprehension of hypertension	0.89	0.82–0.97	0.005
Emotions	0.93	0.88–0.99	0.026

Note: *Odds ratios were adjusted for gender, age, and hypertension duration. Goodness-of-fit *p*-value of the model, 0.307; R-squared, 17.5%.
AbbreviationsCI: confidence interval; OR: odds ratio.

2.5 Data analysis

Descriptive statistics were performed to report the patient's characteristics. We conducted complete-case analyses because some data were observed to be missing. A binary logistic regression was performed to evaluate the associations between the different domains of illness perception and medication nonadherence with manual backward elimination, adjusting for potential confounders in the univariate analysis. The adjusted odds ratios (ORs), 95% confidence interval (CI), *p*-values, and R^2 are reported. All statistical analyses were performed using the SPSS software version 27.0 (IBM, Armonk, NY, United States).

3 Results

3.1 Patient characteristics

A total of 440 participants (response rate of 85%) participated in this study from Bandung City (115 patients from six CHCs), Samarinda City (162 patients from five CHCs), and Special Region of Yogyakarta (163 patients from 18 CHCs). Most of the patients were females (64.3%), aged 60–69 years old (39.5%), and graduated from senior high school (46.8%) (Table 1). Around half of the patients reported nonadherence to antihypertensive medications (41.8%). Among the different domains of illness perception, the highest mean score was recorded for timeline (4.8 ± 3.2), which is followed by concerns (4.7 ± 3.5). The treatment control (2.2 ± 2.0) exhibited the lowest mean score, which is followed by the personal control (2.8 ± 2.3) (Table 1).

3.2 Associations between different domains of illness perception and medication nonadherence

Adjusted analyses were conducted for age, gender, and hypertension duration (p-value < 0.05). Lower treatment control (OR: 0.80, 95% CI: 0.71–0.90), lower patient's comprehension of hypertension (OR: 0.89, 95% CI: 0.82–0.97), and higher patient's emotions (OR: 0.93, 95% CI: 0.88–0.99) were associated significantly with the medication nonadherence (Table 2). No significant associations were observed between the other domains of illness perception and medication nonadherence.

4 Discussion

Among the different domains of illness perception, worry about hypertension timeline followed by patient's concerns about hypertension was the dominant domain of illness perception reported among patients with hypertension in Indonesia. Furthermore, patients showed low treatment control and personal control over hypertension. Treatment control, patient's comprehension of hypertension, and patient's emotions were significantly associated with medication nonadherence No significant associations were observed between the other domains of illness perception and medication nonadherence.

In this study, we found that worry about hypertension timeline and patient's concerns about hypertension were the dominant domain of illness perception. This is in line with a previous study conducted in India which found more emotional problems among patients with hypertension (Nivedita, 2015). This can partly be explained by the patients feeling overwhelmed with the lifelong nature of hypertension or concerned about the complexity of their treatment, which included changes in their treatment regimen, such as switching or adding medications. We further observed that patients showed low treatment control and personal control over hypertension. These patients need to be targeted for tailored intervention because they were recruited from primary healthcare settings, who are without complications and severe conditions, and relatively healthy.

We observed that the treatment control was significantly associated with medication nonadherence. A previous study conducted in Nepal showed that although patients perceived hypertension as highly threatening, those who have a strong belief that medication will cure their hypertension and prevent complications were reported more adherent to medications (Shakya et al., 2020). Although these patients perceive hypertension as a chronic disease, they believe that it can be controlled with regular medication and behavior modification (Ross et al., 2004; Maharjan et al., 2017). Thus, the perception of treatment effectiveness is important because it can predict adherence behavior (Žugelj et al., 2010). This is further supported by a mixed-method study conducted in Malaysia, Hong Kong, South Korea, Taiwan, Indonesia, Thailand, and Philippines, which revealed that patients strongly believed hypertension can be controlled by taking medications but they were resistant to lifestyle modification (Rahman et al., 2015).

We further observed that patient's comprehension of hypertension was significantly associated with medication nonadherence. This is in accordance with the previous studies conducted in Iran (Taheri-Kharameh et al., 2016) and Nepal (Shakya et al., 2020). The previous studies conducted in Hongkong and India showed that poor understanding of illness is common among patients with hypertension (Nivedita, 2015; Lo et al., 2016). Our finding may be related to the asymptomatic nature of hypertension. Furthermore, patients might forget any information obtained from the healthcare professional or that the information available was not tailored for managing their hypertension (Lo et al., 2016). Although some Asian patients reported good understanding of the causes and consequences of hypertension, yet, lack of urgency to control their blood pressure was also reported (Rahman et al., 2015). Therefore, a comprehensive information regarding hypertension from healthcare professionals is needed to address this gap.

While treatment control refers to a cognitive aspect, however, concern and emotional burden due to hypertension refer to emotional aspects of illness representations (Broadbent et al., 2006). We observed that patients' emotions were also significantly associated with medication nonadherence. This is in line with the previous studies conducted in either LMICs and HICs which reported a strong emotional perception affecting nonadherence to antihypertensive medications (Ross et al., 2004; Žugelj et al., 2010; Hsiao et al., 2012). An emotional response may negatively influence medication adherence by stimulating maladaptive coping mechanisms, for example, denial (Ross et al., 2004). Therefore, those who can control their stress levels effectively will show fewer concerns regarding illness and treatment which may lead to better medication adherence. No significant associations were observed between the other domains of illness perception and medication nonadherence.

The strength of this study is that we analyzed the similarities and differences in associations of different domains of illness perception with medication nonadherence were. Therefore, we were able to provide information on which specific domain of illness perception was associated with medication nonadherence and requires further attention from the healthcare professionals. Furthermore, the high response rate in this study illustrates that our findings are generalizable for patients with hypertension in Indonesia who visit the CHCs. The generalizability of our findings was further strengthened by the fact that this study was conducted as a multicenter survey in the three different main cities in Indonesia.

However, some limitations need to be addressed. A nonprobability purposive sampling technique was used to collect data. As a consequence, our findings may be prone to some volunteer bias. We also may have underestimated patients' perceptions about hypertension and overestimated their medication adherence since most of them who participated in this study were those who visited the CHCs regularly and without complications. Therefore, our findings may represent the illness perceptions and medication adherence in relatively healthier patients with hypertension. The overestimated medication adherence in our study may also be due to social desirability, recall bias, and the use of subjective assessment of medication adherence. However, the data were obtained by trained research assistants using a predefined standard protocol to obtain more reliable data. Furthermore, no causal association between illness perceptions and medication nonadherence can be made due to the cross-sectional study design. We also could not capture the dynamic nature of illness perception and medication adherence as these constructs may change over time. Thus, we could not measure any changes in the trend of these constructs over time. Furthermore, previous systematic reviews showed that the evidences regarding the association between illness perceptions and medication adherence in patients with chronic diseases are inconclusive (Kucukarslan, 2012; Shahin et al., 2019; Oliveira et al., 2022). Therefore, our findings may also be confounded by unmeasured factors such as comorbidity, number of medications, distress, treatment satisfaction (Saarti et al., 2015), and medication belief (Alfian et al., 2020). Further studies are needed to evaluate the association between different domains of illness perception and medication nonadherence in uncontrolled patients with hypertension employing longitudinal design and a more objective assessment of adherence, such as medication event monitoring system (MEMS). In addition, further studies controlling for other factors not covered in this study are important to develop effective tailored interventions in the clinical practice.

Our findings emphasized the urgent need for developing interventions to modify patients' perceptions not only about hypertension but also about their treatment in order to improve their medication adherence. These could be tailored interventions taking into consideration that illness perceptions can be changed by educational interventions (Petrie and Weinman, 2006). Furthermore, our findings showed that although patients perceived that hypertension is a chronic disease which may lead to some severe complications and emotional burdens, patients also perceived that hypertension could be controlled by medication and demonstrated an understanding of the illness.

5 Conclusion

Different dimensions of illness perception were associated with non-adherence to antihypertensive medications. The healthcare providers need to pay more attention to patients' illness perceptions, including their treatment control, comprehension of hypertension, and negative emotional response. Therefore, educational interventions should be developed based on patients' perception of their illness.

Data availability statement

The raw data supporting the conclusion 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 Health Research Ethics Committee of Universitas Padjadjaran. The patients/participants provided their written informed consent to participate in this study (No. 1137/UN6. KEP/EC/2018).

Author contributions

Conception and design (SDA, NA, DAP, and RA), analysis and interpretation of the data (SDA, NA, DAP, AC, and RA), the drafting of the paper (SDA, NA, DAP, AC, and RA), and the final approval of the version to be published (all authors).

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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References

Abegaz, T. M., Shehab, A., Gebreyohannes, E. A., Bhagavathula, A. S., and Elnour, A. A. (2017). Nonadherence to antihypertensive drugs: A systematic review and meta-analysis. *Med. Baltim.* 92, e5641. doi:10.1097/MD.0000000000005641

Alfian, R., and Putra, A. M. P. (2017). Uji validitas dan reliabilitas kuesioner medication adherence report scale (MARS) terhadap pasien diabetes mellitus [in Bahasa Indonesia]. *J. Ilm. Ibnu Sina.* 2, 176–183.

Alfian, S. D., Annisa, N., Fajriansyah, F., Perwitasari, D. A., Abdulah, R., Eelko, H., et al. (2020). Modifiable factors associated with non-adherence to antihypertensive or antihyperlipidemic drugs are dissimilar: A multicenter study among patients with diabetes in Indonesia. *J. Gen. Intern. Med.* 1, 2897–2906. –10. doi:10.1007/s11606-020-05809-y

Alfian, S. D., Denig, P., Coelho, A., and Hak, E. (2019). Pharmacy-based predictors of nonadherence, non-persistence and reinitiation of antihypertensive drugs among patients on oral diabetes drugs in The Netherlands. *PLoS One* 14, e0225390. doi:10.1371/journal.pone.0225390

Bae, S. G., Kam, S., Park, K. S., Kim, K. Y., Hong, N. S., Kim, K. S., et al. (2016). Factors related to intentional and unintentional medication nonadherence in elderly patients with hypertension in rural community. *Patient prefer. Adherence* 10, 1979–1989. –1989. doi:10.2147/PPA.S114529

Broadbent, E., Petrie, K. J., Main, J., and Weinman, J. (2006). The brief illness perception questionnaire. *J. Psychosom. Res.* 60, 631–637. doi:10.1016/J.JPSYCHORES.2005.10.020

Broadbent, E., Wilkes, C., Koschwanez, H., Weinman, J., Norton, S., and Petrie, K. J. (2015). A systematic review and meta-analysis of the brief illness perception questionnaire. *Psychol. Health* 30, 1361–1385. doi:10.1080/08870446.2015.1070851

Burnier, M., and Egan, B. M. (2019). Adherence in hypertension. *Circ. Res.* 124, 1124–1140. doi:10.1161/CIRCRESAHA.118.313220

Chan, A. H. Y., Horne, R., Hankins, M., and Chisari, C. (2020). The medication adherence report scale: A measurement tool for eliciting patients' reports of nonadherence. *Br. J. Clin. Pharmacol.* 86, 1281–1288. doi:10.1111/BCP.14193

Chen, S. L., Tsai, J. C., and Chou, K. R. (2011). Illness perceptions and adherence to therapeutic regimens among patients with hypertension: A structural modeling approach. *Int. J. Nurs. Stud.* 48, 235–245. doi:10.1016/J.IJNURSTU.2010.07.005

Corrao, G., Parodi, A., Nicotra, F., Zambon, A., Merlino, L., Cesana, G., et al. (2011). Better compliance to antihypertensive medications reduces cardiovascular risk. *J. Hypertens.* 29, 610–618. doi:10.1097/HJH.0B013E328342CA97

Hamrahian, S. M. (2020). Medication non-adherence: A major cause of resistant hypertension. *Curr. Cardiol. Rep.* 22, 133–137. doi:10.1007/s11886-020-01400-3

Hsiao, C. Y., Chang, C., and Chen, C. D. (2012). An investigation on illness perception and adherence among hypertensive patients. *Kaohsiung J. Med. Sci.* 28, 442–447. doi:10.1016/J.KJMS.2012.02.015

Indonesia, K. K. R. (2016a). *Peraturan menteri kesehatan republik Indonesia nomor 73 tahun 2016 tentang standar pelayanan kefarmasian di Apotek*. Jakarta.

Indonesia, K. K. R. (2016b). *Peraturan menteri kesehatan republik Indonesia nomor 74 tahun 2016 tentang standar pelayanan kefarmasian di Puskesmas*. Jakarta.

Kucukarslan, S. N. (2012). A review of published studies of patients' illness perceptions and medication adherence: Lessons learned and future directions. *Res. Soc. Adm. Pharm.* 8, 371–382. doi:10.1016/J.SAPHARM.2011.09.002

Leventhal, H., and Meyer, D. N. D. (1980). *Contributions to medical psychology*. New York: Pergamon Press.The common sense representation of illness danger

Leventhal, H., Diefenbach, M., and Leventhal, E. A. (1992). Illness cognition: Using common sense to understand treatment adherence and affect cognition interactions. *Cogn. Ther. Res.* 16, 143–163. doi:10.1007/BF01173486

Lo, S. H. S., Chau, J. P. C., Woo, J., Thompson, D. R., and Choi, K. C. (2016). Adherence to antihypertensive medication in older adults with hypertension. *J. Cardiovasc. Nurs.* 31, 296–303. doi:10.1097/JCN.0000000000000251

Lowry, K. P., Dudley, T. K., Oddone, E. Z., and Bosworth, H. B. (2005). Intentional and unintentional nonadherence to antihypertensive medication. *Ann. Pharmacother.* 39, 1198–1203. doi:10.1345/aph.1E594

Maharjan, S., Chinnawong, T., and Kritpracha, C. (2017). Illness perception among patients with hypertension in Nepal | maharjan | GSTF journal of nursing and health care (JNHC). GSTF J. Nurs. Heal. Care 4. Available at: http://dl6.globalstf.org/index.php/jnhc/article/view/1897 (Accessed June 26, 2022).

Mennini, F. S., Marcellusi, • A., Graf Von Der Schulenburg, • J. M., Gray, • A., Levy, • P., Sciattella, • P., et al. (2015). Cost of poor adherence to anti-hypertensive therapy in five European countries. *Eur. J. Health Econ.* 16, 65–72. doi:10.1007/s10198-013-0554-4

Mills, K. T., Stefanescu, A., and He, J. (2020). The global epidemiology of hypertension. *Nat. Rev. Nephrol.* 16, 223–237. doi:10.1038/S41581-019-0244-2

Nielsen, J., Shrestha, A. D., Neupane, D., and Kallestrup, P. (2017). Non-adherence to anti-hypertensive medication in low- and middle-income countries: A systematic review and meta-analysis of 92443 subjects. *J. Hum. Hypertens.* 31, 14–21. doi:10.1038/jhh.2016.31

Nivedita, S. (2015). Illness perception and coping among hypertension patients. *Res. J. Recent Sci.* 4, 270–273. Available at: www.isca.me (Accessed June 26, 2022).

Norfazilah, A., Samuel, A., Law, P. T., Khusairi, A. A. A., Nurul, A. Z., Syahnaz, M. H., et al. (2013). Illness perception among hypertensive patients in primary care centre UKMMC. *Malays. Fam. Physician.* 8, 19–25. Available at: /pmc/articles/PMC4400685/(Accessed June 23, 2022).

Oliveira, J., Sousa, H., Bártolo, A., Figueiredo, D., and Ribeiro, O. (2022). Illness perception and treatment adherence in haemodialysis: A systematic review. *Psychol. Health Med.* 11, 1–15. doi:10.1080/13548506.2022.2099559

Peacock, E., Joyce, C., Craig, L. S., Lenane, Z., Holt, E. W., Muntner, P., et al. (2021). Lowmedication adherence is associatedwith decline in health-related quality of life: Results of a longitudinal analysis among older women andmen with hypertension. *J. Hypertens.* 39, 153–161. doi:10.1097/HJH.0000000000002590

Peduzzi, P., Concato, J., Kemper, E., Holford, T. R., and Feinstein, A. R. (1996). A simulation study of the number of events per variable in logistic regression analysis. *J. Clin. Epidemiol.* 49, 1373–1379. doi:10.1016/s0895-4356(96)00236-3

Petrie, K. J., and Weinman, J. (2006). Why illness perceptions matter. *Clin. Med.* 6, 536–539. doi:10.7861/CLINMEDICINE.6-6-536

Rahmadani, A., Sari, A., Dahlan, A., Jl, Y., Janturan, S., Yogyakarta, U., et al. (2018). Adherence of medication therapy in hypertensive patients with diabetes mellitus at health center Yogyakarta. *Media Farm* 15, 105–112.

Rahman, A. R. A., Wang, J. G., Kwong, G. M. Y., Morales, D. D., Sritara, P., Sukmawan, R., et al. (2015). Perception of hypertension management by patients and doctors in Asia: Potential to improve blood pressure control. *Asia Pac. Fam. Med.* 14, 2–11. doi:10.1186/s12930-015-0018-3

Rajpura, J. R., and Nayak, R. (2014). Role of illness perceptions and medication beliefs on medication compliance of elderly hypertensive cohorts. *J. Pharm. Pract.* 27, 19–24. doi:10.1177/0897190013493806

Rias, Y. A., Abiddin, A. H., Huda, N., Handayani, S., Sirait, H. S., Pien, L. C., et al. (2021). Psychometric testing of the bahasa version of the brief illness perception questionnaire among Indonesians with type 2 diabetes mellitus. *Int. J. Environ. Res. Public Health* 18, 9601. doi:10.3390/IJERPH18189601

Ross, S., Walker, A., and MacLeod, M. J. (2004). Patient compliance in hypertension: Role of illness perceptions and treatment beliefs. *J. Hum. Hypertens.* 189 18, 607–613. doi:10.1038/sj.jhh.1001721

Saarti, S., Hajj, A., Karam, L., Jabbour, H., Sarkis, A., El Osta, N., et al. (2015). Association between adherence, treatment satisfaction and illness perception in hypertensive patients. *J. Hum. Hypertens.* 305 30, 341–345. doi:10.1038/jhh.2015.86

Sabate, E. (2003). *Adherence to long-term therapies: Evidence for action*. Geneva: World Health Organization.

Schutte, A. E., Srinivasapura Venkateshmurthy, N., Mohan, S., and Prabhakaran, D. (2021). Hypertension in low- and middle-income countries. *Circ. Res.* 128, 808–826. doi:10.1161/CIRCRESAHA.120.318729

Shahin, W., Kennedy, G. A., and Stupans, I. (2019). The impact of personal and cultural beliefs on medication adherence of patients with chronic illnesses: A systematic review. *Patient prefer. Adherence* 13, 1019–1035. doi:10.2147/PPA.S212046<

Shakya, R., Shrestha, S., Gautam, R., Rai, L., Maharjan, S., Satyal, G. K., et al. (2020). Perceived illness and treatment adherence to hypertension among patients attending a tertiary hospital in kathmandu, Nepal. *Patient prefer. Adherence* 14, 2287–2300. doi:10.2147/PPA.S270786

Taheri-Kharameh, Z., Hazavehei, S. M. M., Ramezani, T., Vahedi, A., Khoshro, M., and Sharififard, F. (2016). The assessment of illness perception and adherence to therapeutic regimens among patients with hypertension. *J. Edu. Commun. Health* 3, 9–15. doi:10.21859/JECH-03022

Unger, T., Borghi, C., Charchar, F., Khan, N. A., Poulter, N. R., Prabhakaran, D., et al. (2020). 2020 international society of hypertension global hypertension practice guidelines. *Hypertension* 75, 1334–1357. doi:10.1161/HYPERTENSIONAHA.120.15026

van der Laan, D. M., Elders, P. J. M., Boons, C. C. L. M., Beckeringh, J. J., Nijpels, G., and Hugtenburg, J. G. (2017). Factors associated with antihypertensive medication non-adherence: A systematic review. *J. Hum. Hypertens.* 31, 687–694. doi:10.1038/jhh.2017.48

Žugelj, U., Zupančič, M., Komidar, L., Kenda, R., Varda, N. M., and Gregorič, A. (2010). Self-reported adherence behavior in adolescent hypertensive patients: The role of illness representations and personality. *J. Pediatr. Psychol.* 35, 1049–1060. doi:10.1093/JPEPSY/JSQ027

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Analysing breast cancer survivors' acceptance profiles for using an electronic pillbox connected to a smartphone application using Seintinelles, a French community-based research tool

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Introduction: Up to 50% of breast cancer (BC) survivors discontinue their adjuvant endocrine therapy (AET) before the recommended 5 years, raising the issue of medication non-adherence. eHealth technologies have the potential to support patients to enhance their medication adherence and may offer an effective way to complement the healthcare. In order for eHealth technologies to be successfully implemented into the healthcare system, end-users need to be willing and accepting to use these eHealth technologies.

Aim: This study aims to evaluate the current usability of eHealth technologiesin and to identify differences in BC SURVIVORS BC survivors accepting a medication adherence enhancing eHealth technology to support their AET to BC survivors that do not accept such a medication adherence enhancing eHealth technology.

Methods: This study was conducted in 2020 including volunteering BC survivors belonging to the Seintinelles Association. Eligible participants were women, diagnosed with BC within the last 10 years, and been exposed to, an AET. Univariable and multivariable logistic regression analyses were performed to investigate medication adherence enhancing eHealth technology acceptance profiles among BC survivors. The dependent variable was

Abbreviations: BC, Breast Cancer; AET, Adjuvant endocrine therapy.

defined as acceptance of an electronic pillbox connected to a smartphone application (hereafter: medication adherence enhancing eHealth technology).

Results: Overall, 23% of the participants already use a connected device or health application on a regular basis. The mean age of the participants was 52.7 (SD 10.4) years. In total, 67% of 1268 BC survivors who participated in the survey declared that they would accept a medication adherence enhancing eHealth technology to improve their AET. BC survivors accepting a medication adherence enhancing eHealth technology for their AET, are younger (OR = 0.97, 95% CI [0.95; 0.98]), do take medication for other diseases (OR = 0.31, 95% CI [0.13; 0.68]), already use a medication adherence enhancing eHealth technology or technique (OR = 1.74, 95% CI [1.06; 2.94]) and are willing to possess or currently possess one or more connected devices or health applications (OR = 2.89, 95% CI [2.01; 4.19]).

Conclusion: Understanding acceptance profiles of BC survivors is fundamental for conceiving an effective eHealth technology enhancing AET among BC survivors. Hence, such profiling will foster the development of personalized medication adherence enhancing eHealth technology.

KEYWORDS

medication adherence, medication adherence enhancing interventions, eHealth, breast cancer, user-centered design, patient adherence

1 Introduction

Breast cancer (BC) is the most common cancer among women, as 355,000 are estimated to be diagnosed with BC each year in Europe (International Agency for Research on Cancer et al., 2020). The majority (80%) of BC patients are hormone receptor–positive and most (>90%) have stage I to III and are eligible for adjuvant endocrine therapy (AET) (Partridge et al., 2003).

The shift, that BC survivors experience from the acute phase of treatment (e.g., surgery, chemotherapy, radiotherapy) to the post-acute phase (e.g., AET), is associated with social and medical challenges (Kantsiper et al., 2009; Hurtado-de-Mendoza et al., 2017; Goetzinger et al., 2020). Patients recurrently reported the need for increased support in terms of AET management (adherence and side effects) as well as increased patient–healthcare provider communication and follow-up (Finitsis et al., 2019; Pouls et al., 2021). During this post-acute treatment period, most BC survivors report anxiety, fear, and struggle to find their way back into everyday life. In addition, BC survivors usually do not visit their oncologist for a relatively long period during the post-acute treatment phase (Ringwald et al., 2017; Goetzinger et al., 2020). Thus the value of HCP support during this survivorship period of BC patients is undebatable for medication adherence and disease management (Kini and Michael Ho, 2018).

Medication adherence is a dynamic behaviour influenced by various factors (Sabaté and World Health Organization, 2003; Kardas et al., 2013) and is defined as the process by which patients take their medication as prescribed. This medication adherence process is further categorized into three distinct phases: 1. *Initiation* (patient takes the first dose of prescribed medication), 2. *Implementation* (the extent to which a patient's actual dosing corresponds to the prescribed dosing regimen, from initiation until the last dose is taken) and 3. *Discontinuation* (occurs when the patient stops taking the prescribed medication, for whatever reason(s)) (Vrijens et al., 2012). Previous work demonstrated that 30%–50% of BC survivors discontinue their AET before the recommended 5 years end depending on the AET agent and method of medication adherence measurement (Huiart et al., 2011). Moreover, it was shown that AET reduces BC recurrence rate by 50% and mortality by a third (Davies et al., 2011; Pistilli et al., 2020). Therefore, it is key to identify AET non-adherence, to reduce the risk for poorer health outcomes (Pistilli et al., 2020). To date, there is no gold standard to identify non-adherence. Indirect methods such as pharmacy prescription refills or patient-administered questionnaires are mostly used, yet fail to measure the real medication intake or even overestimate adherence (Lu et al., 2018).

The World Health Organization defines eHealth 'as the cost-effective and secure use of information and communications technologies in support of health and health-related fields, including health-care services, health surveillance, health literature, and health education, knowledge and research (World Health Organization, 2022)'. Concerning the field of medication adherence research and eHealth, medication adherence technologies (MATech) such as electronic pillboxes or smartphone applications have been developed (Ahmed et al., 2018). Car

et al. highlighted that these MATechs are the future for self-management of treatment and medication adherence monitoring (Car et al., 2017). A systematic review by Nieuwlaat et al. showed that MATechs are most effective if multiple components, trying to overcome barriers to adherence by means of tailored ongoing support from allied health professionals are used (Nieuwlaat et al., 2014). Nevertheless, the most effective interventions did not lead to large improvements in adherence or clinical outcomes (Hadji et al., 2013; Finitsis et al., 2019; Rosenberg et al., 2020). This is because most of those interventions were created without the involvement of the end-user, whereas patient involvement is key in research and implantation into the healthcare setting (De Geest et al., 2020; Aguayo et al., 2021). Thus, BC survivor involvement is key to conceive effective MATechs to enhance AET. In order to personalize medication adherence enhancing interventions for subtypes of BC survivor users, it is important to profile the acceptance of BC survivors to use medication adherence enhancing eHealth technology for AET enhancement.

Therefore, the present study aims to 1) evaluate the current usability of eHealth technologies in BC survivors and to 2) identify differences in BC survivors accepting medication adherence enhancing eHealth technology to enhance their AET to BC survivors that do not accept such a medication adherence enhancing eHealth technology. In this study, we define medication adherence enhancing eHealth technology as an electronic pillbox connected to a smartphone application.

2 Method

2.1 Study design

A cross-sectional, e-survey was conducted from July to December 2020 among BC survivors from the French Seintinelles platform (www.seintinelles.com). Seintinelles is a non-profit community-based research platform, developed in collaboration with psycho-oncologists to facilitate the implication of patients into cancer research (Bauquier et al., 2017; Pannard et al., 2020). Volunteering citizens, regardless of their current health condition and/or cancer type, can participate in this platform, comprised of over 8000 BC patients (in 2020), the target population of the present study. Thus, this platform has the ability to recruit a large number of participants in a very limited time.

2.2 Recruitment and study population

Seintinelles sent an email to all its BC members, informing them about the study objectives, along with the information sheet (Supplementary Appendix 1). If they were interested in participating, they were asked to complete a short questionnaire on the website to verify that they met all the inclusion criteria (Supplementary Appendix 2). Inclusion criteria for this e-survey were:

- Women,
- BC diagnosed within the last 10 years,
- at least temporarily exposed to an AET.

If participants met all inclusion criteria and still wanted to participate, they signed an e-consent form before starting the e-survey (Supplementary Appendix 2).

2.3 e-survey

The e-survey used within the present study aims to establish a state of art on current eHealth usability and potential acceptability of medication adherence enhancing eHealth technology in BC survivors.

The e-survey consists of about 30 questions and required participants' attention for at least 20 min. They had the option to interrupt the questionnaire, and could save their answers to continue later. There were no incentives given to participants. BC survivors (N = 2) proofread the final version of the e-survey. CG and CA as well as employees of Seintinelles pre-tested the e-survey with respect to technical errors and incorrect utilisation of question filters. While conducting the e-survey, participants could only see one question at a time. It was mandatory to answer the question in order to get to the next. This method was used to ensure that no questions was left unanswered.

2.4 Measurement

The e-survey was subdivided into five sections to collect data on socio-demographic characteristics, health status and disease experience, medication adherence, eHealth utilization and a specific section on medication adherence enhancing eHealth technology. For more information, Supplementary Appendix 3 illustrates the structure and definitions of the e-survey.

2.4.1 Sociodemographic characteristics

The first section of the e-survey collected data on participants' age, marital status, having children and number of children. In addition, participants responded to questions asking about their educational, professional and financial status. These items were adapted from the questionnaire used in Vican 5, a French nationwide population-based questionnaire aiming to explore life 5 years after cancer diagnosis (Bauquier et al., 2017).

2.4.2 Health status and disease experience

The second section investigated participant's general health status and their experience with BC in the acute phase of treatment. These questions were either developed by CA and CG or taken from Vican 5 (Bouhnik et al., 2015).

2.4.3 AET adherence

The third section analyzed the adherence to AET in terms of persistence and if discontinuation for which reasons. In addition, this third section investigated experienced side effects and use of support by psychologists or alternative medicine. Furthermore, current techniques or eHealth technologies used to support participants with their AET intake were investigated.

This section sums up by evaluating the patient–physician relationship and communication. CA and CG developed these questions.

2.4.4 eHealth utilization

Section 4 evaluated current eHealth utilisation. This section of the questionnaire-survey was based on a self-administered qualitative questionnaire used in social psychology science in the DISCO trial (DISpositif COnnecté', connected device in English) investigating the use and acceptability of connected devices in breast cancer (Touillaud et al., 2021). As in the questionnaire from the DISCO trial, we provided the participant with two definitions, explaining 'connected device' and 'mobile application'. In contrast to the DISCO trial questionnaire, the present study focuses more precisely on adherence to OHT in BC survivors, thus additional items, created by CG and CA, were based on the results found by Goetzinger et al. (2020).

2.4.5 Medication adherence enhancing eHealth technology

The fifth section investigated acceptability and related barriers and facilitators to acceptability and usability of a proposed medication adherence enhancing eHealth technology supporting AET management in BC survivors. This paper will only focus on the first question of this section, as it is the dependent variable used for the univariable and multivariable logistic regression analyses.

2.5 Dependent variable

The dependent variable 'Acceptance of a Medication adherence enhancing eHealth technology (electronic pillbox connected to a smartphone application)'' (1 = yes, 0 = no) was computed from 'Would you accept to use an electronic blister connected to an application on your phone to support your AET treatment'. Hence, we categorized the following answers together to receive a binary variable;

'Yes' includes the following answer options:

- 'Yes, I accept voluntarily',
- 'Yes, if my Doctor asks me to',
- 'Yes, depending on the information provided'.

'No' includes these answer options;

- 'No, I do not trust connected devices',
- 'No, I don't know how to use new technology',
- 'No, I don't have a smartphone and I don't want one',
- 'No, for other reasons'.

2.6 Ethical provision

The study received approval by the National Commission for Information and Freedoms (Commission nationale de l'informatique et des libertés, CNIL: 1955704) and the Sud-EST II data protection committee (Comité de Protection des données, Numéro EudraCT: 2020-A00665-34).

2.7 Statistical analysis

This study uses descriptive statistics to characterize the study population and to highlight current patterns of eHealth use in BC survivors. Univariable and multivariable logistic regression analyses were performed to evaluate differences in BC survivors that accept an electronic blister connected to app to support AET adherence with those that do not. Odds ratios were used as the measure of association to compare the strength of the correlation between 'Medication adherence enhancing eHealth technology acceptance' and relative predictors. We performed a both-way stepwise logistic regression analysis to investigate factors that are significantly associated with accepting an electronic blister connected to the app to support AET adherence. The final model was retained as the lowest AIC was achieved. Significance was accepted at a p-value lower than 0.05, with a 95% Confidence Interval. We used the R software version 4.0.3 including the 'ISwR', 'oddsratio', 'StepReg', 'forestplot' and 'dyplr' packages to analyse the data and conceive the figure. This study used only completed questionnaires in order to avoid weighing and computation of missing values.

3 Results

Overall, 1,516 eligible Seintinelles members started the questionnaire, 1268 BC survivors responded to the complete online questionnaire and were used for the analysis. No missing values were recorded in our dataset as participants could only

TABLE 1 Descriptive characteristics of BCS (Seintinelles study, 2020).

	Overall (N = 1,268)	Acceptance of an electronic blister connected to an app		
		Yes (N = 845)	No (N = 423)	*p-value*
Total	100%	66.6%	33.4%	
Sociodemographic characteristics				
Age (mean, SD)	52.7 +-10.4	51.4 +- 10.3	55.3 +- 10.3	<0.001
Marital status				
Single	156 (12.3%)	95 (11.2%)	61 (14.4%)	0.031
Married	937 (73.9%)	646 (76.4%)	291 (68.8%)	
Widow	34 (2.7%)	19 (2.3%)	15 (3.6%)	
Divorced	141 (11.1%)	85 (10.1%)	56 (13.2%)	
Children				
Yes	1,021 (80.5%)	686 (81.2%)	335 (79.2%)	0.443
No	247 (19.5%)	159 (18.8%)	88 (20.8%)	
Education				
High school degree	205 (16.2%)	128 (15.2%)	77 (18.2%)	0.144
Bachelor or equivalent	390 (30.8%)	268 (31.7%)	122 (28.8%)	
Master or equivalent	554 (43.7%)	371 (43.9%)	183 (43.3%)	
Professional diploma	94 (7.4%)	66 (7.8%)	28 (6.6%)	
Other	25 (1.9%)	12 (1.4%)	13 (3.1%)	
Professional status				
Employed	764 (60.3%)	538 (63.7%)	226 (53.4%)	<0.001
Sick leave	61 (4.8%)	36 (4.3%)	25 (5.9%)	
Job hunting	49 (3.7%)	31 (3.7%)	18 (4.3%)	
Retired	248 (19.6%)	138 (16.3%)	110 (26.0%)	
Self-employed	78 (6.2%)	51 (6.0%)	27 (6.4%)	
Other	68 (5.4%)	51 (6.0%)	17 (4.0%)	
Financial status				
At ease	948 (74.8%)	627 (74.2%)	321 (75.9%)	0.560
Difficult	320 (25.2%)	218 (25.8%)	102 (24.1%)	
Health status and experience with breast cancer				
General health status				
Very good	164 (12.9%)	108 (12.8%)	56 (13.2%)	0.379
Good	586 (46.2%)	403 (47.7%)	183 (43.3%)	
Ok	462 (36.4%)	295 (34.9%)	167 (39.5%)	
Bad	56 (4.5%)	39 (4.6%)	17 (4.0%)	
Medication for other disease				
Daily	456 (35.9%)	294 (34.8%)	162 (38.3%)	<0.001
Regularly	39 (3.1%)	15 (1.8%)	24 (5.6%)	
In case of need	104 (8.2%)	69 (8.2%)	35 (8.3%)	
No	669 (52.8%)	467 (55.2%)	202 (47.8%)	
Year of diagnosis				
<2012	261 (20.6%)	164 (19.4%)	97 (22.9%)	0.113
2013	119 (9.4%)	76 (9.0%)	43 (10.2%)	
2014	144 (11.4%)	93 (11.0%)	51 (12.1%)	
2015	153 (12.1%)	95 (11.2%)	58 (13.7%)	
2016	154 (12.1%)	101 (12.0%)	53 (12.5%)	

(Continued on following page)

TABLE 1 (*Continued*) Descriptive characteristics of BCS (Seintinelles study, 2020).

	Overall (N = 1,268)	Acceptance of an electronic blister connected to an app		
		Yes (N = 845)	No (N = 423)	*p-value*
2017	169 (13.3%)	121 (14.3%)	48 (11.3%)	
>2018	268 (21.1%)	195 (23.1%)	73 (17.3%)	
Quality of life/BC impact on life (bc->BC)				
No effect at all	163 (12.9%)	97 (11.5%)	66 (15.6%)	0.027
Does not affect much	363 (28.6%)	231 (27.3%)	132 (31.2%)	
Some effect	414 (32.6%)	283 (33.5%)	131 (30.9%)	
Does effect	245 (19.3%)	180 (21.3%)	65 (15.4%)	
Does effect severely	83 (6.6%)	54 (6.4%)	29 (6.9%)	
Control over BC				
No control	194 (15.3%)	115 (13.6%)	79 (18.7%)	0.027
Not very much control	302 (23.8%)	217 (25.7%)	85 (20.1%)	
Some control	414 (32.6%)	289 (34.2%)	125 (29.5%)	
Control	260 (20.5%)	165 (19.5%)	95 (22.5%)	
A lot of control	98 (7.7%)	59 (7.0%)	39 (9.2%)	
Knowledge of BC				
No knowledge	33 (2.6%)	20 (2.4%)	13 (3%)	0.262
No real knowledge	65 (5.1%)	42 (4.9%)	23 (5%)	
Some knowledge	270 (21.3%)	190 (22.5%)	80 (19%)	
Good knowledge	412 (32.5%)	283 (33.5%)	129 (300%)	
Very good knowledge	488 (38.5%)	319 (36.7%)	178 (42%)	
BC recurrence				
Yes	149 (11.8%)	102 (12.1%)	47 (11.1%)	0.683
No	1,119 (88.2%)	743 (87.9%)	376 (88.9%)	
Treatment adherence				
Taking an AET				
Yes	882 (69.6%)	604 (71.5%)	278 (65.7%)	0.042
No	386 (30.4%)	241 (28.5%)	145 (34.3%)	
Side-effects				
Yes	1,160 (91.5%)	776 (91.8%)	384 (90.8%)	0.598
No	108 (8.5%)	69 (8.2%)	39 (9.2%)	
AET interruptions				
Yes	117 (9.2%)	71 (8.4%)	46 (10.9%)	0.183
No	1,151 (90.8%)	774 (91.6%)	377 (89.1%)	
Patient-Physician communication				
GP implication in bc follow-up				
Yes, regularly	383 (30.2%)	261 (30.9%)	122 (28.8%)	0.197
Yes, occasionally	287 (22.6%)	202 (23.9%)	85 (20.1%)	
Yes, exceptionally	239 (18.9%)	149 (17.6%)	90 (21.3%)	
No, never	359 (28.3%)	233 (27.6%)	126 (29.8%)	
Bcs′ satisfaction on physicians information given regarding the: nature of the treatment				
Very unsatisfying	87 (6.9%)	51 (6.0%)	36 (8.5%)	0.067
Unsatisfying	196 (15.5%)	132 (15.6%)	64 (15.1%)	
Correct	433 (34.1%)	273 (32.3%)	160 (37.8%)	
Satisfying	353 (27.8%)	250 (29.6%)	103 (24.4%)	
Very satisfying	199 (15.7%)	139 (16.5%)	60 (14.2%)	

(Continued on following page)

TABLE 1 (*Continued*) Descriptive characteristics of BCS (Seintinelles study, 2020).

	Overall (N = 1,268)	Acceptance of an electronic blister connected to an app		
		Yes (N = 845)	No (N = 423)	*p-value*
Expected benefits of the treatment				
Very unsatisfying	58 (4.6%)	34 (4.0%)	24 (5.7%)	0.017
Unsatisfying	143 (11.3%)	93 (11.0%)	50 (11.8%)	
Correct	405 (31.9%)	249 (29.5%)	156 (36.9%)	
Satisfying	429 (33.8%)	306 (36.2%)	123 (29.1%)	
Very satisfying	233 (18.4%)	163 (19.3%)	70 (16.5%)	
Treatment side-effects				
Very unsatisfying	198 (15.6%)	125 (14.8%)	73 (17.3%)	0.077
Unsatisfying	342 (27.0%)	227 (26.9%)	115 (27.2%)	
Correct	364 (28.7%)	231 (27.3%)	133 (31.4%)	
Satisfying	247 (19.5%)	182 (21.5%)	65 (15.4%)	
Very satisfying	117 (9.2%)	80 (9.5%)	37 (8.7%)	

proceed in the questionnaire when the previous question was answered.

The overall study sample is on average 52.7 years (SD 10.4) old, over half is married (73.9%), and employed (60.3%) (Table 1). Furthermore, 46% of the overall sample reported good general health, and more than half of the study sample did not use any other medication for other diseases (52.8%). 21% of the participants were diagnosed with BC before 2012, 12% in 2015 and 21% after 2018. About a third (32.6%) of the BC survivors state that their BC does have 'some effect' on their life. Only 7.7% of the BC survivors evaluate themselves to be able to control their disease and almost 40% claim to have very good knowledge about the disease. Moreover, 88% highlighted that they had no BC recurrence up to the date of the questionnaire completion.

At the time of the questionnaire, 69.6% of the BC survivors were taking an AET, 91.5% experienced side effects and 9.2% interrupted their AET. Most women stated that their GP is somewhat implicated in their BC follow-up. A third (33.8) of the BC survivors stated that the information provided by their physician regarding the benefits of their AET is satisfying.

3.1 Current eHealth use among BC survivors

Approximately 38% of the included BC survivors did already possess one or more connected devices or health applications and 39% of those use these tools every day (Table 2). 18.7% of these women use these tools to motivate themselves, followed by 14.3% to monitor their health. Current techniques or devices to help BC survivors to adhere to their AET are specific locations to store their AET blister (47.2%), phone alarm (13.0%) and Pillbox (13.3%). About 12% of the BC survivors use at least two of those aids regularly. Most participants (90.3%) claim that these aids help them to adhere to their AET.

3.2 Medication adherence support tool acceptance

Specific features that support medication adherence and are important for BC survivors to use real-time side effect declaration (49.7%), information disposition (43.7%) and dematerialised patient-physician communication (41.2%) among others. Finally, the study showed that 27.1% of the participants would voluntarily accept to use an electronic pillbox connected to an app on their phone to manage their AET.

3.3 Factors associated with BC survivors acceptance of an eHealth tool to manage AET

Table 3 illustrates the univariable logistic regression analysis, which analysed factors associated with accepting an electronic pillbox connected to an app to enhance AET among BC survivors. Some of the factors associated with accepting an electronic pillbox connected to an app were age (OR = 0.96, 95% CI 0.95, 0.98), being married (OR = 1.43, 95% CI 1.00, 2.02), retired (OR = 0.53, 95% CI 0.39, 0.71), taking regular medication for other diseases (OR = 0.34, 95% CI 0.17, 0.67) and using more

TABLE 2 Current eHealth use of BCS and acceptance to use a connected electronic blister with an app to manage AET (Seintinelles study, 2020).

	Overall (N = 1,268, %)
Do you possess 1 or more connected devices or health applications?	
No, it doesn't interest me	603 (47.6%)
No, but I know someone close to me who uses them and I am interested	105 (8.3%)
No, but I plan to get one within the next 6 months	76 (6.0%)
Yes but I do not use them	102 (8.0%)
Yes I use them for 1 year	92 (7.2%)
Yes I use them already longer than a year	290 (22.9%)
If yes, how often did you use the connected device or health app in the last 3 months? (N = 382)	
Never	24 (6.3%)
Less than once a month	52 (13.6%)
1–3 x a month	51 (13.4%)
Once a week	27 (7.1%)
Twice a week	16 (4.2%)
3x a week	20 (5.2%)
More than 3x a week	43 (11.2%)
Everyday	149 (39.0%)
If used at "least less than once a month" or more, how do these tools help you? (N = 358)	
To manage my health	19 (5.3%)
To motivate me	67 (18.7%)
To monitor my health	51 (14.3%)
To motivate me and monitor my health	20 (5.6%)
Other reason(s)	52 (14.5%)
No reason	149 (41.6%)
During your AET, do you use any devices or specific techniques to help you with your treatment? (multiple answers possible)	
Phone alarm (yes, %)	165 (13.0%)
Pillbox (yes, %)	168 (13.3%)
A specific location to store the blister (yes, %)	599 (47.2%)
The implication of closed one (yes, %)	73 (5.8%)
Application (yes, %)	15 (1.2%)
Other (yes, %)	59 (4.7%)
None (yes, %)	452 (35.7%)
Nr of medication adherence support devices/specific techniques used	
0	452 (35.7%)
1	607 (47.9%)
2	153 (12.1%)
>3	56 (4.3%)
If at least 1-support devices/specific techniques used, do these tools help you to adhere to your medication? (N = 816)	
Yes	737 (90.3%)
No	30 (3.7%)
I don't know	49 (6.0%)
Which of the following features/facts are important for you regarding your medication adherence? (Multiple answers possible)	
Auto Surveillance (yes)	459 (36.2%)
Information disposition (yes)	554 (43.7%)
Real-time side effect declaration (yes)	630 (49.7%)
Real-time follow-up by health care professional (yes)	499 (39.4%)
Patient-Physician communication (dematerialised) (yes)	522 (41.2%)
Pharmacy Refill Alarm (yes)	304 (24.0%)

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TABLE 2 (*Continued*) Current eHealth use of BCS and acceptance to use a connected electronic blister with an app to manage AET (Seintinelles study, 2020).

	Overall (N = 1,268, %)
Reduce face-to-face consultations (yes)	298 (23.5%)
Personalized follow-up (yes)	518 (40.9%)
Adherence management (yes)	213 (16.8%)
Exchange with others on treatment (yes)	344 (27.1%)
None (yes)	164 (12.9%)
Would you accept an electronic pillbox connected to an app on your phone to follow your AET (Dependent variable)?	
Yes, voluntarily	344 (27.1%)
Yes, if asked by my Doctor	109 (8.6%)
Yes, depending on the information I receive	392 (30.9%)
No, I have no confidence in connected health devices	59 (4.7%)
No, I do not know how to use new technologies	17 (1.3%)
No, because I don't want a smartphone	28 (2.2%)
No, for other reasons	319 (25.2%)

than one support tool for AET adherence (OR = 1.53, 95%CI 0.18, 0.67).

Figure 1 highlights the stepwise multivariable logistic regression, presenting factors that are significantly associated with accepting an electronic pillbox connected to an app to enhance AET among BC survivors. The final adjusted model includes 'Age', 'Medication intake for other diseases', 'Number of medication adherence support devices used', 'BC survivors satisfaction on physicians information given on expected benefits of the treatment' and 'Possession of connected devices or health applications'. We performed both forward and backward stepwise regression and both methods selected the same variables.

Hence, accepting an electronic pillbox connected to an app to enhance AET among BC survivors is inversely associated with age (OR = 0.97, 95% CI 0.95, 0.98) and the use of regular intake of other medication compared to no other medication intake (OR = 0.31, 95% CI 0.13, 0.68) (Figure 1). Using at least two medication adherence support tools increases the odds of accepting an electronic pillbox connected to an app to enhance AET among BC survivors (OR = 1.74, 95% CI 1.06, 2.94). Finally, BC survivors using connected devices for more than a year is 2.89 times (95% CI 2.01, 4.19) more likely to accept an eHealth tool to enhance AET compared to those that do not possess or are not interested in connected devices or health applications.

4 Discussion

This study investigated differences in BC survivors that accept an electronic pillbox connected to an app to enhance AET with those who do not.

Drewes et al. analysed the correlation between sociodemographic factors, the health status of BC patients and the willingness to use the Internet and apps (Drewes et al., 2016). They found that decisive factors influencing BC patients' willingness to use new communication technologies are younger, have a large number of people per household, and a short time since breast cancer diagnosis. Other commonly reported barriers to medication adherence across diseases, patient beliefs/perceptions, comorbidities and poor patient–provider communication among others (Konstantinou et al., 2020). We found similar results and add to the current knowledge that polypharmacy positively effects acceptance of a medication adherence enhancing eHealth technology. Furthermore, we found that those patients that have already created an AET adherence habit/technique or are willing to use a smartphone or health applications are more likely to use an AET enhancing eHealth tool. Similar eHealth acceptance trends can be found for patients with cardiometabolic diseases, mental health disorders, infectious diseases (Talal et al., 2019; AshaRani et al., 2021; Gire et al., 2021).

In our study, we found that at the time of the survey, only 1.2% actively used an app yet 67% of the BC survivors would accept to use the proposed electronic pillbox connected to an app to enhance their AET. As Car et al. mentioned, eHealth is the future of medications management in terms of personalisation, monitoring and adherence (Car et al., 2017). To date, digitally delivered interventions including components such as medication and condition education, motivational interviewing, reinforcement and motivational messages led to improvements in medication adherence (Hadji et al., 2013; Nieuwlaat et al., 2014; Finitsis et al., 2019; Rosenberg et al., 2020; Pouls et al., 2021). In addition, qualitative papers showed that patients are ready and willing to integrate eHealth technologies into their daily life to monitor and enhance their health status and medication intake (Currie et al., 2015; Goetzinger et al., 2020). Yet, the challenge we face is to conceive effective eHealth intervention for end-users and implement them into the healthcare sector (Car et al., 2012). Thus integrating patients into the development phase of these

TABLE 3 Factors associated with accepting an eHealth tool to manage OHT in BCS (Seintinelles study, 2020).

	Acceptance of an electronic blister connected to an app		
Univariable logistic regression analysis	**OR**	**95% CI**	***p*-value**
Age (years)	0.96	0.95–0.98	<0.001
Marital Status			
Single	Ref		
Married	1.43	1.00–2.02	0.047
Widow	0.81	0.39–1.74	0.589
Divorced	0.98	0.61–1.56	0.914
Professional Status			
Employed	Ref		
Sick leave	0.61	0.36–1.04	0.065
Job hunting	0.72	0.40–1.34	0.291
Retired	0.53	0.39–0.71	<0.001
Self-employed	0.79	0.49–1.31	0.816
Other	1.26	0.73–2.29	0.427
Medication for other diseases			
Daily	Ref		
Regularly	0.34	0.17–0.67	0.002
In case of need	1.09	0.70–1.72	0.718
No	1.27	0.99–1.64	0.061
Quality of life			
No effect at all	Ref		
Does not affect much	1.19	0.81–1.74	0.367
Some affect	1.47	1.01–2.14	0.044
Does affect	1.88	1.24–2.88	0.003
Does affect severely	1.27	0.74–2.21	0.398
Control over breast BC			
No control at all	Ref	Ref	
Not very much control	1.75	1.20–2.57	0.004
Some control	1.59	1.11–2.27	0.011
Control	1.19	0.81–1.75	0.365
A lot of control	1.04	0.63–1.71	0.879
taking an adjuvant endocrine therapy			
Yes	Ref		
No	0.77	0.60–0.98	0.036
Number of medication adherence support devices/specific techniques used			
1	Ref	Ref	
2	2.09	1.36–3.28	0.001
>3	2.00	1.05–4.14	0.047
0	0.71	0.55–0.92	0.008
BCS′ Satisfaction On Physicians Information Given regarding the			
Nature Of The Treatment	Ref	Ref	
Very unsatisfying	1.46	0.86–2.45	0.157
Unsatisfying	1.20	0.75–1.92	0.437
Correct	1.71	1.05–2.78	0.029
Satisfying	1.64	0.97–2.76	0.065

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TABLE 3 (*Continued*) Factors associated with accepting an eHealth tool to manage OHT in BCS (Seintinelles study, 2020).

	Acceptance of an electronic blister connected to an app		
Univariable logistic regression analysis	**OR**	**95% CI**	***p*-value**
Expected Benefits Of The Treatment			
Very unsatisfying	Ref	Ref	
Unsatisfying	1.31	0.70–2.45	0.394
Correct	1.13	0.64–1.96	0.676
Satisfying	1,76	0.99–3.07	0.050
Very satisfying	1.64	0.90–2.97	0.100
Treatment Side-Effects			
Very unsatisfying	Ref	Ref	
Unsatisfying	1.15	0.80–1.66	0.446
Correct	1.01	0.71–1.45	0.938
Satisfying	1.64	1.09–2.46	0.007
Very satisfying	1.26	0.78–2.06	0.346
Possession of connected devices or health applications			
No, it doesn't interest me	Ref	Ref	
No, but I know someone close to me who uses them and I am interested	1.37	0.87–1.92	<0.001
No, but I plan to get one within the next 6 months	0.70	0.20–1.23	0.008
Yes but I do not use them	1.40	0.89–1.97	<0.001
Yes I use them for 1 year	1.35	0.82–1.93	<0.001
Yes I use them already longer than a year	1.11	0.79–1.43	<0.001

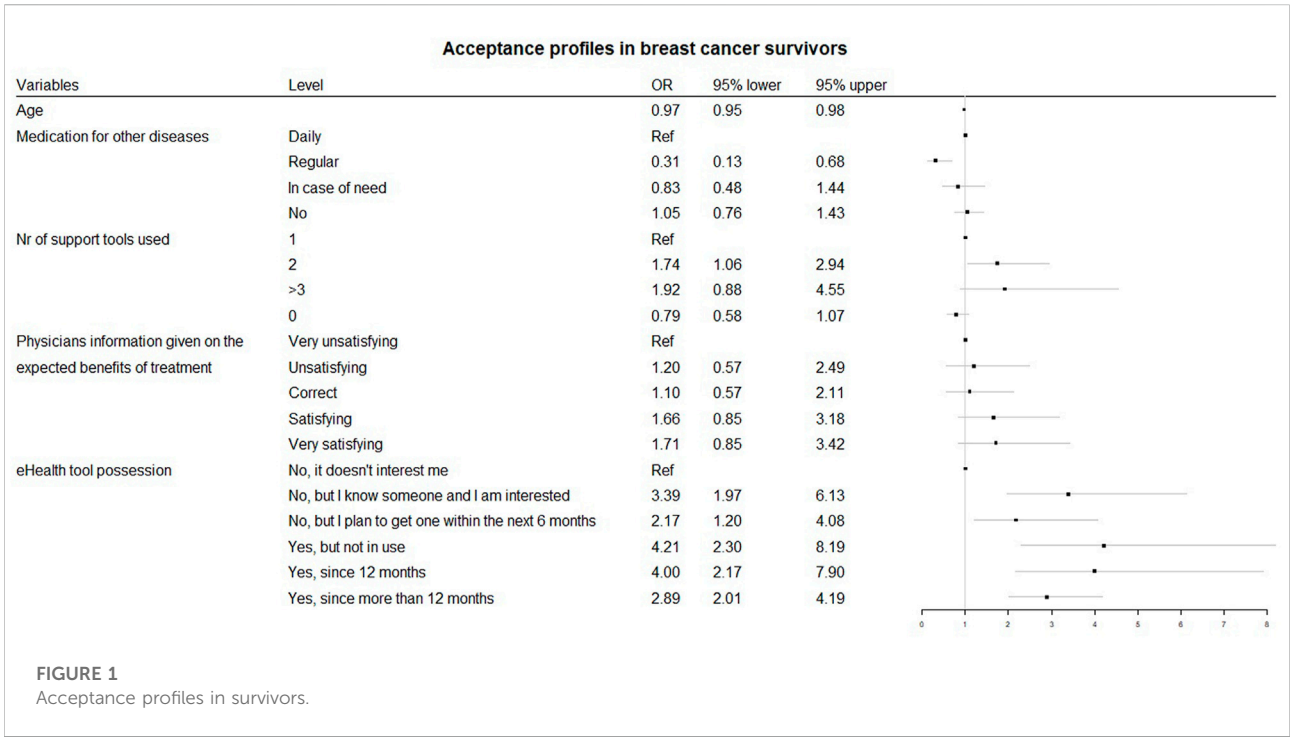

FIGURE 1
Acceptance profiles in survivors.

eHealth technologies is key to creating feasible tools for the end-user that are implementable into the healthcare setting (Ross et al., 2016; Bauquier et al., 2017; Pannard et al., 2020; Aguayo et al., 2021).

Understanding the disease and/or patient profiles will allow personalising healthcare in the future. Characterising patient groups will allow defining new strategies for individual patients benefiting their needs to optimise health outcomes. Recent research, using profiling principles, found that healthcare for patients with cardiometabolic disease could benefit from more targeted and tailored strategies for the prevention of cardiometabolic diseases at a population level (Fagherazzi et al., 2021). Eventually, post-acute treatment for BC survivors using a medication adherence enhancing eHealth technology can move from a "one-size-fits-all" vision to a tailored follow-up strategy, personalizing care to each BC survivor.

This study evaluated the association between BC survivors characteristics and the acceptance of an eHealth intervention among BC survivors. Hence, the results produced will be fundamental when conceiving an eHealth support tool to enhance AET among BC survivors. Using patient acceptance profiling strategies will allow them to provide them with personalised care and develop effective, sustainable, and implementable eHealth support tools. Future studies should have a closer look into the specific features of such an AET support tool, examine the acceptable time point(s) of intervention and evaluate the implication of HCP. In addition, implementation strategies to adopt these eHealth technologies into the healthcare system need to be investigated.

4.1 Limitations

The present study entails several limitations. Also, the present study deals with selection bias, as the Seintinelles platform only includes volunteering members. Meaning the participants showed interest in the study topic, also we observed a high educational level among the study sample. The present study thus provides only a snapshot of characteristics for accepting eHealth tools. Some categories have a small sample and should be regarded with caution.

5 Conclusion

This study found that although 1.2% currently used and health related app over two thirds would accept to use a medication adherence enhancing eHealth technology to enhance their AET. BC survivors are accepting to and willing to be supported during their AET, yet, the medication adherence enhancing eHealth technology needs to fit their needs and profiles. Thus, understanding acceptance profiles among BC survivors is fundamental for conceiving an effective medication adherence enhancing eHealth technology enhancing AET among BC survivors.

Data availability statement

The datasets presented in this article are not readily available because participants could be identifiable. The included tables provide the anonymized and summarized data. Requests to access the datasets should be directed to the corresponding author, catherine.goetzinger@gmail.com.

Ethics statement

The studies involving human participants were reviewed and approved by National Commission for Information and Freedoms (Commission nationale de l'informatique et des libertés, CNIL: 1955704) and the Sud-EST II data protection committee (Comité de Protection des données, Numéro EudraCT: 2020-A00665-34). The patients/participants provided their written informed consent to participate in this study.

Author contributions

CG contributed to the study conception and design, data analysis and interpretation, and manuscript preparation. CG, CA, MP, and LH contributed to the study conception and design. AS and BV contributed to the data analysis and interpretation. GF contributed to manuscript preparation and editing. All authors contributed to the manuscript review.

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Conflict of interest

BV was employed by AARDEX Group.

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.

Supplementary Material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2022.889695/full#supplementary-material

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References

Aguayo, G. A., Goetzinger, C., Scibilia, R., Fischer, A., Till, S., Tran, V.-T., et al. (2021). Methods to generate innovative research ideas and improve patient and public involvement in modern epidemiological research: Review, patient viewpoint, and guidelines for implementation of a digital cohort study. *J. Med. Internet Res.* 23 (12), e25743. doi:10.2196/25743

Ahmed, I., Ahmad, N. S., Ali, S., George, A., Danish, H. S., Uppal, E., et al. (2018). Medication adherence apps: Review and content analysis. *JMIR Mhealth Uhealth* 6 (3), e62. doi:10.2196/mhealth.6432

AshaRani, P. V., Jue Hua, L., Roystonn, K., Siva Kumar, F. D., Peizhi, W., Ying Jie, S., et al. (2021). Readiness and acceptance of eHealth services for diabetes care in the general population: Cross-sectional study. *J. Med. Internet Res.* 23 (9), e26881. doi:10.2196/26881

Bauquier, C., Pannard, M., and Préau, M. (2017). The seintinelles: An innovative approach to promoting community-based research and sustaining health democracy in oncology. *Sante publique* 29 (4), 547–550. doi:10.3917/spub.174.0547

Bouhnik, A.-D., Bendiane, M.-K., Cortaredona, S., Sagaon Teyssier, L., Rey, D., Berenger, C., et al.members of VICAN Group (2015). The labour market, psychosocial outcomes and health conditions in cancer survivors: Protocol for a nationwide longitudinal survey 2 and 5 Years after cancer diagnosis (the VICAN survey). *BMJ Open* 5 (3), e005971. doi:10.1136/bmjopen-2014-005971

Car, J., Huckvale, K., and Hermens, H. (2012). Telehealth for long term conditions. *BMJ* 344, e4201. doi:10.1136/bmj.e4201

Car, J., Tan, W. S., Huang, Z., Sloot, P., and Franklin, B. D. (2017). eHealth in the future of medications management: Personalisation, monitoring and adherence. *BMC Med.* 15 (1), 73. doi:10.1186/s12916-017-0838-0

Currie, M., Philip, L. J., and Roberts, A. (2015). Attitudes towards the use and acceptance of eHealth technologies: A case study of older adults living with chronic pain and implications for rural healthcare. *BMC Health Serv. Res.* 15, 162. doi:10.1186/s12913-015-0825-0

Davies, C., Godwin, J., Gray, R., Clarke, M., Cutter, D., Darby, S., et al.Early Breast Cancer Trialists' Collaborative Group (EBCTCG) (2011). Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: Patient-level meta-analysis of randomised trials. *Lancet* 378 (9793), 771–784. doi:10.1016/s0140-6736(11)60993-8

De Geest, S., Zúñiga, F., Brunkert, T., Deschodt, M., Zullig, L. L., Wyss, K., et al. (2020). Powering Swiss health care for the future: Implementation science to bridge 'the valley of death. *Swiss Med. Wkly.* 150, w20323. doi:10.4414/smw.2020.20323

Drewes, C., Kirkovits, T., Schiltz, D., Schinkoethe, T., Haidinger, R., Goldmann-Posch, U., et al. (2016). EHealth acceptance and new media preferences for therapy assistance among breast cancer patients. *JMIR cancer* 2 (2), e13. doi:10.2196/cancer.5711

Fagherazzi, G., Zhang, L., Aguayo, G., Pastore, J., Goetzinger, C., Fischer, A., et al. (2021). Towards precision cardiometabolic prevention: Results from a machine learning, semi-supervised clustering approach in the nationwide population-based ORISCAV-LUX 2 study. *Sci. Rep.* 11 (1), 16056. doi:10.1038/s41598-021-95487-5

Finitsis, D. J., Vose, B. A., Mahalak, J. G., and Salner, A. L. (2019). Interventions to promote adherence to endocrine therapy among breast cancer survivors: A meta-analysis. *Psychooncology.* 28 (2), 255–263. doi:10.1002/pon.4959

Gire, N., Caton, N., McKeown, M., Mohmed, N., Duxbury, J., Kelly, J., et al. (2021). Care co-ordinator in my pocket': A feasibility study of mobile assessment and therapy for psychosis (TechCare). *BMJ open* 11 (11), e046755. doi:10.1136/bmjopen-2020-046755

Goetzinger, C. B., Vrijens, G., Fagherazzi, M., Preau, J., Mancini, M. K., Ben-Diane, et al. (2021). "Beliefs and attitudes towards an ehealth tool to improve medication adherence in breast cancer survivors" in In Abstracts of the 24th Annual Meeting of ESPACOMP, the International Society for Medication Adherence, November 10–20, 2020. Int J Clin Pharm 43, 286–308. doi:10.1007/s11096-020-01213-Y

Hadji, P., Blettner, M., Harbeck, N., Jackisch, C., Lück, H-J., Windemuth-Kieselbach, C., et al. (2013). The patient's Anastrozole compliance to therapy (pact) program: A randomized, in-practice study on the impact of a standardized information program on persistence and compliance to adjuvant endocrine therapy in postmenopausal women with early breast cancer. *Ann. Oncol.* 24, 1505–1512. doi:10.1093/annonc/mds653

Huiart, L., Dell'Aniello, S., and Suissa, S. (2011). Use of tamoxifen and aromatase inhibitors in a large population-based cohort of women with breast cancer. *Br. J. Cancer* 104 (10), 1558–1563. doi:10.1038/bjc.2011.140

Hurtado-de-Mendoza, A., Jensen, R. E., Jennings, Y., and Sheppard, V. B. (2017). Understanding breast cancer survivors' beliefs and concerns about adjuvant hormonal therapy: Promoting adherence. *J. Cancer Educ.* 33, 436–439. doi:10.1007/s13187-017-1180-0

International Agency for Research on Cancer, European Network of Cancer Registries, Joint Reserach Center. 2020 Cancer incidence and mortality in EU-27 countries 2020. Available from: https://ec.europa.eu/jrc/en/news/2020-cancer-incidence-and-mortality-eu-27-countries. Accessed date 22/07/2020.

Kantsiper, M., McDonald, E. L., Geller, G., Shockney, L., Snyder, C., and Wolff, A. C. (2009). Transitioning to breast cancer survivorship: Perspectives of patients, cancer specialists, and primary care providers. *J. General Intern. Med.* 24 (2), 459–466. doi:10.1007/s11606-009-1000-2

Kardas, P., Pawel, L., and Matyjaszczyk, M. (2013). Determinants of patient Adherence: A review of systematic reviews. *Front. Pharmacol.* 4, 91. doi:10.3389/fphar.2013.00091

Kini, V., and Michael Ho, P. (2018). Interventions to improve medication adherence: A review. *JAMA J. Am. Med. Assoc.* 320, 2461–2473. doi:10.1001/jama.2018.19271

Konstantinou, P., Kassianos, A. P., Georgiou, G., Panayides, A., Papageorgiou, A., Almas, I., et al. (2020). Barriers, facilitators, and interventions for medication adherence across chronic conditions with the highest non-adherence rates: A scoping review with recommendations for intervention development. *Transl. Behav. Med.* 10 (6), 1390–1398. doi:10.1093/tbm/ibaa118

Lu, C. Y., Zhang, F., Wagner, A. K., Nekhlyudov, L., Earle, C. C., Callahan, M., et al. (2018). Impact of high-deductible insurance on adjuvant hormonal therapy use in breast cancer. *Breast Cancer Res. Treat.* 171 (1), 235–242. doi:10.1007/s10549-018-4821-z

Nieuwlaat, R., Wilczynski, N., Navarro, T., Hobson, N., Jeffery, R., Keepanasseril, A., et al. (2014). Interventions for enhancing medication adherence. *Cochrane Database Syst. Rev.* 2014 (11), Cd000011. doi:10.1002/14651858.CD000011.pub4

Pannard, M., Bauquier, C., Bassoleil, L., Sablone, L., Jacob, G., Reyal, F., et al. (2020). Citizens who volunteer as participants for cancer research-results of the Seintinelles Barometer 2018. *Bull. Cancer* 107 (3), 333–343. doi:10.1016/j.bulcan.2019.11.012

Partridge, A. H., Wang, P. S., Winer, E. P., and Avorn, J. (2003). Nonadherence to adjuvant tamoxifen therapy in women with primary breast cancer. *J. Clin. Oncol.* 21 (4), 602–606. doi:10.1200/JCO.2003.07.071

Pistilli, B., Paci, A., Ferreira, A. R., Di Meglio, A., Poinsignon, V., Bardet, A., et al. (2020). Serum detection of nonadherence to adjuvant tamoxifen and breast cancer recurrence risk. *J. Clin. Oncol.* 38 (24), 2762–2772. doi:10.1200/JCO.19.01758

Pouls, B. P. H., Vriezekolk, J. E., Bekker, C. L., Linn, A. J., van Onzenoort, H. A. W., Vervloet, M., et al. (2021). Effect of interactive ehealth interventions on

improving medication adherence in adults with long-term medication: Systematic review. *J. Med. Internet Res.* 23 (1), e18901. doi:10.2196/18901

Ringwald, J., Marwedel, L., Junne, F., Ziser, K., Schäffeler, N., Gerstner, L., et al. (2017). Demands and needs for psycho-oncological eHealth interventions in women with cancer: Cross-sectional study. *JMIR cancer* 3 (2), e19. doi:10.2196/cancer.7973

Rosenberg, S. M., Petrie, K. J., Stanton, A. L., Ngo, L., Finnerty, E., and Partridge, A. H. (2020). Interventions to enhance adherence to oral antineoplastic agents: A scoping review. *J. Natl. Cancer Inst.* 112 (5), 443–465. doi:10.1093/jnci/djz244

Ross, J., Stevenson, F., Lau, R., and Murray, E. (2016). Factors that influence the implementation of E-health: A systematic review of systematic reviews (an update). *Implement. Sci.* 11 (1), 146. doi:10.1186/s13012-016-0510-7

Sabaté, E.World Health Organization (2003). *Adherence to long-term therapies: Evidence for action*. Geneva, Switzerland: World Health Organization.

Talal, A. H., McLeod, A., Andrews, P., Nieves-McGrath, H., Chen, Y., Reynolds, A., et al. (2019). Patient reaction to telemedicine for clinical management of hepatitis C virus integrated into an opioid treatment program. *Telemed. J. E. Health.* 25 (9), 791–801. doi:10.1089/tmj.2018.0161

Touillaud, M., Fournier, B., Pérol, O., Delrieu, L., Maire, A., Belladame, E., et al. (2021). Connected device and therapeutic patient education to promote physical activity among women with localised breast cancer (DISCO trial): Protocol for a multicentre 2×2 factorial randomised controlled trial. *BMJ Open* 11 (9), e045448. doi:10.1136/bmjopen-2020-045448

Vrijens, B., De Geest, S., Hughes, D. A., Przemyslaw, K., Demonceau, J., Ruppar, T., et al. (2012). A new taxonomy for describing and defining adherence to medications. *Br. J. Clin. Pharmacol.* 73 (5), 691–705. doi:10.1111/j.1365-2125.2012.04167.x

World Health Organization (2022) World health organization - regional office for the eastern mediterranean, Available at: http://www.emro.who.int/health-topics/ehealth/. Accessed July 25, 2022.

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Comparison of different methods to assess tacrolimus concentration intra-patient variability as potential marker of medication non-adherence

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Background and objective: Non-adherence to tacrolimus commonly manifests as low drug concentrations and/or high intra-patient variability (IPV) of concentrations across multiple measurements. We aimed to compare several methods of tacrolimus IPV calculation and evaluate how well each reflects blood concentration variation due to medication non-adherence in kidney transplant recipients.

Methods: This Czech single-center retrospective longitudinal study was conducted in 2019. All outpatients ≥18 years of age, ≥3 months post-transplant, and on tacrolimus-based regimens were approached. After collecting seven consecutive tacrolimus concentrations we asked participating patients to self-report adherence to immunosuppressants (BAASIS© scale). The IPV of tacrolimus was calculated as the medication level variability index (MLVI), the coefficient of variation (CV), the time-weighted CV, and *via* nonlinearly modeled dose-corrected trough levels. These patient-level variables were analyzed using regression analysis. Detected nonlinearities in the dose-response curve were controlled for by adding tacrolimus dosing and its higher-order terms as covariates, along with self-reported medication adherence levels.

Results: Of 243 patients using tacrolimus, 42% (n = 102) reported medication non-adherence. Non-adherence was associated with higher CVs, higher time-weighted CVs, and lower dose-corrected nonlinearly modeled trough levels; however, it was not associated with MLVIs. All of the significant operationalizations suggested a weak association that was similar across the applied methods.

Abbreviations: 95% CI, 95% confidence interval; CV, coefficient of variation; IPV, intra-patient variability; KTx, kidney transplantation; MLVI, medication level variability index.

Discussion and conclusion: Implementation non-adherence was reflected by higher CV or time-weighted CV and by lower blood concentrations of tacrolimus. As an additional tool for identifying patients at risk for non-adherence, simple IPV calculations incorporated into medical records should be considered in everyday clinical practice.

KEYWORDS

immunosuppression, kidney transplantation, intra-patient variability, medication adherence, tacrolimus immunosuppression, tacrolimus

1 Introduction

Patients who undergo kidney transplantation (KTx) require lifelong immunosuppression. Maintenance immunosuppression includes a combination of medications, with tacrolimus-based regimens a top choice. Due to tacrolimus' narrow therapeutic range and high pharmacokinetic variability, regular assessment of its concentration in the patient's blood is necessary to guide tacrolimus management (Kidney Disease: Improving Global Outcomes Transplant Work Group, 2009). Its concentration varies both inter-individually [mainly due to demographic factors and metabolism on CYP450 (Gonzales et al., 2020)] and intra-individually [mainly due to medication non-adherence (Schumacher et al., 2021)].

Even small deviations in post-transplant medication adherence (>5%), i.e., the degree to which patients take their medication as prescribed, have been associated with an elevated risk of graft rejection (Butler et al., 2004; Gustavsen et al., 2019). Adherence consists of three phases: initiation, implementation, and discontinuation–each of which must be specifically assessed. Persistence is the length of time between initiation and the last dose, which immediately precedes discontinuation (Vrijens et al., 2012; Eliasson et al., 2020).

Immunosuppression is initiated before and during hospitalization. During this phase, as every dose is administered or supervised by a health care professional, non-adherence is not possible. It is in the following phase, implementation, that adherence becomes a critical issue, as this is when patients begin to establish the behaviors they will need for long-term self-management and persistence on the treatment. Approximately one-third of KTx patients begin to show non-adherence during their implementation phase. This proportion increases over time (De Geest et al., 2014). Treatment discontinuation is rare and can be assessed by drug monitoring if patients stay in follow-up (Neuberger et al., 2017).

During implementation, non-adherence to tacrolimus can manifest itself as low blood concentrations or as high intra-patient variability of concentrations (IPV) over several measurements (Rozen-Zvi et al., 2017). Simple IPV calculations, such as the medication level variability index (MLVI) or the coefficient of variation (CV), are commonly used in research (Schumacher et al., 2021). To separate dosing adjustments or timing influences on blood tacrolimus levels, both dose-adjusted (Kim et al., 2019) and time-adjusted (Rozen-Zvi et al., 2017) methods were proposed.

This study's aim was to compare various methods of tacrolimus IPV calculations and evaluate how well each reflected blood tacrolimus concentration variation due to non-adherence to immunosuppressants in KTx recipients.

2 Materials and methods

2.1 Study design and setting

This single-center retrospective observational study was conducted in the outpatient transplant clinic of the University Hospital Hradec Kralove in the Czech Republic from May to December 2019. It was approved by the Ethics Committee of the University Hospital Hradec Kralove, and was conducted in accordance with the Helsinki and Istanbul Declarations.

The Czech healthcare system is a social health insurance system: all patients have free access to medical care. The Coordination Center for Transplantation allocates organs, manages transplant registries, and gathers regular statistics[1]. Seven transplant centers provide over 500 kidney grafts annually for the Czech Republic's approximately 10 million inhabitants. The Transplantation Center in Hradec Kralove, where this study was conducted, performs approximately 50 KTx per year.

The frequency of follow-ups at the outpatient clinic varies mainly based on time since transplantation and each patient's health status. Visits are scheduled several times for each of the first three months post-transplantation, then once per month for the rest of the year. In the second year post-transplant, the frequency varies from once each month to once every second month. From the beginning of the third year, the usual follow-up frequency is four times per year.

The first-choice maintenance immunosuppressive regimen is a combination of tacrolimus, mycophenolate mofetil, and corticosteroids. While medication costs are normally subject to limited surcharges, immunosuppressants (except corticosteroids) are fully covered.

1 Data of the Coordination Center for Transplantation. https://www.kst.cz/en/[Accessed 25 May 2021]

2.2 Data collection

Data were collected by reviewing medical records and patient questionnaires. Participating patients were approached by a nephrology nurse during their scheduled visits.

2.3 Sampling methods

We first screened all consecutive patients at the outpatient transplant clinic for eligibility. All who were eligible were then approached for participation in the study. Inclusion criteria were ≥18 years of age, stable clinical status, ≥3months post-transplant, a tacrolimus-based immunosuppression regimen and provision of written informed consent. Patients not fluent in the Czech language, those suffering from severe cognitive or health impairment, as well as those on acute anti-rejective therapy or hospitalized were excluded. Re-transplantation was not an exclusion criterion.

2.4 Variables and measurement

2.4.1 Socio-demographic and transplant variables

We assessed education level and working status through a structured written questionnaire. Age, gender and transplant characteristics, e.g., time post-transplant in years, donor type, type of KTx, current immunosuppressants, were all collected from medical records (detailed information in Table 1).

2.4.2 Self-reported medication adherence

Adherence to immunosuppressants (implementation phase) was assessed by the written version of the Basel Assessment of Adherence to Immunosuppressive Medications Scale (BAASIS©) (Dobbels et al., 2010), translated from English to the Czech language (Kostalova et al., 2021). The BAASIS consists of five self-report items: one on initiation; three on implementation and one on persistence to the prescribed immunosuppression regimen. The initiation phase item is assessed for co-medications only, as chronic immunosuppression is typically started during the post-transplant inpatient phase. The BAASIS assesses medication adherence for the four weeks preceding the report.

The three implementation items assess "taking" (i.e., missing any dose of medication), "timing" (i.e., taking the medication two hours or more before or after the usual time), and "dosing" (i.e., changing the amount of medication taken without input from a physician). All three either begin with or consist entirely of binary (i.e., yes/no) questions. Any positive answer was considered non-adherence. To evaluate the frequency of implementation problems, positive answers to the "taking" and "timing" items were followed by five response categories: once, twice, 3 times, 4 times and more than 4 times.

2.4.3 Tacrolimus concentrations

Immunosuppressive regimen details regarding prescribed drugs, dosage forms, dosing schedule and possible switches in drug regimen were abstracted from medical records. Before adherence assessments began, seven tacrolimus trough concentrations were collected over the course of each patient's scheduled follow-up visits. Based on hospital guidelines, the target range of tacrolimus was 10–15 μg/L in newly transplanted patients and 5–10 μg/L in those at least 30 days post-transplant. Tacrolimus concentrations were calculated based on ethylenediaminetetraacetic acid blood levels measured *via* chemiluminescent microparticle immunoassay in an Architect i1000 analyzer. All tacrolimus trough concentrations included in the IPV calculation were obtained during steady states of tacrolimus therapy, with no dose changes in the 3 days prior to sampling.

Extreme deviations in tacrolimus concentrations were excluded from the analysis if the medical documentation provided explanations (e.g., drug-drug interactions or incorrect administration). If a change was observed from a tacrolimus to a non-tacrolimus-based regimen during the observation period, we noted the reason for the change and included all available tacrolimus values preceding the change.

2.4.4 Intra-patient variability of tacrolimus concentrations

Tacrolimus IPV values were assessed *via* MLVI, CV and time-weighted CV. Both MLVI and CV are calculated from the variance, i.e., $s^2 = \Sigma(x_i - \bar{x})^2$, where x_i is the assay value for observation i, and $\bar{x}$ is the mean. The MLVI represents the standard deviation of all measured tacrolimus concentrations (i.e., $\sqrt{s^2}$). The CV is calculated by multiplying each patient's MLVI by 100, then dividing the product by the mean tacrolimus concentration, i.e., (100*MLVI) /$\bar{x}$, thus allowing comparisons between patients with different adherence target levels (Shneider et al., 2018). The calculation of the time-weighted average differed from the non-time-weighted average in that, to determine it, each assay value (x_i) was multiplied by the time of exposure (t_i), i.e., half the time interval between the measurement and the value preceding it, plus half the time interval after the measurement. The standard deviation was the square root of the time-weighted variance, i.e., $\Sigma(x_i-\bar{x})^{2*}t_i$. A detailed explanation of the time-weighted calculations can be found in Rozen-Zvi et al., 2017.

2.5 Statistical analysis

Descriptive statistics were applied to summarize variables as appropriate for data type and distribution (e.g., frequencies; percentages; mean/standard deviation; median/interquartile ranges).

The next step was to apply inferential statistics. First, we used generalized additive modeling to explore possible nonlinearities in the association between tacrolimus dosing and its trough concentration. Second, we predicted the dependent variable trough concentration–using random-intercept regression analysis, with additional robust estimation of the standard errors to account for the repeated measurements within patients and, if necessary, the addition of a random slope next to the random intercept. Nonlinearities in the dose-concentration curve were modeled by adding dosing and its higher-order terms as covariates (i.e., tacrolimus dose, its second- (quadratic) and third-order (cubic) parameters), along with the

TABLE 1 Patient characteristics (*N* = 243).

Characteristic		Number
Patient characteristics		
Male (n,%)		165 (67.90%)
Age (median, IQR)	(in years)	56.75 (47.38–65.44)
Education (n,%)	Elementary	25 (10.29%)
	Secondary	184 (75.72%)
	Higher/professional school	8 (3.29%)
	University	25 (10.29%)
	Missing	1 (0.41%)
Working status* (n,%)	Working	112 (46.50%)
	Retired	73 (30.04%)
	Invalid	109 (44.86%)
Transplant characteristics		
Number of Tx (n (%))	First	212 (87.24%)
	Second	30 (12.35%)
	Third	1 (0.41%)
Time post-transplant (median, IQR)	(in years)	5.64 (2.79–10.30)
Donor type (n,%)	Cadaveric	222 (91.36%)
	Living unrelated	5 (2.06%)
	Living related	16 (6.58%)
Pre-emptive Tx (n,%)		29 (11.93%)
Immediate onset of kidney function (n,%)		187 (76.95%)
Rejection post-Tx (n,%)	<1-month post-Tx	29 (11.93%)
	≥1-month post-Tx**	48 (19.75%)
Tacrolimus-based immunosuppressive regimen (at the time of data collection)*		
+ Antiproliferative agents (n,%)	Mycophenolate mofetil or mycophenolic acid	222 (91.36%)
	Azathioprine	2 (0.82%)
+ mTOR inhibitors (n,%)	Sirolimus	5 (2.06%)
+ Corticosteroids (n,%)	Prednisone	225 (92.59%)
	Methylprednisolone	3 (1.23%)

*multiple answers possible.
**related to current transplantation, rejection leading to re-transplantation was not counted.IQR, interquartile range; N, denominator; Tx, transplantation.

BAASIS score. IPV-derived dependent variables (i.e., logarithmically transformed MLVI, CV and time-weighted CV) were analyzed by ordinary regression analysis.

A p-value of <0.05 was considered statistically significant. Analyses were performed in SAS 9.4 (SAS Institute, Cary, NC) and the 'Mixed GAM Computation Vehicle' (mgcv) package in R 4.0.0 for the exploration of nonlinearities.

3 Results

3.1 Socio-demographic and transplant variables

Of the 410 patients scheduled to receive regular follow-up care at the post-transplant outpatient clinic until December 2019, 275 were on tacrolimus-based immunosuppression. Based on our inclusion and exclusion criteria (noted above), 256 eligible patients were approached, of whom 243 agreed to participate and completed the survey (Figure 1). Included patients had a median age of 57 years; 165 (67.9%) were male; the median number of years post-transplant was 5.6 (Table 1). Thirty-one (12.8%) were re-transplanted.

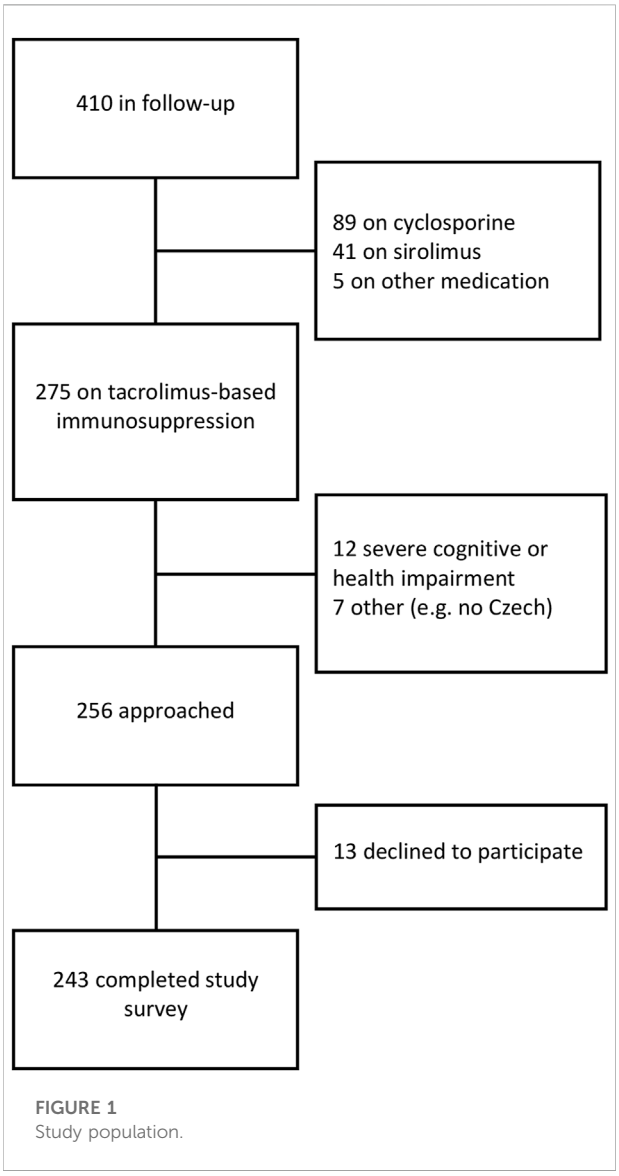

FIGURE 1
Study population.

3.2 Self-reported medication adherence (implementation phase)

Non-adherence to immunosuppressants was found in 102 (42.0%) patients; 35 (14.4%) were non-adherent with the "taking," 92 (37.9%) with the "timing," and 1 (0.4%) with the "dosing" aspects of their immunosuppressant regimens.

3.3 Tacrolimus concentrations

Most patients (98.8%) took a prolonged-release formulation of tacrolimus; three (1.2%) were treated with immediate-release capsules. Tacrolimus dosage adjustments were made in 102 (42.0%) cases during the observed period: dosages were adjusted once in 79 patients and at least twice in 23 patients.

Seven consecutive tacrolimus concentrations were available for 227 (93.4%) patients. These measurements spanned an average of 14.4 ± 4.5 months (minimum 3 months; maximum 21.5 months). Individual patients' timespans corresponded with their transplant centers' care management policies.

Only 6 measurements were available for 15 (6.2%) patients: 10 (4.1%) admitted incorrect administration; 3 (1.2%) were switched from tacrolimus to sirolimus for cancer diagnosis; 1 (0.4%) was switched to a different brand name of tacrolimus extended-release capsule; and 1 (0.4%) discontinued tacrolimus use on physician's recommendation (because of possible drug-drug interaction). This patient initiated the treatment with diltiazem which is known to be an inhibitor of tacrolimus metabolism. Only 5 measurements were included for 1 (0.4%) patient, who was switched to sirolimus during the observed period.

3.4 Intra-patient variability of tacrolimus concentrations

The mean MLVI was 1.54 (median 1.33; SD 0.98; IQR 0.95–1.76); the mean CV was 22.56 (median 20.89; SD 10.82; IQR 15.17–26.51).

Analysis of the association between tacrolimus dose and blood concentrations revealed a nonlinear curve. Significantly lower blood concentrations were found in patients who admitted omission of at least one dose [−0.08; 95% confidence interval

TABLE 2 Modeling of blood tacrolimus by the BAASIS©, corrected for dosing (*N* = 243)*.

BAASIS question	Estimate	Confidence intervals	Pr > |t|
Taking (yes/no)	−0.0773	−0.1476; −0.0070	0.0313 **
Taking (frequency)	−0.0434	−0.0966; 0.0098	0.1099
Timing (yes/no)	−0.0445	−0.0935; 0.0045	0.0751
Timing (frequency)	−0.0230	−0.0424; -0.0036	0.0201 **

*logarithmically transformed tacrolimus levels to yield a normal distribution, adjusted for tacrolimus dose, dose in quadrate and dose to the third power.
**statistically significant difference from zero (p-value <0.05). BAASIS, basel assessment of adherence to immunosuppressive medications scale;
N, denominator; Pr > |t|, two-tailed p-value computed using the t distribution.

(CI) −0.15 to −0.01; $p = 0.03$] or a higher frequency of "timing" problems [−0.02; 95% CI -0.04 to −0.00; $p = 0.02$] (Table 2). However, these associations were not strong: the generalized for both equivalent models using "taking" and "timing" non-adherence as a covariate, our additive modeling approach suggested an R^2 value of only 3%. Problems with tacrolimus "dosing" could not be evaluated due to their small number of occurrences.

Analysis of IPV variables is shown in Table 3. Significantly higher CVs were found for "taking" non-adherence measured either dichotomously [0.20; 95% CI 0.05–0.36; $p = 0.01$; $R^2 = 3\%$] or ordinally [0.13; 95% CI 0.01–0.24; $p = 0.03$; $R^2 = 2\%$]. Also, the time-weighted CVs showed significantly higher variability for dichotomously measured "taking" adherence [0.22; 95% CI 0.02–0.43; $p = 0.03$; $R^2 = 2\%$].

4 Discussion

Regular blood level monitoring for calcineurin inhibitors and mTOR inhibitors is available in most transplant centers. However, many transplant centers do not perform standard therapeutic drug monitoring, examining only single drug concentrations at each patient visit (Kidney Disease: Improving Global Outcomes Transplant Work Group, 2009; Shuker et al., 2015). Single concentration testing is valid for a short period after medication intake and may be biased by so called "white coat adherence." The IPV calculation, which covers multiple drug concentrations, might be more meaningful and less bias-prone surrogate for drug exposure over time. In transplant recipients, higher calculated tacrolimus concentration IPVs have already been associated with negative clinical outcomes including acute rejection, *de novo* donor-specific antibodies formation, graft loss, and mortality (Schumacher et al., 2021).

Comparing various IPV calculations, we found a correlation between self-reported medication non-adherence and higher CVs or time-weighted CVs; however, this relationship did not extend to MLVIs. In a recent systematic review, Schumacher et al. (2021) recommended the CV over other candidates for IPV calculation. The authors' choice was based on widespread reporting of CV use in the literature, the ease of calculating it, and its standardization for the scale of the dataset. It has also been

TABLE 3 Modeling of tacrolimus intra-patient variability by the BAASIS (*N* = 243).

	BAASIS© question	Estimate	Confidence intervals	Pr > |t|
MLVI*	Taking (yes/no)	0.1125	−0.0004; 0.2254	0.0507
	Taking (frequency)	0.0749	−0.0077; 0.1575	0.0754
	Timing (yes/no)	−0.0061	−0.0880; 0.0758	0.8828
	Timing (frequency)	−0.0001	−0.0373; 0.0372	0.9973
CV*	Taking (yes/no)	0.2050	0.0501; 0.3599	0.0097 **
	Taking (frequency)	0.1259	0.0120; 0.2399	0.0304 **
	Timing (yes/no)	0.0332	−0.0798; 0.1462	0.5634
	Timing (frequency)	0.0240	−0.02728; 0.0754	0.3271
TWCV*	Taking (yes/no)	0.2245	0.0235; 0.4255	0.0287 **
	Taking (frequency)	0.1340	−0.0136; 0.2816	0.0750
	Timing (yes/no)	0.0200	−0.1251; 0.1681	0.7901
	Timing (frequency)	0.0246	−0.0423; 0.0915	0.4964

*logarithmically transformed to yield a normal distribution.
**statistically significant difference from zero (p-value <0.05).
BAASIS, basel assessment of adherence to immunosuppressive medications scale; CV, coefficient of variation; MLVI, medication level variability index; N, denominator; Pr >|t|, two-tailed p-value computed using the t distribution; TWCV, time-weighted coefficient of variation.

recommended by various other researchers (Shuker et al., 2015; Kuypers, 2020).

This sample's median CV was generally comparable to those of other studies: variation ranged from 17.7% (Shuker et al., 2016) to 43.1% (Solomon et al., 2020), but data were mostly concentrated around 23% (Schumacher et al., 2021). For example, the same median of CV (20.5%) was found by Mo et al. in their post-KTx study of 671 patients (Mo et al., 2019). MLVI was also comparable to that calculated by Shemesh et al. in a sample of 379 liver transplant patients [mean 1.7; median 1.3; SD 1.6] (Shemesh et al., 2017).

On the other hand, IPV calculation using time-weighted averages appears to reduce the effect of short periods of multiple measurements (e.g., during hospitalization). Using a study sample of 803 KTx patients, Rozen-Zvi et al. (2017) multivariate analysis showed a clear link between high time-weighted tacrolimus blood concentration CVs and reduced graft survival [hazard ratio 1.74; 95% CI 1.14–2.63; $p = 0.01$]. As a part of our study, we assessed the correlation between time-weighted CV calculation and self-reported medication adherence. Despite their limited use to date, time-weighted CVs also show potential for regular assessment of adherence in clinical practice.

When evaluating IPV calculations' prognostic value, researchers and clinicians should consider not only inter-measurement intervals but also the time since transplant, as this may also effect the therapeutic value of tacrolimus concentrations (Shuker et al., 2015). Immediately after KTx, factors including the frequent need to adjust dosages (leading to a lack of fixed-target concentrations), or the varying periods patients take to build a stable tacrolimus use routine, IPV calculations appear to have the highest predictive potential when initiated 3–6 months post-transplant. After this period, IPVs better reflect patient medication-taking behavior (Schumacher et al., 2021). For this reason, we included all patients at least 3 months post-transplant.

Another approach assumed a non-linear relationship between tacrolimus trough concentrations and dosing. Using functional regression modeling, a variety of real-world settings (e.g., continuously changing variability over time, irregular observations per patient) could be accommodated. This assumption was tested in a study evaluating data from 960 KTx patients (Kim et al., 2019). In line with that study's findings, we found a nonlinear function of tacrolimus dose and tacrolimus blood concentrations. Moreover, implementation non-adherence to tacrolimus was associated with lower blood concentrations. Specifically, in line with Kim et al. (2019), we found a direct relationship between the blood tacrolimus level and tacrolimus "taking" and "timing."

The main limitation of our study was that our instruments lacked the sensitivity to differentiate low-level relationships between IPV calculations and self-reported medication adherence. Regardless of the method used, the explained variability was always around 3%. Weak or even no correlations were also observed in other studies where the IPV of tacrolimus concentration was combined with various methods of adherence measurement such as electronic monitoring (Foster et al., 2018) or self-reports (Foster et al., 2018; Gustavsen et al., 2019; Herblum et al., 2021). Considering the fact that no correlation between IPV and electronic monitoring has yet been found in the literature, IPV should be considered only adherence measure among others. However, the IPV of tacrolimus is probably determined by a set of influencing factors; therefore, it lacks the power to capture medication adherence on its own. This supports Gustavsen et al.'s recommendation to use multiple tools to capture different patients at risk for non-adherence (Gustavsen et al., 2019).

The retrospective single-centered design also limits our results' applicability to a broader transplant population. Even though a tacrolimus-based regimen is the therapy of choice, at the time of our study, only 60% of our transplant center's patients were using tacrolimus (Vankova et al., 2018). Compared with ciclosporin A, tacrolimus is known to have lower individual concentration variability (Heemann and Viklicky, 2017). Therefore, further research should evaluate the IPV calculations when involving patients using numerous types of immunosuppression. We did not include patients on ciclosporin A due to their small number during data collection. Moreover, no more patients are newly initiated with ciclosporin A in our transplant center nowadays.

Our analysis of the association between self-reported adherence and IPV calculation was also limited by the fact that, whereas the BAASIS scale measures adherence to all immunosuppressants for the preceding 4 weeks, tacrolimus blood concentration reflects only a short period after the medication's intake. There is no gold standard for monitoring adherence in clinical practice. The currently preferred method is combining tools that capture various non-adherent behaviors. Specifically for transplant populations, adherence assessment may be done by combining patient-reported outcome measures with evaluation of immunosuppressant's trough blood concentration (Gustavsen et al., 2019). We chose the BAASIS scale based on the range of literature using it with transplant populations as well as the fact that its validity has been established in an ongoing validation study (Denhaerynck et al. paper in preparation).

Despite notable limitations, this study showed that high IPVs for tacrolimus concentration reflected implementation non-adherence in KTx recipients. Specifically, the combination of a self-report (e.g., the BAASIS scale) and a CV (calculated using data from medical records), may enable precise regular adherence assessment in clinical practice. Both the BAASIS and the CV are simple, inexpensive, and easy to evaluate. The BAASIS consists of five self-report items, with any positive answer signifying non-adherence. Two versions exist: one is completed as an interview between a healthcare professional and the transplant recipient; the other is a questionnaire that can be completed by transplant recipients on their own. The BAASIS scale is under copyright at the University of Basel. Detailed information about its use can be found on the BAASIS website: https://baasis.nursing.unibas.ch/.

The CV calculation can be incorporated into medical records, making it easy for clinicians to monitor it regularly. High CVs reflect potential non-adherence; however, the definition of "high" varies among studies. Schumacher et al. (2021)'s literature review found that a CV was generally considered high if it was greater than the cohort median or highest quartile. In most studies, CV values of 25% and above were associated with acute rejection at or after 1 year posttransplant.

Due to the high prevalence of non-adherence to immunosuppressants and its negative consequences, it is now recommended to actively screen patients for increased risk for non-adherence (Neuberger et al., 2017). In any case where potential medication non-adherence is identified by a high tacrolimus concentration IPV, the patient should be questioned about possible influencing factors such as drug administration in relation to food, recent acute diseases (e.g., diarrhea), and the use of possible interacting agents (e.g., initiation of new medication by another physician, self-medication and known interactive nutrients).

Patients at risk for non-adherence should be targeted with adherence-enhancing interventions and their adherence redetermined in association with calculated IPV and self-reports (Herblum et al., 2021). To date, no randomized controlled trial has been found on this topic (Schumacher et al., 2021).

5 Conclusion

Immunosuppressant implementation non-adherence was reflected by higher CVs or time-weighted CVs of tacrolimus concentration, as well as lower concentrations in the blood. Simple IPV calculations incorporated into medical records should be considered for everyday clinical practice as an additional tool to identify patients at risk for non-adherence.

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 Ethic committe of the University Hospital Hradec Kralove, Sokolská 581, Hradec Králové, 500 05, Czech Republic. The patients/participants provided their written informed consent to participate in this study.

Author contributions

BK, KM-L, KD, SDS, and JM participated in research design. KM-L and SG participated in the interpretation of the analyses. BK, KM-L, and KD drafted the manuscript. SDS, SG, and JM reviewed the manuscript and contributed domain-specific expertise to the manuscript's intellectual scientific content.

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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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References

Butler, J. A., Roderick, P., Mullee, M., Mason, J. C., and Peveler, R. C. (2004). Frequency and impact of nonadherence to immunosuppressants after renal transplantation: A systematic review. *Transplantation* 77 (5), 769–776. doi:10.1097/01.tp.0000110408.83054.88

De Geest, S., Burkhalter, H., Bogert, L., Berben, L., Glass, T. R., Denhaerynck, K., et al. (2014). Psychosocial interest Group, and Swiss transplant cohort StudyDescribing the evolution of medication nonadherence from pretransplant until 3 years post-transplant and determining pretransplant medication nonadherence as risk factor for post-transplant nonadherence to immunosuppressives: The Swiss transplant cohort study. *Transpl. Int.* 27 (7), 657–666. doi:10.1111/tri.12312

De Geest, S., Ribaut, J., Denhaerynck, K., and Dobbels, F. (2021). "Adherence management in transplantation", in *Psychosocial aspects of chronic kidney disease: Exploring the impact of ckd, dialysis, and transplantation on patients*. Editors D. Cukor, S. D. Cohen, and P. L. Kimmel (Elsevier), 409–450.

Dobbels, F., Berben, L., De Geest, S., Drent, G., Lennerling, A., Whittaker, C., et al.Transplant360 Task Force (2010). The psychometric properties and practicability of self-report instruments to identify medication nonadherence in adult transplant patients: A systematic review. *Transplantation* 90 (2), 205–219. doi:10.1097/TP.0b013e3181e346cd

Eliasson, L., Clifford, S., Mulick, A., Jackson, C., and Vrijens, B. (2020). How the EMERGE guideline on medication adherence can improve the quality of clinical trials. *Br. J. Clin. Pharmacol.* 86 (4), 687–697. doi:10.1111/bcp.14240

Foster, B. J., Pai, A., Zelikovsky, N., Amaral, S., Bell, L., Dharnidharka, V. R., et al. (2018). A randomized trial of a multicomponent intervention to promote

medication adherence: The teen adherence in kidney transplant effectiveness of intervention trial (TAKE-IT). *Am. J. Kidney Dis.* 72 (1), 30–41. doi:10.1053/j.ajkd.2017.12.012

Gonzales, H. M., McGillicuddy, J. W., Rohan, V., Chandler, J. L., Nadig, S. N., Dubay, D. A., et al. (2020). A comprehensive review of the impact of tacrolimus intrapatient variability on clinical outcomes in kidney transplantation. *Am. J. Transpl.* 20 (8), 1969–1983. doi:10.1111/ajt.16002

Gustavsen, M. T., Midtvedt, K., Lønning, K., Jacobsen, T., Reisaeter, A. V., De Geest, S., et al. (2019). Evaluation of tools for annual capture of adherence to immunosuppressive medications after renal transplantation - a single-centre open prospective trial. *Transpl. Int.* 32 (6), 614–625. doi:10.1111/tri.13412

Heemann, U., and Viklicky, O. (2017), Is trough level variability the new tool for identifying patients at risk for rejection after transplantation? *Nephrol. Dial. Transplant.* official publication of the European Dialysis and Transplant Association - European Renal Association, 32. 214–215. doi:10.1093/ndt/gfw447

Herblum, J., Dacouris, N., Huang, M., Zaltzman, J., Prasad, G. V. R., Nash, M., et al. (2021). Retrospective analysis of tacrolimus intrapatient variability as a measure of medication adherence. *Can. J. Kidney Health Dis.* 8, 20543581211021742. doi:10.1177/20543581211021742

Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group (2009). KDIGO clinical practice guideline for the care of kidney transplant recipients. *Am. J. Transpl.* 9, S1–S155. doi:10.1111/j.1600-6143.2009.02834.x

Kim, J., Wilson, S., Undre, N. A., Shi, F., Kristy, R. M., and Schwartz, J. J. (2019). A novel, dose-adjusted tacrolimus trough-concentration model for predicting and estimating variance after kidney transplantation. *Drugs R. D.* 19 (2), 201–212. doi:10.1007/s40268-019-0271-2

Kostalova, B., Mala-Ladova, K., Kubena, A. A., Horne, R., Dusilova Sulkova, S., and Maly, J. (2021). Changes in beliefs about post-transplant immunosuppressants over time and its relation to medication adherence and kidney graft dysfunction: A follow-up study. *Patient prefer. Adherence* 15, 2877–2887. doi:10.2147/PPA.S344878

Kuypers, D. (2020). Intrapatient variability of tacrolimus exposure in solid organ transplantation: A novel marker for clinical outcome. *Clin. Pharmacol. Ther.* 107 (2), 347–358. doi:10.1002/cpt.1618

Mo, H., Kim, S. Y., Min, S., Han, A., Ahn, S., Min, S. K., et al. (2019). Association of intrapatient variability of tacrolimus concentration with early deterioration of chronic histologic lesions in kidney transplantation. *Transplant. direct* 5 (6), e455. doi:10.1097/TXD.0000000000000899

Neuberger, J. M., Bechstein, W. O., Kuypers, D. R., Burra, P., Citterio, F., De Geest, S., et al. (2017). Practical recommendations for long-term management of modifiable risks in kidney and liver transplant recipients: A guidance report and clinical checklist by the consensus on managing modifiable risk in transplantation (commit) group. *Transplantation* 101 (4S Suppl 2), S1–S56. doi:10.1097/TP.0000000000001651

Rozen-Zvi, B., Schneider, S., Lichtenberg, S., Green, H., Cohen, O., Gafter, U., et al. (2017)., Association of the combination of time-weighted variability of tacrolimus blood level and exposure to low drug levels with graft survival after kidney transplantation. *Nephrol. Dial. Transplant.* official publication of the European Dialysis and Transplant Association - European Renal Association, 32. 393–399. doi:10.1093/ndt/gfw394

Schumacher, L., Leino, A. D., and Park, J. M. (2021). Tacrolimus intrapatient variability in solid organ transplantation: A multiorgan perspective. *Pharmacotherapy* 41 (1), 103–118. doi:10.1002/phar.2480

Shemesh, E., Bucuvalas, J. C., Anand, R., Mazariegos, G. V., Alonso, E. M., Venick, R. S., et al. (2017). The medication level variability index (MLVI) predicts poor liver transplant outcomes: A prospective multi-site study. *Am. J. Transpl.* 17 (10), 2668–2678. doi:10.1111/ajt.14276

Shneider, C., Dunphy, C., Shemesh, E., and Annunziato, R. A. (2018). Assessment and treatment of nonadherence in transplant recipients. *Gastroenterol. Clin. North Am.* 47 (4), 939–948. doi:10.1016/j.gtc.2018.07.015

Shuker, N., Shuker, L., van Rosmalen, J., Roodnat, J. I., Borra, L. C., Weimar, W., et al. (2016). A high intrapatient variability in tacrolimus exposure is associated with poor long-term outcome of kidney transplantation. *Transpl. Int.* 29 (11), 1158–1167. doi:10.1111/tri.12798

Shuker, N., van Gelder, T., and Hesselink, D. A. (2015). Intra-patient variability in tacrolimus exposure: Causes, consequences for clinical management. *Transpl. Rev.* 29 (2), 78–84. doi:10.1016/j.trre.2015.01.002

Solomon, S., Colovai, A., Del Rio, M., and Hayde, N. (2020). Tacrolimus variability is associated with de novo donor-specific antibody development in pediatric renal transplant recipients. *Pediatr. Nephrol.* 35 (2), 261–270. doi:10.1007/s00467-019-04377-6

Vankova, B., Mala-Ladova, K., Kubena, A., Maly, J., and Sulkova, S. D. (2018). Immunosuppressive therapy related adherence, beliefs and self-management in kidney transplant outpatients. *Patient Prefer Adherence* 12, 2605–2613. doi:10.2147/PPA.S184166

Vrijens, B., De Geest, S., Hughes, D. A., Przemyslaw, K., Demonceau, J., Ruppar, T., et al.ABC Project Team (2012). A new taxonomy for describing and defining adherence to medications. *Br. J. Clin. Pharmacol.* 73 (5), 691–705. doi:10.1111/j.1365-2125.2012.04167.x

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Identification of target groups and individuals for adherence interventions using tree-based prediction models

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Background: In chronically ill patients, medication adherence during implementation can be crucial for treatment success and can decrease health costs. In some populations, regression models do not show this relationship. We aim to estimate subgroup-specific and personalized effects to identify target groups for interventions.

Methods: We defined three cohorts of patients with type 1 diabetes (n = 12,713), type 2 diabetes (n = 85,162) and hyperlipidemia (n = 117,485) from German claims data between 2012 and 2015. We estimated the association of adherence during implementation in the first year (proportion of days covered) and mean total costs in the three following years, controlled for sex, age, Charlson's Comorbidity Index, initial total costs, severity of the disease and surrogates for health behavior. We fitted three different types of models on training data: 1) linear regression models for the overall conditional associations between adherence and costs, 2) model-based trees to identify subgroups of patients with heterogeneous adherence effects, and 3) model-based random forests to estimate personalized adherence effects. To assess the performance of the latter, we conditionally re-estimated the personalized effects using test data, the fixed structure of the forests, and fixed effect estimates of the remaining covariates.

Results: 1) our simple linear regression model estimated a positive adherence effect, that is an increase in total costs of 10.73 Euro per PDC-point and year for diabetes type 1, 3.92 Euro for diabetes type 2 and 1.92 Euro for hyperlipidemia (all $p \leq 0.001$). 2) The model-based tree detected subgroups with negative estimated adherence effects for diabetes type 2 (-1.69 Euro, 24.4% of cohort) and hyperlipidemia (-0.11 Euro, 36.1% and -5.50 Euro, 5.3%). 3) Our model-based random forest estimated personalized adherence effects with a significant proportion (4.2%–24.1%) of negative effects (up to -8.31 Euro). The precision of these estimates was high for diabetes type 2 and hyperlipidemia patients.

Discussion: Our approach shows that tree-based models can identify patients with different adherence effects and the precision of personalized effects is measurable. Identified patients can form target groups for adherence-promotion interventions. The method can also be applied to other outcomes such as hospitalization risk to maximize positive health effects of an intervention.

KEYWORDS

adherence, costs, personalized effects, subgroups, model-based trees, model-based random forest

Introduction

While adherence to medication is believed to play a crucial role in the efficacy of a treatment in many real life settings, its full implementation remains challenging (Dunbar-Jacob and Mortimer-Stephens 2001). This is also the case in chronically ill patients. Hence, a vast variety of different interventions to increase adherence has been suggested (Nieuwlaat et al., 2014). These interventions finally aim to avoid negative health outcomes and/or additional health care costs. Ideally, an intervention can cover its expenditures by avoiding the costs of more severe health developments, which requires higher adherence to be associated with lower total costs and increased health. However, some studies have shown that higher adherence can also be associated with higher total costs, for example when additional drug costs exceed savings in inpatient and outpatient costs (Iuga and McGuire 2014; Cutler et al., 2018).

These and many other studies model the relationship of adherence and costs in a study population and estimate an overall effect of adherence. For example, the usually applied linear regression model estimates the average effect of adherence for the population. In our case, in contrast, we assumed that there might be individual effects that express in different size or even sign. For example, even when the overall effect is positive, there might still be some patients with a negative effect of adherence on costs. We therefore exploited methods provided by the increasing field of personalized medicine research (Weisberg 2015). The objective was to model treatment effects depending on patients' characteristics, to explore the stratified and personalized effects of adherence.

The identification of patients with a negative relation between adherence and costs can be an aspect of selecting a target group for an intervention. This has been considered to be important for the efficiency of an intervention and can help to reduce the number of people who need to be targeted (Fuchs 2008). An intervention often is applied to a specific group where the need or the expected effect is highest. One area of application is to identify a subgroup of patients of which we can expect the avoided costs (by increased adherence) to be greater than the additional costs of its expenditures.

The identification of these subgroups can be defined theoretically in a hypothesis-driven approach. So far, to our knowledge there are only two studies about subgroup-specific effects in adherence-costs relationship. One of it, by Roebuck et al. (2015) analyzed a population of Medicaid enrollees with low income. They segmented the population according to their basis of eligibility for Medicaid in blind or disabled, other adults, and children and modeled these subpopulations separately. In a preceding study, Roebuck et al. (2011) used interaction effects to estimate age and sex-specific effects of adherence within a single model. The main disadvantage of this approach is that it either requires prior knowledge or strongly depends on assumptions about the functional form of the underlying effect. A major advantage is that subgroups can be compared directly when modeled simultaneously.

The other main approach for the identification of subgroups is data-driven, often by using modern statistical methods to automatically detect subgroups in the data structure. For this purpose, we use decision-tree-based methods to detect subgroups and to estimate subgroup-specific regression models of adherence effects (Seibold et al., 2016). Respective model-based random forests can even be exploited to differentiate between effects on the individual patient level (Seibold et al., 2018). The goal of the present paper is threefold: 1) evaluate the overall relation between adherence and costs, 2) identify subgroups with significantly better response to medication adherence, and 3) provide a model to estimate a patient's individual conditional adherence effects. To reach our research goals, we focused on the development and the application of novel predictive models which transfer the regression approach to a machine learning procedure. We specifically do not want to propose or apply a specific intervention to a group of patients. Instead, we suggest an approach to identify target groups and individuals to maximize the effect of an intervention, given that this intervention is able to increase adherence.

Materials and methods

Data

We used a database of German claims data of the years 2007–2016. It contains over 3.5 million statutory insured persons with data about their age, sex, charges, diagnoses coded

according to the German modification of the international classification of diseases (ICD-10-GM), filled prescription drugs by date, package size, Anatomical Therapeutic Chemical (ATC) classification code and Defined Daily Dose (DDD) according to WHO Collaborating Centre for Drug Statistics Methodology (2021). Also, information about the participation in one of six disease management programs (DMP) for asthma, breast cancer, chronic obstructive pulmonary disease, type 1 diabetes, type 2 diabetes and coronary heart disease are available for all persons in the complete period.

Study population

We extracted data of the latest 4.5 fully available years (July 2011 until December 2015) and defined data of 2012 as baseline and the years 2013–2015 as follow-up. Only patients with year-round coverage in these years were considered in the present study. We focused on patients with chronic diseases to observe the adherence-costs relationship over a longer period of time. Patients with at least one diagnosis within each observational year of type 1 diabetes (T1D: ICD-10-GM code E10), type 2 diabetes (T2D: E11), or hyperlipidemia (E78) were selected for three cohorts. Patients with multiple of the diagnoses of interest were selected for multiple cohorts.

We excluded patient years with excess costs (top 5% total charges of each cohort) to avoid costs which are rather influenced by expensive treatments like dialysis or severe accidents than by the chronic disease itself. These patient years might distort the estimation of adherence effects. Moreover, all patients having no data or fills of corresponding prescription drugs in 2012 were excluded. See Supplementary Table S1 for the definition of diseases and drugs.

Definition of variables

The outcome variable was mean annual total costs in follow up years. We used a time lag between adherence measured at baseline and costs measured during follow-up to avoid reverse causality. Reverse causality might appear when major adverse health events and hospitalization increase costs and likewise result in initiation of drug therapy and influence adherence (Stuart et al., 2014; Roebuck et al., 2015). In an earlier, not yet published work, we found that the mean annual total costs are appropriate for our approach. Therefore, we summed up all patient's individual charges per year and calculated the mean of the follow-up years 2013–2015 with all prices converted to Euros 2015 according to the annual inflation of the healthcare sector as stated by the German Federal Statistical Office (Statistisches Bundesamt (Destatis) 2022).

In this paper, we focus on medication adherence during treatment as the "extent to which a patient's actual dosing corresponds to the prescribed dosing regimen" (Vrijens et al., 2012). Adherence at baseline year 2012 was defined as proportion of days covered (PDC) by any diagnosis specific medication. We used the PDC, because even in case of oversupply—in contrast to the often used medication possession ratio (MPR)—it is still limited to the range 0–100. To calculate the PDC, we counted a day as covered when at least one dose of any diagnosis specific drug, distinguished by its ATC code (WHO Collaborating Centre for Drug Statistics Methodology 2021), was available to the patient. We assumed this was the case 1) within the period after the prescription fill for the number of days calculated by total package size divided by the DDD (WHO Collaborating Centre for Drug Statistics Methodology 2021) or 2) during hospitalization if the patient had filled the same drug within 3 months before or after the hospital visit. In both cases we proportionally considered fills and hospitalizations in the last half of 2011 if the covered days reached into 2012. We divided the number of covered days by the number of days between the first covered day and the last day of 2012 and used the continuous PDC—instead of a dichotomized PDC—to avoid loss of information and the risk of bias (Tueller et al., 2016).

We further extracted some baseline characteristics, such as age and sex as sociodemographic variables, Charlson's Comorbidity Index (CCI) in its ICD-10 version with updated weights (Charlson et al., 1987; Quan et al., 2005, 2011) and initial total costs to reflect the general health status, and a two- or three-level severity variable of the chronic diseases based on treatment guidelines and prescription drug fills to include the degree of severity of a given disease (Supplementary Table S2). Furthermore, participation in any DMP and influenza vaccination at baseline were used as proxys for health behavior which has been discussed to be an important confounder but is not directly available in the analyzed claims data (Shrank et al., 2011).

Statistical analysis

All statistical analyses were performed in R version 3.6.2 (R Core Team 2019). Hypothesis testing was performed at exploratory two-sided 5% levels of significance. We split our cohorts into a training and a test data set of 50% each and fitted the different types of models on the training data set. The test data set was used to evaluate the model-based random forest.

Linear regression

To estimate the overall conditional effect of adherence on total costs we used a multivariable linear regression model with mean annual total costs as outcome; adherence as main predictor; and age, sex, CCI, initial total costs, severity, participation in any DMP, and influenza vaccination as

covariates. The linear regression model assumes the estimated adherence effect is constant for all patients.

Model based decision tree

To identify potential subgroups of patients with different estimated conditional adherence effects, we used a model-based tree in the framework of model-based recursive partitioning (Seibold et al., 2016). This method builds a decision tree which splits the cohort into subgroups by pre-specified candidate partitioning variables. A split is performed when the model parameters are found to be statistically significant dependent on any of the partitioning variables. Then, an optimal cut-point of the partitioning variable is determined as it maximizes the sum of the likelihoods of the two resulting models fit to the respective subsets of the data. This procedure of refitting models to subsets of the data continues recursively until no further statistically significant associations are found or no further splits are possible because of restrictions on the minimally required subgroup sizes.

In our case, we used a linear regression model as the base model and searched for subgroups that differ in the estimated effect of adherence on total costs. In the model-based tree, we specified initial costs, age, CCI and severity as candidate partitioning variables because we expected them to potentially modify the effect of adherence. The procedure thereby implicitly models interactions between the partitioning variables and adherence. We further defined the minimal subset size (terminal node size) to 5% of the cohort to avoid subgroups that are too small for interventions in practice.

Model-based trees again assume the estimated effect is constant for patients within each subgroup, while this must not be true for all patients as a whole (Seibold et al., 2018). The effect is essentially modeled as a step function of the selected partitioning variables. This assumption may be too restrictive when the interaction function is smooth and personalized effect estimates are more appropriate.

Model based random forest

To estimate personalized effects, we used weighted linear regression models derived from a model-based random forest (Seibold et al., 2018). The random forest is an ensemble of the aforementioned model-based trees fitted to random samples of the data and random selections of the partitioning variables. The procedure provides a natural measure of similarity between observations. Therefore, one can count the number of times each pair of observations is allocated to the same subset in each of the many trees of the forest. For example, in a forest consisting of 500 trees, patient A could be in the same defined subgroup as patient B or patient C in 250 and 300 trees. Fitting a personalized model for patient A would consequently assign weights of 1, 250/500 = 0.5 and 300/500 = 0.6 to the observations of patient A, B and C in the data. The linear regression models are otherwise specified as outlined above. We fitted the model-based random forest by the implementation of transformation forests introduced by Hothorn and Zeileis (2021). We applied different specifications of the minimal subset size (terminal node size) of the trees (n_s = 200, 500 or 1,000) to allow three levels of similarity, with larger subgroups consisting of less similar patients and *vice versa*.

For further investigation of estimated personalized effects, we plotted partial dependence plots which show the relation of the partitioning variables age, initial costs, CCI, and severity to the personalized adherence effects by means of a smooth curve (Seibold et al., 2018). We also developed a new calibration-like approach. Therefore, we conditionally re-estimated the personalized adherence effects by using the test data, the fixed structure of the forests and fixed effect estimates of the remaining covariates of the model. We fixed the estimates of the covariates as we subtracted their estimated effects from the outcome before re-estimating the adherence effect in the test data. For a subsample of 1,000 patients, we compared the effects estimated by the forest to the conditional effects re-estimated on test data. We used univariate regression models of these two estimates to explore model calibration and to assess the precision the estimates. Because the scatter plot of the two estimates showed deviations from a linear fit, we fitted three GAMLSS regression models with different assumptions (Stasinopoulos et al., 2017). The first assumes a linear fit, the second assumes a nonlinear fit estimated with cubic splines, and the third additionally models the variance with cubic splines.

The 95% prediction intervals of the regression models were used to identify patients of which we can expect a negative adherence effect with the given certainty based on the respective personalized effect estimation of the forest. When the upper limit of the prediction interval is negative, we can expect a negative personalized adherence effect on costs with the corresponding certainty. We henceforth call them certainty-controlled personalized estimated effects.

Results

Of the 2,644,212 patients with at least one year-round coverage between 2012 and 2015 in the database, we finally include 12,713 patients with T1D, 85,162 patients with T2D and 117,485 patients with hyperlipidemia. Figure 1 shows a flow chart of included, and excluded patients per diagnose.

In T1D and T2D patients, the median PDC was higher than in hyperlipidemia patients with 88 and 84 compared to 64 respectively. Being extremely left skewed, 62% and 54% of the diabetes patients had a PDC higher than 80. In the hyperlipiedemia cohort, only 30% had a PDC higher than

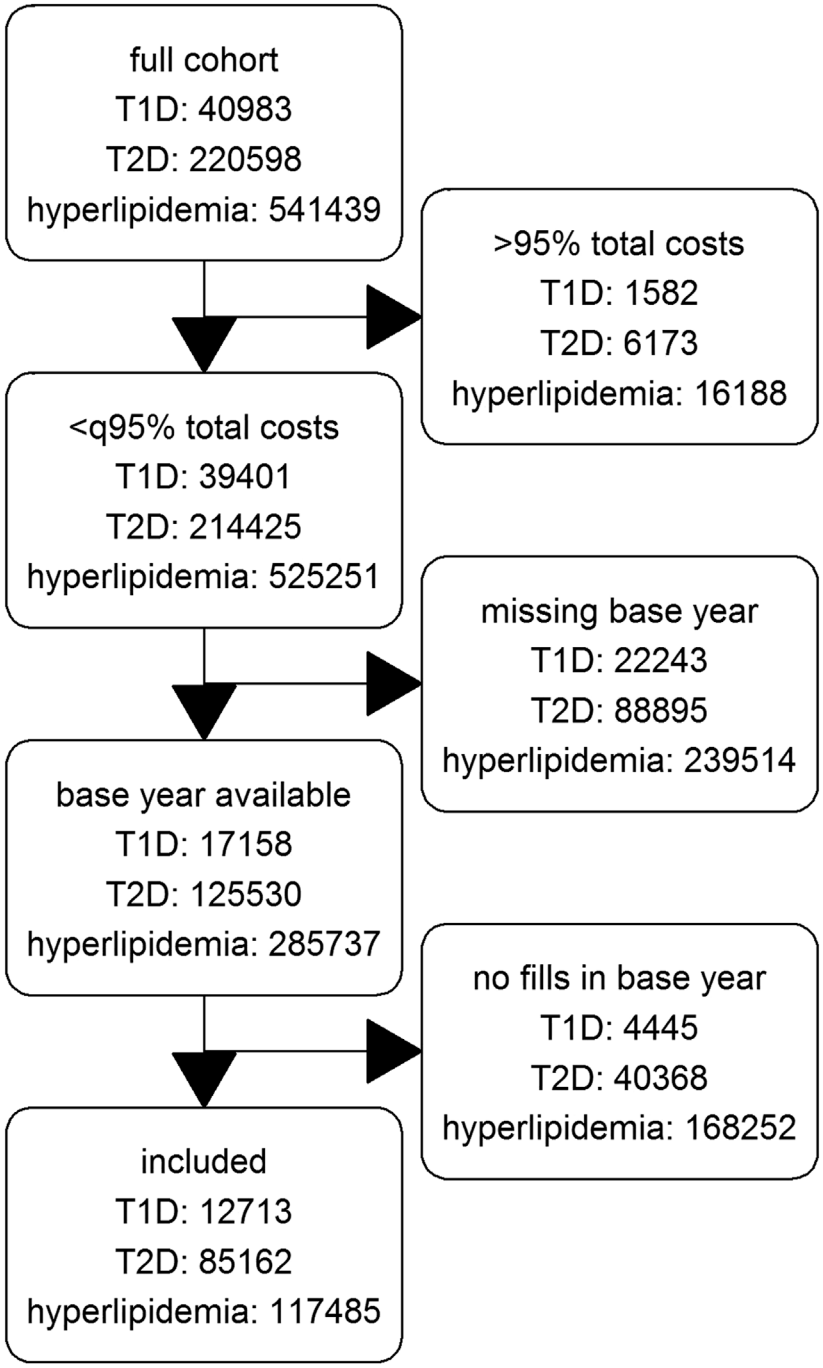

FIGURE 1
Flowchart of cohorts.

80 and the distribution was more balanced. The total costs of all cohorts were right skewed. The median of the mean annual total costs were highest in T1D with 4,848 Euro followed by T2D with 3,404 Euro and hyperlipidemia with 2,329 Euro. These and further descriptive statistics are given in Table 1.

The simple linear regression model estimated a positive adherence effect on total costs of 10.73 Euro per PDC-point and year for T1D, 3.92 Euro for T2D and 1.92 Euro for hyperlipidemia (all $p \leq 0.001$) when we controlled for age, sex, CCI, initial total costs, severity, participation in any DMP

TABLE 1 Descriptive summary statistics of cohorts of 3 chronic diseases: Median (IQR) for continuous and absolute (relative) frequencies for categorical variables.

Variable	T1D[a]	T2D[b]	hyperlipidemia
PDC[c]	88.3 (68.0, 99.7)	83.6 (53.8, 98.1)	63.9 (37.6, 88.2)
Female (Yes)	6,155 (48.4%)	44,709 (52.5%)	61,159 (52.1%)
Age	59.0 (44.0, 72.0)	68.0 (58.0, 76.0)	69.0 (59.0, 76.0)
Severity			
light	4,892 (38.5%)	28,824 (33.8%)	107,061 (91.1%)
medium	7,821 (61.5%)	26,885 (31.6%)	10,424 (8.9%)
severe	-	29,453 (34.6%)	-
Initial Costs	4,183.4 (2,662.0, 7,325.8)	2,534.5 (1,247.1, 5,305.1)	1,792.8 (847.7, 4,147.9)
CCI[d]	3.0 (2.0, 5.0)	3.0 (2.0, 5.0)	2.0 (1.0, 4.0)
DMP (Yes)[e]	9,537 (75.0%)	63,537 (74.6%)	47,016 (40.0%)
Vaccination (Yes)	3,222 (25.3%)	26,228 (30.8%)	35,733 (30.4%)
Total Costs	4,847.9 (3,089.6, 8,159.1)	3,403.7 (1,730.0, 6,489.4)	2,328.7 (1,126.3, 4,755.6)

[a]Type 1 Diabetes.
[b]Type 2 Diabetes.
[c]Proportion of Days Covered.
[d]Charlson's Comorbidity Index.
[e]Disease Management Program.

TABLE 2 Adherence effect estimates and subgroups detected by model-based decision trees.

Diagnosis	Subgroup	Estimate	*p*-value	n (%)
T1D	initial costs <= 15,996 and initial costs <= 7,813	4.21	0.069	4,927 (77.5)
T1D	initial costs <= 15,996 and initial costs >7,813	13.41	0.062	1,055 (16.6)
T1D	initial costs >15,996	16.45	0.248	374 (5.9)
T2D	initial costs <= 7,307 and initial costs <= 3,130 and age <= 63	-1.69	0.087	10,394 (24.4)
T2D	initial costs <= 7,307 and initial costs <= 3,130 and age >63	1.86	0.069	14,154 (33.2)
T2D	initial costs <= 7,307 and initial costs >3,130 and age <= 76	9.17	0.000	7,930 (18.6)
T2D	initial costs <= 7,307 and initial costs >3,130 and age >76	1.60	0.612	2,851 (6.7)
T2D	initial costs >7,307	6.21	0.012	7,252 (17.0)
hyperlipidemia	initial costs <= 3,179 and initial costs <= 1,563 and cci <= 2	-0.11	0.819	21,233 (36.1)
hyperlipidemia	initial costs <= 3,179 and initial costs <= 1,563 and cci >2	2.98	0.009	5,661 (9.6)
hyperlipidemia	initial costs <= 3,179 and initial costs >1,563 and age <= 60	-5.50	0.000	3,125 (5.3)
hyperlipidemia	initial costs <= 3,179 and initial costs >1,563 and age >60	3.60	0.000	9,593 (16.3)
hyperlipidemia	initial costs >3,179	2.03	0.027	19,130 (32.6)

and influenza vaccination (Supplementary Table S3). In all three cohorts, higher adherence was associated with higher total costs.

When we applied model-based trees, we detected subgroups defined by initial total costs, CCI and age in all three cohorts (Table 2). Of the candidate partitioning variables, only severity was never used to define the subgroups. T1D patients were split in three subgroups by initial total costs: in the largest subgroup (77.5% of T1D patients) with initial total costs lower than 7,813 Euro, the subgroup-specific estimated effect of adherence on total costs was lowest with 4.21 Euro per PDC-point and year. It was therefore lower than the overall effect, but still positive. The other two subgroups defined by higher initial costs had an adherence effect above average. Due to the small sample size of the T1D cohort, the effect in all subgroups did not reach statistical significance.

T2D patients were split in five subgroups by initial total costs and age. Patients with lower initial total costs than 3,130 Euro and an age of 63 or younger formed a large subgroup (24.4%) in which higher adherence was associated with lower total costs with an estimated effect of -1.69 Euro per PDC-point and year. Of the other subgroups, two had an adherence effect below average. The

TABLE 3 Proportion (range) of negative personalized estimated effects of adherence on costs.

Diagnosis	Model	Estimated effect	Certainty-controlled estimated effect
T1D	n_s = 200	4.2% (-1.17; -0.06)	6.3% (-1.17; 0.22)
	n_s = 500	0.0% (-)	0.0% (-)
	n_s = 1,000	0.0% (-)	0.0% (-)
T2D	n_s = 200	20.5% (-7.45; -0.01)	3.9% (-7.45; -3.21)
	n_s = 500	10.9% (-3.53; -0.02)	3.9% (-3.53; -1.18)
	n_s = 1,000	6.0% (-0.77; 0.00)	0.6% (-0.77; -0.59)
hyperlipidemia	n_s = 200	24.1% (-8.31; -0.01)	8.3% (-8.31; -1.72)
	n_s = 500	21.3% (-3.50; -0.01)	5.0% (-3.50; -1.50)
	n_s = 1,000	16.6% (-1.43; 0.00)	4.0% (-1.43; -0.96)

effects in all of these mentioned subgroups were not statistically significant.

In hyperlipidemia patients we detected five subgroups defined by initial costs, age and CCI. In two subgroups higher adherence was associated with lower costs. In a large subgroup (36.1%) of patients with initial costs lower than 1,563 Euro and a CCI of two or lower, the estimated effect was -0.11 Euro per PDC-point and year. In another small subgroup (5.3%) with medium initial costs between 1,563 Euro and 3,179 Euro and an age of 60 or younger, the estimated effect was -5.50 Euro. In the latter subgroups the effect was statistically significant. The other subgroups had an adherence effect higher than the overall effect. Table 2 gives an overview of all subgroups. A graphical representation of the trees can be found in the Supplementary Figures S1–S3.

The model-based random forest estimated a significant proportion of negative personalized adherence effects (Table 3). These proportions ranged from 0.0% to 4.2% for T1D, 6.0%–20.5% for T2D and 16.6%–24.1% for hyperlipidemia, depending on the level of similarity, which is controlled by the minimally required subset size (n_s) in the forest models. We estimated personalized adherence effects of up to -1.17 Euro, -7.45 Euro, and -8.31 Euro, respectively. For higher levels of similarity—and therefore lower subset sizes—we obtained more diverse personalized effect estimates and, in consequence, a larger proportion of negative effects.

However, smaller subset sizes may also lead to increased variability and therefore decreased precision in effect estimation. We therefore applied our calibration-like approach to assess the quality of effect estimation. The estimated personalized effects are plotted against the conditional ones re-fitted on test data, while regression models were used to assess their relation. A visual comparison of model fits showed the best fit for the GAMLSS model with a nonlinear fit of mean and variance in almost all cases (Supplementary Figures S4, S5). The calibration plot in Figure 2, where perfect precision is illustrated by a diagonal red line, shows that the effect estimates for T2D and hyperlipidemia patients were well-calibrated, which is not the case for those for T1D patients. In the latter, lower estimated effects seem to be overestimated because the regression curve of the GAMLSS model (blue line) is systematically lower than expected in case of perfect precision (red line). The regression curve of T2D and hyperlipidemia is closer to perfect precision.

The 95%-prediction interval of the GAMLSS regression models (light blue area) identifies 0.0%–6.3% of patients with T1D, 0.6%–3.9% of patients with T2D and 4.0%–8.3% of patients with hyperlipidemia with a negative certainty-controlled personalized estimated effect. For high level of similarity we can expect a negative adherence effect with the given certainty when the estimated effect of the forest was lower than 0.22 Euro, -3.21 Euro and -1.72 Euro, respectively. The value for T1D is counterintuitivly positive because this model is not well calibrated. Again, the variance of re-estimated effects is higher and the prediction intervals wider—indicating lower precision—if the defined level of similarity was higher.

The partial dependence plots of T2D with a high level of similarity (Figure 3) show the relation of the personalized effect estimates to the partitioning variables. They increase continuously by initial costs until around 6,000 Euro. The data gets more sparse and the smooth curve starts fluctuating. The age effect on the personalized effect estimates also increases in the main age groups between 50 an 80, as well as the CCI's effect. More severe T2D patients' effect estimates are higher on average. Patients with T1D and hyperlipidemia show similar patterns (Supplementary Figures S6–S13). In T1D patients, the increase of personalized effects by initial costs can be observed at higher initial costs and there are no differences in severity. For hyperlipidemia patients, there was almost no effect of initial costs and a reverse severity effect. In all partial dependence plots, apart from some age

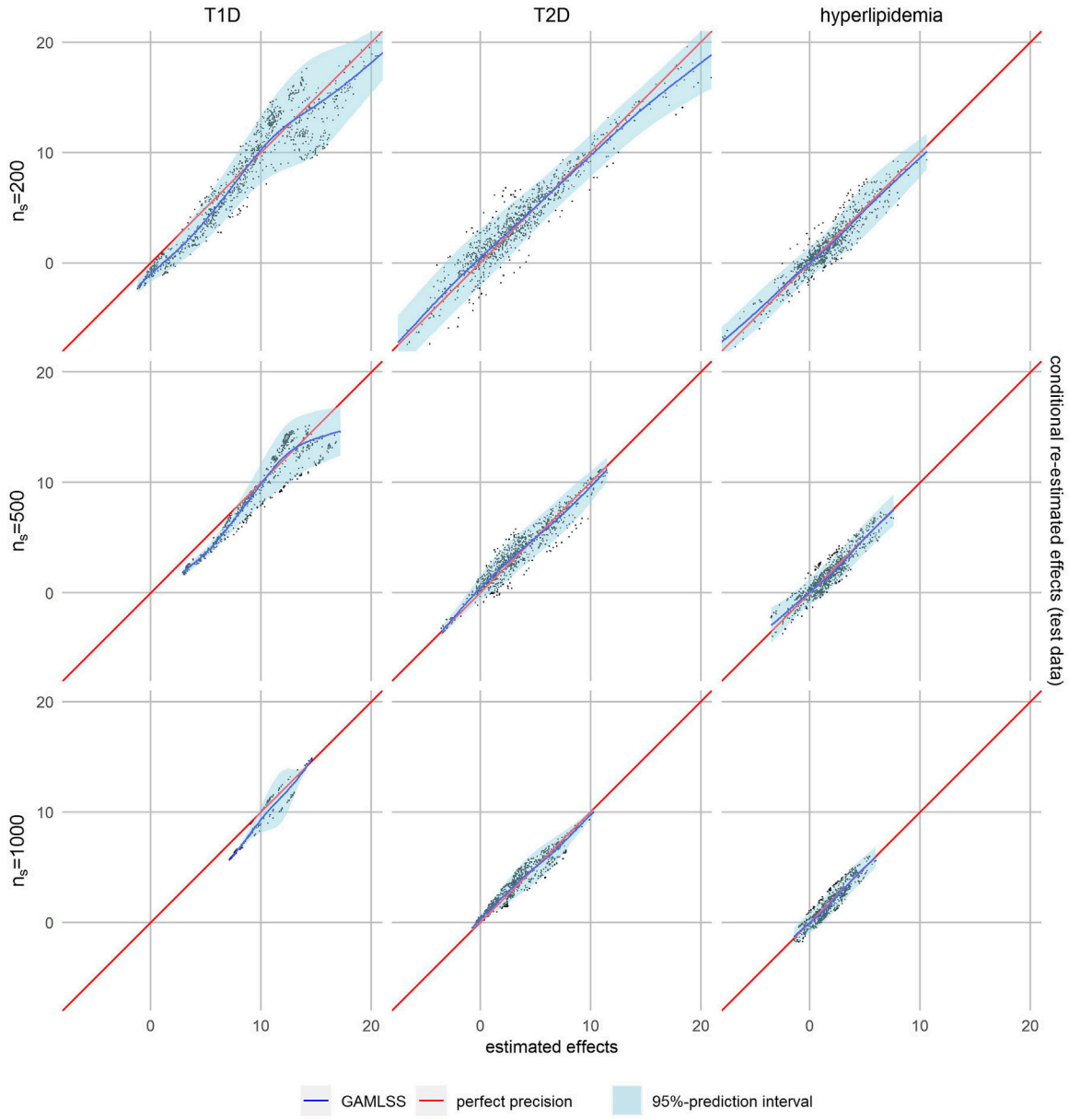

FIGURE 2
Calibration plots with non-linear fit (blue line) and 95% prediction interval (light blue area).

groups of hyperlipidemia patients, the smoothed curve of the adherence effects is positive. Comparison of different levels of similarity showed similar patterns, but the between-person differences were smaller as expected.

Discussion

In T1D, T2D and hyperlipidemia patients, model-based trees and forests often identified patients with negative estimated effects of adherence on costs, while simple multivariable linear regression models showed a positive association overall. In general, patients with negative estimated effects of adherence on costs were healthier and younger. Our approach shows that tree-based models can identify patients with different effects up to the individual level, while the quality of effect estimation of such models can be assessed simultaneously.

Using model-based trees, we stratified the overall effects estimated by the linear regression models and detected large

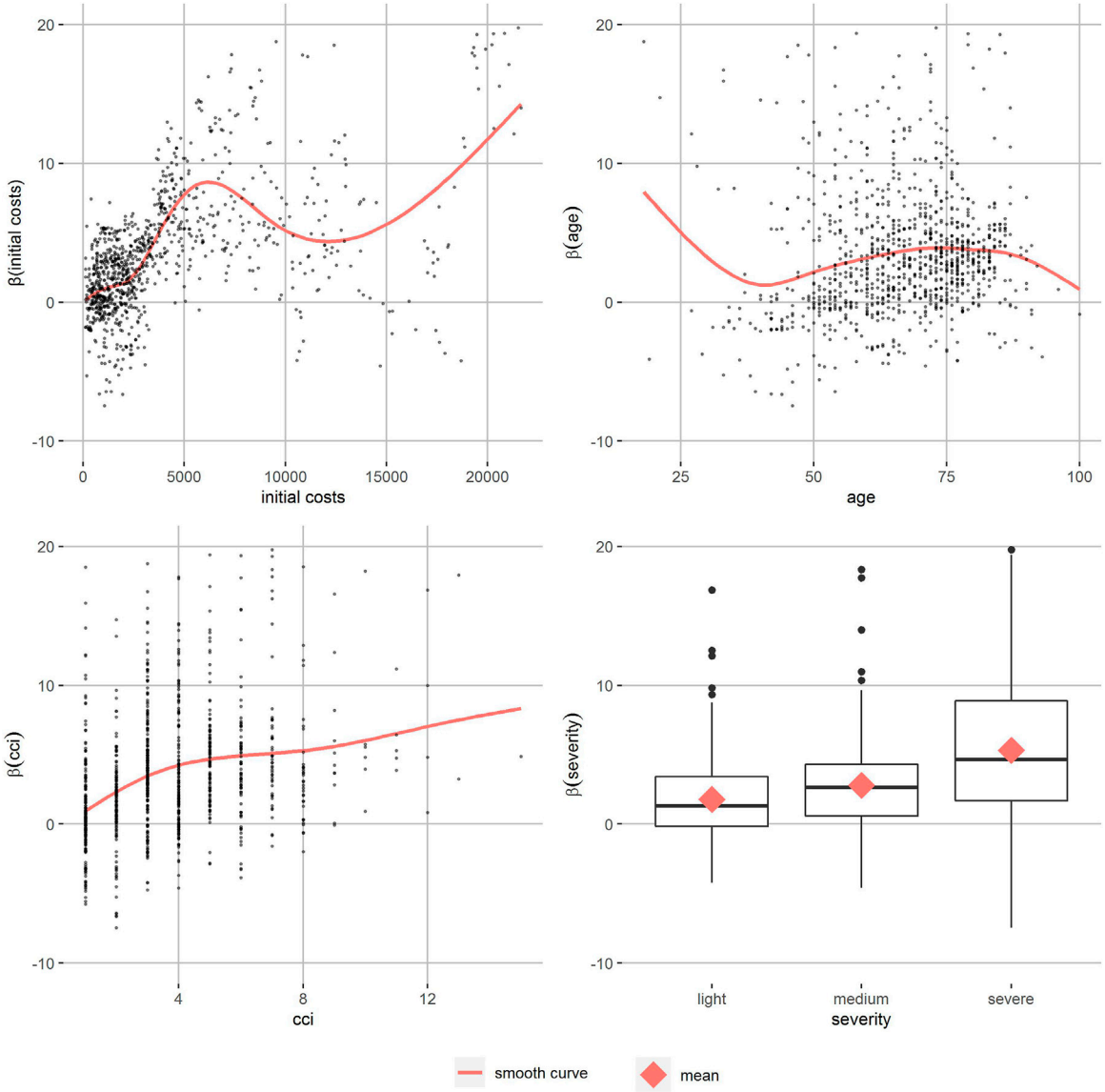

FIGURE 3
Partial dependence plots of T2D patients with high level of similarity.

subgroups with an estimated effect below average in all cohorts. In T2D and hyperlipidemia, there were subgroups with a negative estimated effect of adherence on costs, which consists of around 25% and 40% of our cohort respectively. This was not the case in T1D in which the subgroup with the lowest adherence effect still had a positive association of adherence and costs. With few exceptions, the effect of adherence on costs is lower in younger patients, as well as when initial costs are low and the CCI indicates less comorbidities. Although the cut-points are model-specific, it seems like healthier patients have a lower, and in some cases even negative, effect of adherence on costs.

Going beyond stratified effects towards personalized effects, the model-based random forest also identified patients with an estimated adherence effect below average. Here, in all three cohorts up to around 5%, 20% and 25% of patients could be identified as having a negative estimated effect of adherence on costs. Further investigation of the personalized effects showed a similar pattern as observed in the model-based decision trees. The effects of adherence on costs increase with higher initial costs, more comorbidities and higher age. Again, differences by severity of disease were inconsistent and comparatively low. In addition, it seems like there is no single variable which explains negative individual

differences alone, but it might be a combination of different characteristics—like low initial costs and few comorbidities—that make a negative effect of adherence on costs more likely.

Despite the similarities between the three diagnoses, we also found some differences. In the T1D cohort, no or considerably fewer patients were identified having a negative adherence effect. The reason might be that the overall effect was comparatively high, but also—as smallest cohort—sample size may have restricted detection of differences in the data structure. The cohort of hyperlipidemia patients had less initial costs, lower CCI, and—according to our classification of severity—mainly milder forms of the disease. Here, initial costs do not substantially explain differences of personalized effects in the random forest. Furthermore, the subgroup with the lowest estimated effect consists of medium initial costs.

In the only study with an interaction model, Roebuck et al. (2011) found statistically significant age differences on the effect of adherence in dyslipidemia and diabetes patients with higher cost savings in patients older than 65 and no statistically significant sex differences on the effect in these populations. This is in contrast to our findings where younger patients had costs savings. Hence, the applied methods to stratify and personalize the effect estimates of adherence on costs are only the first step and further studies are necessary to explain the effect of the identified patients' characteristics and differences between diagnoses.

With our calibration-like approach, we were able to assess the quality of the effect estimation by model-based random forests. In such models, the estimated personalized effects depend not only on the structure of the fitted forest, but also on the data used to fit the personalized models. We exchanged this data by using test data to assess the quality of effect estimation. Visual comparison of the effect estimates obtained from training data and test data—conditional on the forest structure and effect estimates of other covariates—show whether the effect estimates are precise. Precision was reduced in the models for T1D patients, where we observed deviations between the two estimated effects. Hence, the results should be interpreted with caution. In the other two cohorts, the personalized effect estimates were more precise. Moreover, the prediction interval of the regression models of the two estimates show the range of the expected personalized effects if fitted on test data with a certainty of 95%. We identified patients with negative estimated effect also when using these certainty-controlled estimated effects.

Of course, there are some limitations to the present study. The training as well as the test data came from the same population and the generalization of the results is limited. An external validation would solve this problem and can make use of the proposed method of calibration. In Germany, health insurance is compulsory and the stationary insurances cover almost 90% of the total population (Statistisches Bundesamt (Destatis) 2020). Therefore, we expect our data to be generalizable for Germany and with some limitations also for other countries. Nevertheless, we would recommend training the models on data as similar as possible to the final target population.

In the model-based random forests, we observed a trade-off between the variance and precision of estimates depending on the defined level of similarity between patients. With decreasing minimal subset size of the trees, in other words increasing level of similarity, the variance of personalized effect estimates increases for training and test data. This results in a larger proportion of negative effect estimates on the one hand. On the other hand, the prediction intervals are wider and thus there is a smaller proportion of certainty-controlled negative effect estimate. Further research on this aspect with the aim to identify an optimal value is necessary.

Other methods to investigate the effect of patients' characteristics on the effect of the main predictor are available. A linear interaction of a continuous covariate and the main predictor gives a robust estimation of the effect in many scenarios, especially when the true underlying effect is linear, and outperforms common approaches like categorization by the median (Haller et al., 2019). An advantage of the applied methods compared to a regression model with interaction, is that they do not only automatically select partitioning variables, but also select their optimal cut-points to define the subgroups (Seibold et al., 2016). In their study, Roebuck et al. (2011) chose a cut-point of 65 for age without a reported justification and it is unclear how a different cut-point would have influenced his results. Especially when visualized graphically, model-based trees are easy to interpret (Zeileis et al., 2008). The structure of the tree and the underlying decision rules are both less complex than higher order interactions of a regression model and more flexible than other available methods (Seibold et al., 2016). An important disadvantage of decision trees is their instability, even when the data only changes slightly (James et al., 2021). However, this is expected to be less of a problem given the large sample size in the present study. In this respect, random forests are more stable compared to a single tree due to the large amount of included trees. But because the effects are calculated from the ensemble of all trees, the model cannot be interpreted directly anymore (Hastie et al., 2009). Instead, partial dependence plots can give insights into some properties of the forest and its effects. In our case, the main advantage of model-based forests is their ability to estimate personalized effects (Seibold et al., 2018).

The identified patients can be assigned to target groups for adherence-promotion interventions with the aim to increase health and decrease associated costs. The proposed method can also be applied to predict other outcomes such as hospitalization risk to maximize positive health effects of an intervention. Originally developed for clinical trails, the

methods can also be applied to directly detect subgroups and personalized effects during an intervention study.

Data availability statement

The data analyzed in this study is subject to the following licenses/restrictions: Requests to access these datasets should be directed to johannes.wendl@mri.tum.de.

Author contributions

All authors contributed to the study conception and design. Material preparation and data collection were performed by JW, AS, and MK. Analysis was performed by JW and AH. The first draft of the manuscript was written by JW and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Conflict of interest

AS, MK, and JH were employed by the Company Vilua Healthcare GmbH which may use the results of the study for commercial purposes.

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.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2022.1001038/full#supplementary-material

References

Charlson, Mary E., Peter, Pompei, Ales, Kathy L., and Ronald MacKenzie, C. (1987). A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. *J. Chronic Dis.* 40 (5), 373–383. doi:10.1016/0021-9681(87)90171-8

Cutler, Rachelle L., Fernandez-Llimos, Fernando, Frommer, Michael, Benrimoj, Charlie, and Garcia-Cardenas, Victoria (2018). Economic impact of medication non-adherence by disease groups: A systematic review. *BMJ Open* 8, e016982. doi:10.1136/bmjopen-2017-016982

Dunbar-Jacob, Jacqueline, and Mortimer-Stephens, M. K. (2001). Treatment adherence in chronic disease. *J. Clin. Epidemiol.* 54, 57–60. doi:10.1016/s0895-4356(01)00457-7

Fuchs, A. (2008). "Target group," in *Encyclopedia of public health*. Editor Wilhelm Kirch (Dordrecht: Springer Netherlands).

Haller, B., Ulm, K., and Alexander, H. (2019). A simulation study comparing different statistical approaches for the identification of predictive biomarkers. *Comput. Math. Methods Med.* 2019, 7037230. doi:10.1155/2019/7037230

Hastie, Trevor, Tibshirani, Robert, and Friedman, Jerome (2009). *The elements of statistical learning: Data mining, inference, and prediction*. 2nd ed. New York, NY: Springer Series in StatisticsSpringer.

Hothorn, Torsten, and Zeileis, Achim (2021). Predictive distribution modeling using transformation forests. *J. Comput. Graph. Statistics* 30 (4), 1181–1196. doi:10.1080/10618600.2021.1872581

Iuga, Aurel O., and McGuire, Maura J. (2014). Adherence and health care costs. *Risk Manag. Healthc. Policy* 7, 35–44. doi:10.2147/RMHP.S19801

James, Gareth, Witten, Daniela, Hastie, Trevor, and Tibshirani, Robert (2021). *An introduction to statistical learning: With applications in R*. 2nd ed. New York NY: Springer Texts in StatisticsSpringer.

Nieuwlaat, Robby, Wilczynski, Nancy, Navarro, Tamara, Hobson, Nicholas, Jeffery, Rebecca, Keepanasseril, Arun, et al. (2014). Interventions for enhancing medication adherence. *Cochrane Database Syst. Rev.* 11, CD000011. doi:10.1002/14651858.CD000011.pub4

Quan, Hude, Li, Bing, Couris, Chantal M., Fushimi, Kiyohide, Graham, Patrick, Hider, P., et al. (2011). Phil hider, jean-marie januel, and vijaya SundararajanUpdating and validating the Charlson comorbidity Index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. *Am. J. Epidemiol.* 173, 676–682. doi:10.1093/aje/kwq433

Quan, Hude, Sundararajan, Vijaya, Halfon, Patricia, Fong, Andrew, Bernard, Burnand, Luthi, Jean-Christophe, et al. (2005). Coding algorithms for defining comorbidities in icd-9-Cm and icd-10 administrative data. *Med. Care* 43 (11), 1130–1139. doi:10.1097/01.mlr.0000182534.19832.83

R Core Team (2019). *R: A language and environment for statistical computing*. Vienna, Austria: R Foundation for Statistical Computing.

Roebuck, M. Christopher, Liberman, Joshua N., Gemmill-Toyama, Marin, and Troyen, A. (2011). Medication adherence leads to lower health care use and costs despite increased drug spending. *Health Aff.* 30 (1), 91–99. doi:10.1377/hlthaff.2009.1087

Roebuck, M. Christopher, Samantha Dougherty, J., Kaestner, Robert, and Laura, M. (2015). Increased use of prescription drugs reduces medical costs in Medicaid populations. *Health Aff.* 34 (9), 1586–1593. doi:10.1377/hlthaff.2015.0335

Seibold, Heidi, Zeileis, Achim, and Hothorn, Torsten (2016). Model-based recursive partitioning for subgroup Analyses. *Int. J. Biostat.* 12 (1), 45–63. doi:10.1515/ijb-2015-0032

Seibold, Heidi, Zeileis, A., and Hothorn, T. (2018). Individual treatment effect prediction for amyotrophic lateral sclerosis patients. *Stat. Methods Med. Res.* 27 (10), 3104–3125. doi:10.1177/0962280217693034

Shrank, William H., Patrick, Amanda R., and Alan Brookhart, M. (2011). Healthy user and related biases in observational studies of preventive interventions: A

primer for physicians. *J. Gen. Intern. Med.* 26 (5), 546–550. doi:10.1007/s11606-010-1609-1

Stasinopoulos, Mikis D., Rigby, Robert A., Heller, Gillian Z., Voudouris, Vlasios, and de Bastiani, Fernanda (2017). *Flexible regression and smoothing: Using gamlss in R*. New York, NY: CRC Press.

Statistisches Bundesamt(Destatis) (2020). *Angaben zur Krankenversicherung 2019 (Ergebnisse des Mikrozensus)*. Fachserie 13 Reihe 1.1. Available at https://www.destatis.de/DE/Themen/Gesellschaft-Umwelt/Gesundheit/Gesundheitszustand-Relevantes-Verhalten/Publikationen/Downloads-Gesundheitszustand/krankenversicherung-mikrozensus-2130110199004.pdf?__blob=publicationFile.

Statistisches Bundesamt(Destatis) (2022). Genesis-online. Available at https://www-genesis.destatis.de/genesis/online?operation=previous&levelindex=3&levelid=1651587189714&levelid=1651587136948&step=2#abreadcrumb.

Stuart, Bruce, Loh, F. Ellen, Roberto, Pamela, and Laura, M. (2014). Incident user cohorts for assessing medication cost-offsets. *Health Serv. Res.* 49 (4), 1364–1386. doi:10.1111/1475-6773.12170

Tueller, Stephen J., Deboeck, Pascal R., and van Dorn, Richard A. (2016). Getting less of what you want: Reductions in statistical power and increased bias when categorizing medication adherence data. *J. Behav. Med.* 39 (6), 969–980. doi:10.1007/s10865-016-9727-9

Vrijens, Bernard, de Geest, Sabina, Hughes, Dyfrig A., Przemyslaw, Kardas, Jenny, Demonceau, Todd, Ruppar, et al. (2012). A new taxonomy for describing and defining adherence to medications. *Br. J. Clin. Pharmacol.* 73 (5), 691–705. doi:10.1111/j.1365-2125.2012.04167.x

Weisberg, Herbert I. (2015). What next for randomised clinical trials? *Significance* 12 (1), 22–27. doi:10.1111/j.1740-9713.2015.00798.x

WHO Collaborating Centre for Drug Statistics Methodology (2021). *ATC classification Index with ddds, 2022.*

Zeileis, Achim, Hothorn, Torsten, and Kurt, Hornik (2008). Model-based recursive partitioning. *J. Comput. Graph. Statistics* 17 (2), 492–514. doi:10.1198/106186008X319331

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Patterns of statin adherence in primary cardiovascular disease prevention during the pandemic

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Background: Study of medication adherence patterns can help identify patients who would benefit from effective interventions to improve adherence.

Objectives: To identify and compare groups of statin users based on their adherence patterns before and during the COVID-19 pandemic, to characterize the profile of users in each group, and to analyze predictors of distinct adherence patterns.

Methods: Participants of the CARhES (CArdiovascular Risk factors for HEalth Services research) cohort, comprising individuals aged >16 years, residing in Aragón (Spain), with hypertension, diabetes mellitus and/or dyslipidemia, took part in this observational longitudinal study. Individuals who began statin therapy during January–June 2019 were selected and followed up until June 2021. Those with a cardiovascular event before or during follow-up were excluded. Data were obtained from healthcare system data sources. Statin treatment adherence during the implementation phase was estimated bimonthly using the Continuous Medication Availability (CMA9) function in the AdhereR package. Group-based trajectory models were developed to group statin users according to their adherence pattern during July 2019–June 2021. Group characteristics were compared and predictors of each adherence pattern were analyzed using multinomial logistic regression.

Results: Of 15,332 new statin users, 30.8% had a mean CMA9 ≥80% for the entire study period. Four distinct adherence patterns were identified: high adherence (37.2% of the study population); poor adherence (35.6%); occasional use (14.9%); and gradual decline (12.3%). The latter two groups included users who showed a change in adherence (increase or decrease) during the pandemic emergence. Users with suboptimal adherence were likely to be younger, not pensioners, not institutionalized, with low morbidity burden and a low number of comorbidities. Female sex and switching between statins of different intensity increased the likelihood of belonging to the occasional use group, in which improved adherence coincided with the pandemic.

Conclusion: We identified four distinct adherence patterns in a population of new statin users; two of them modified their adherence during the pandemic. Characterization of these groups could enable more effective distribution of resources in future similar crisis and the routine implementation of patient-centered interventions to improve medication adherence.

KEYWORDS

medication adherence, statin, chronic disease, healthcare system, disease management, computer modeling, cluster analysis, COVID-19

1 Introduction

In line with current recommendations (Visseren et al., 2021) statins are widely prescribed for prevention of cardiovascular disease (CVD). However, while statin efficacy in primary prevention of CVD has been well demonstrated in clinical trials, their effectiveness in clinical practice is less clear. This is in part because the desired clinical effects are only achievable if the patient adheres to the treatment plan (Chaure-Pardos et al., 2022). Adherence to long-term therapies for chronic illnesses has been described as suboptimal (Menditto et al., 2018), particularly in the case of statins for primary CVD prevention (Ofori-Asenso et al., 2018).

In addition to poor health outcomes, nonadherence is associated with increased healthcare costs and reduced patient quality of life (Hassan et al., 2021). A recent study of a cohort of statin users showed that, after adjusting for patient characteristics, poor adherence increased the probability of preventable healthcare utilization and spending, especially among minorities and groups with low socioeconomic status (Zhang et al., 2022). Conversely, noncontinuous access to both healthcare services and medications may jeopardize adherence and self-care behavior and, consequently, effective management of chronic conditions (Ágh et al., 2021).

The last 2 decades have seen a growing emphasis placed on the lack of transparency in the operationalization of medication adherence measures, and on the overabundance of terms used to describe medication use (Arnet et al., 2016). This complicates comparison of adherence findings across studies and their translation to real-world clinical practice. In 2012, to overcome potential confusion and misunderstanding, the European-funded Ascertaining Barriers to Compliance (ABC) project proposed a new medication adherence taxonomy (Vrijens et al., 2012). The ABC taxonomy, which has been widely adopted internationally, subdivides adherence into three essential elements: initiation, implementation, and discontinuation. Thus, poor medication adherence can occur in the following situations or combinations thereof: non-initiation of the prescribed treatment after its prescription; suboptimal implementation of the dosing regimen; and discontinuation of treatment (nonpersistence). In the study of implementation (i.e., the degree to which the patient's dose corresponds to the prescribed dose regimen), application of group-based trajectory modeling (GBTM) is increasingly used, as it constitutes a powerful tool with which to represent adherence behaviors using longitudinal data (Librero et al., 2016; Walsh et al., 2021). Given the dynamic nature of adherence patterns, which can vary over time, the superiority of this approach over classical adherence point estimators, expressed as mean values, is evident. Indeed, certain circumstances can induce changes in the adherence patterns of patients with relatively constant behaviors.

The COVID-19 pandemic has impacted the management and behavior of chronic patients due to changes in lifestyle (diet, physical activity, alcohol and tobacco consumption) and social situation (stress, anxiety, social isolation). Similarly, changes in the organization and provision of healthcare resources have likely influenced the continuity of care received by these patients (Palmer et al., 2020; Lau and McAlister, 2021). Given that the aforementioned parameters are all considered determinants of medication adherence (Kardas et al., 2013), analysis at a population level of the implementation adherence during the different stages of the pandemic could help identify the most affected groups of patients. This information in turn could be used to facilitate better distribution of resources in the context of future crises, helping avoid such negative impacts on patient medication adherence.

The objectives of this study were 1) to compare adherence patterns before and during the COVID-19 pandemic among adults in Aragón, Spain, taking statins for primary CVD prevention, 2) to describe the individual, clinical, and therapeutic characteristics of users in each group and 3) to analyze predictors of distinct adherence patterns.

2 Materials and methods

2.1 Study design and setting

This observational longitudinal study was conducted among participants of the CARhES (CArdiovascular Risk factors for HEalth Services research) cohort. This is a population-based dynamic cohort of individuals aged >16 years, registered as users of the Aragón Health System, with hypertension, diabetes mellitus and/or dyslipidemia. Information collected from this

cohort includes quantitative real-world data extracted from administrative databases from the healthcare system.

Aragón is an Autonomous Community located in the northeast of Spain with a population of 1.3 million inhabitants. It has a high level of aging, with more than 20% of the population aged >64 years (Instituto Aragonés de Estadística. Gobierno de Aragón, 2022). In Spain, the health system is based in the principles of universal, equitable, free access and fairness of financing, and is predominantly funded by taxes (Bernal-Delgado et al., 2018). The 17 Spanish Autonomous Communities, to which healthcare competences have been devolved, manage most of the public health resources. Primary care constitutes the core element of the health system, and encompasses the majority of health care, health maintenance, health recovery, rehabilitation, and social work activities. Pharmaceutical care, one of the services provided by the National Health Service, covers all medicines and health products that are approved, registered, and eligible for reimbursement, and ensures that patients receive the correct formulation and dose of their medication at the lowest possible cost (Bernal-Delgado et al., 2018). Management of medication adherence is overseen by doctors (prescribers); primary care nurses (who supervise adherence and side-effects); pharmacists (who dispense medications and supervise treatment adherence and early detection of side-effects). However, routine assessment of adherence is not mandatory in the management of chronic patients, nor are specific adherence support programs widely offered on a routine basis.

2.2 Study population and data sources

In the present study, participants in the CARhES cohort identified as new statin users during the period January–June 2019 were followed-up until June 2021. New statin users were defined as those who had not received any statin prescription during the 6-month period preceding the date of treatment initiation. Analyses were restricted to participants treated exclusively with statins (Anatomical Therapeutic Chemical [ATC] codes C10AA [plain statins], C10BA [statins in combination] and C10BX [statins in combination with other drugs]), and not with other lipid-lowering agents in monotherapy, during the period January 2019 to June 2021. From those selected, we excluded individuals with a diagnosis of a major adverse cardiovascular event before or during the study period, as defined by a diagnosis of acute myocardial infarction, nontraumatic intracranial hemorrhage, or cerebral infarction (codes I21, I22 and I60–I63; International Classification of Diseases, 10th Revision) during hospitalization. Individuals who died during follow-up were also excluded.

Data were obtained from BIGAN, a platform for the secondary use of health data from the Aragón Health System. BIGAN provides pseudonymized individual level patient's data from the following information systems: Users Database, which records sociodemographic information including age, sex, pharmacy copayment level, type of pharmaceutical provision, type of economic activity, and institutionalization status; Pharmaceutical Dispensation Database, which records the dispensing date, ATC code, number of pills per package and the number of packages dispensed by pharmacies and covered by the Aragón Health System; Minimum Basic Data Set database, which records diagnoses and dates of hospitalizations; Emergency Database, which gathers diagnoses and dates of visits to emergency services; Primary Care Database, which records information on visits to primary care and corresponding medical diagnoses; Adjusted Morbidity Groups, which records diagnostic data collected from the Minimum Basic Data Set and the Primary and Emergency Care Databases, including the total number of chronic diseases and affected systems, the morbidity burden (obtained through aggregation of all the patient's diagnoses), and the presence of specific chronic morbidities such as hypertension, diabetes, and depression. This information is later reviewed, cleansed and integrated to feed the CARhES cohort.

Socioeconomic level was determined based on pharmacy copayment level and type of economic activity. Based on the combination of these two variables, seven mutually exclusive categories were created: employed individuals earning <€18,000 per annum (p.a.); employed individuals earning ≥€18,000 p.a.; individuals receiving unemployment allowance; individuals with a contributory pension <€18,000 p.a.; individuals with a contributory pension ≥€18,000 p.a.; individuals receiving free medicines (those with minimum integration income or who no longer receive unemployment allowance); and other situations not included in the aforementioned categories.

Based on the first statin prescribed during the follow-up period, individuals were classified as "high-intensity statin users" (i.e., those receiving atorvastatin or rosuvastatin and combinations thereof) or "low–moderate intensity statin users" (i.e., those receiving simvastatin, lovastatin, pravastatin, fluvastatin or pitavastatin and combinations thereof). Based on this, we created a new variable which identified users who switched from low–moderate to high intensity statin use and *vice versa*. In cases in which more than one switch occurred during the study period, only the first was considered.

2.3 Estimation of adherence

Statin implementation adherence was assessed in the study population from July 2019 to June 2021 using two different approaches: first, as a summary estimation of adherence, calculated using AdhereR, a package in the R-free software environment developed for transparent and reproducible analysis of electronic healthcare data (Dima and Dediu, 2017);

and second, as a dynamic longitudinal measure that allows grouping of statin users based on their adherence pattern or trajectory.

The conceptualization of adherence was performed according to the consensus-based Medication Adherence Reporting Guideline (EMERGE) (de Geest et al., 2018) and the TEOS framework (Dima et al., 2021). The latter was developed as a guide to the conceptual analysis of adherence Timelines and key Events in relation to research Objectives and data Sources in order to improve the transparency and reproducibility of adherence studies.

2.3.1 Measurement of summary adherence

Adherence was estimated bimonthly in statin users. AdhereR implements a set of functions that are consistent with current adherence guidelines, definitions, and operationalizations. It allows the computation of nine different versions of the Continuous measure of Medication Availability (CMA), a summary adherence estimate which can be mapped onto Medication Possession Ratio (MPR) and Proportion of Days Covered (PDC), with the advantage of allowing the selection of different analysis options according to health conditions and types of medication.

In this study, the CMA9 function was computed as the number of days of theoretical medication use divided by the duration of the adherence assessment period, allowing for carryover of supply from before and during this period and excluding the supply left at the end. CMA9 differs from other CMA indicators in that it assumes persistence, based on which it adjusts implementation. CMA9 computes a ratio of days' supply for each individual in the study period, and then weighs all days by their corresponding ratio to generate a mean adherence value that remains constant from one supply until the next or until the end of the assessment period (Dima and Dediu, 2017; Allemann et al., 2019). CMA9 was computed for repeated sliding windows within the adherence assessment period. These sliding windows had a duration of 2 months (the usual period between dispensations in the study region), without overlaps.

Given that the usual prescribed statin dose is one pill per day, the number of days of medication supplied was estimated based on the number of pills contained in the package(s) dispensed (i.e., 28 or 30, depending on the statin). During a hospitalization period, it was assumed that treatment was supplied by the hospital, and therefore the remaining supplies were extended accordingly.

The mean adherence (CMA9 value) was calculated in the study population. Also, the mean CMA9 indicator obtained for each statin user was dichotomized using an arbitrary cut-off of 0.8 (i.e., 80%).

2.3.2 Adherence trajectory groups

The bimonthly CMA9 estimates were incorporated into GBTM, which grouped patients based on their adherence patterns. For this purpose, longitudinal data were clustered by performing K-means analysis (Allemann et al., 2019). The optimal number of groupings was selected based on the Calinski & Harabasz criterion, considering the Genolini variant (Genolini et al., 2015). This is a non-parametric criterion that can be calculated without any previous hypothesis on data.

TABLE 1 Characteristics of the study population.

Characteristics	N = 15,332
Sex, n (%)	
Women	7,903 (51.5%)
Age, n (%)	
16–44 years	1,670 (10.9%)
45 to 64 years	7,901 (51.5%)
65 to 79 years	4,369 (28.5%)
≥80 years	1,392 (9.1%)
Socioeconomic level, n (%)	
Employed, < €18,000 p.a	2,457 (16.0%)
Employed ≥ €18,000 p.a	3,172 (20.7%)
Pensioner < €18,000 p.a	2,567 (16.7%)
Pensioner ≥ €18,000 p.a	2,894 (18.9%)
Unemployed	695 (4.5%)
Free medicines	2,736 (17.8%)
Other	811 (5.3%)
Institutionalized, n (%)	243 (1.6%)
Number of chronic diseases, mean (SD)	4.1 (2.3)
Number of affected systems, mean (SD)	3.1 (1.5)
Morbidity burden, mean (SD)	6.8 (4.2)
Comorbidities, n (%)	
Hypertension	6,443 (42.7%)
Diabetes	2,932 (19.4%)
Depression	2,401 (15.9%)
Statin switching during the study period, n (%)	
High to low–moderate intensity statins	245 (1.6%)
Low–moderate to high intensity statins	728 (4.7%)
No switching	14,359 (93.7%)
Adherence (CMA9), mean (SD)	0.5 (0.4)
Mean adherence (CMA9) ≥ 0.8, n (%)	4,724 (30.8%)

Abbreviations: N, number; p.a., per annum; SD, standard deviation.
The mean morbidity burden was estimated in individuals for whom information was available (total, 15,088).

2.4 Statistical analysis

Sociodemographic, clinical, and treatment characteristics of the study population were described using the mean and standard deviation (SD) or median and interquartile range (IQR) for continuous variables, and frequency and percentage for categorical variables. The frequency and percentage of users with a mean composite CMA9 ≥80% was estimated.

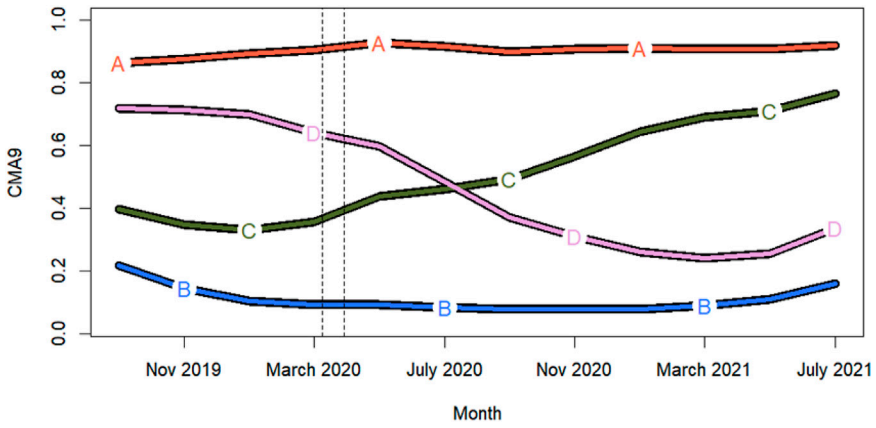

FIGURE 1
Patient groups according to adherence trajectory: A (37.2% of study population); B (35.6%); C (14.9%); and D (12.3%). Dashed lines indicate the strict COVID-19 lockdown implemented in Spain from March 15 to April 26 2020.

To achieve the first objective of grouping statin users according to their adherence pattern from July 2019 to June 2021, GBTM was conducted. Next, key pandemic dates were identified and linked with the evolution of adherence patterns.

In order to achieve the second objective, the same individual, clinical, and treatment characteristics described above were compared between statin users within each trajectory group. Continuous covariates, depending on their parametric distribution, were compared using either a Student's *t*-test or analysis of variance (ANOVA), and categorical variables using the Chi-squared or Fisher's exact test.

Finally, multinomial logistic regression was performed to identify the sociodemographic, clinical, and treatment factors associated with belonging to each group, answering the third objective.

3 Results

The characteristics of the study population are described in the 3.1 subsection. The following subsections (3.2, 3.3 and 3.4) respond, respectively, to the three main study objectives.

3.1 Patient characteristics

Data from 15,332 individuals were analyzed. All were new statin users with neither prior cardiovascular events nor cardiovascular events or death during the follow-up period. Mean age was of 60.6 (SD, 13.2) years. Table 1 presents additional sociodemographic and clinical data.

A total of 4,724 (30.8%) new statin users showed a mean adherence (CMA9) of at least 0.8 (80%). Of the total study population, 6.3% switched from low–moderate to high intensity statins or *vice versa* during the study period (Table 1).

3.2 Adherence trajectories

The method used estimated the optimal number of clusters as 4. Thus, the following adherence trajectories were identified within the study population (Figure 1):

Group A: High and constant adherence.

Group B:Poor adherence, without significant variations.

Group C: Occasional use, with a trend towards improved adherence from March 2020.

Group D: Gradual decline, with a sharp decrease between March 2020 and March 2021.

In two groups of statin users (C and D) a change in the adherence pattern coincided with the onset of the COVID-19 pandemic (specifically, the strict lockdown implemented in Spain).

3.3 Characterization of the identified groups

Table 2 presents the sociodemographic, clinical and treatment characteristics, including adherence, of the four groups of statin users. Comparison of most of the characteristics across user groups revealed statistically significant differences. In general, statin users in the high adherence group (group A) were older, with a higher proportion of pensioners and institutionalized individuals, a higher mean number of chronic pathologies and affected systems, and a higher morbidity burden. Hypertension and diabetes were also more frequent in this group. Conversely, statin users in the poor adherence group (group B) were more likely to be aged 16–44 years, employed receiving <€18,000 p.a., with fewer comorbidities and a lower morbidity burden. Individuals in the occasional users and the gradual decline

TABLE 2 Comparison of characteristics of statin users in each group.

Characteristics	Group A (n = 5,702)	Group B (n = 5,460)	Group C (n = 2,284)	Group D (n = 1,886)	*p*-value
Sex, n (%)					
Women	2,931 (51.4%)	2,713 (49.7%)	1,271 (55.6%)	988 (52.4%)	<0.001
Age, n (%)					
16–44 years	337 (5.9%)	872 (16.0%)	226 (9.9%)	235 (12.5%)	<0.001
45–64 years	2,897 (50.8%)	2,805 (51.4%)	1,214 (53.2%)	985 (52.2%)	
65–79 years	1941 (34.0%)	1,290 (23.6%)	633 (27.7%)	505 (26.8%)	
≥80 years	527 (9.2%)	493 (9.0%)	211 (9.2%)	161 (8.5%)	
Socioeconomic level, n (%)					<0.001
Employed < €18,000 p.a	920 (16.1%)	1,358 (24.9%)	464 (20.3%)	430 (22.8%)	
Employed ≥ €18,000 p.a	809 (14.2%)	944 (17.3%)	386 (16.9%)	318 (16.9%)	
Pensioner < €18,000 p.a	1,104 (19.4%)	805 (14.7%)	375 (16.4%)	283 (15.0%)	
Pensioner ≥ €18,000 p.a	1,305 (22.9%)	826 (15.1%)	419 (18.3%)	344 (18.2%)	
Unemployed	216 (3.8%)	292 (5.4%)	95 (4.2%)	92 (4.9%)	
Free medicines	1,116 (19.6%)	869 (15.9%)	422 (18.5%)	329 (17.4%)	
Other	232 (4.1%)	366 (6.7%)	123 (5.4%)	90 (4.8%)	
Institutionalized, n (%)	121 (2.1%)	61 (1.1%)	29 (1.3%)	32 (1.7%)	<0.001
Number of chronic pathologies, mean (SD)	4.3 (2.3)	3.9 (2.2)	4.1 (2.2)	4.0 (2.3)	<0.001
Number of affected systems, mean (SD)	3.3 (1.5)	3.0 (1.5)	3.1 (1.5)	3.1 (1.5)	<0.001
Morbidity burden, mean (SD)	7.3 (4.4)	6.4 (4.0)	6.8 (4.0)	6.7 (4.4)	<0.001
Comorbidities, n (%)					
Hypertension	2,749 (48.4%)	1986 (37.4%)	955 (42.7%)	753 (40.4%)	<0.001
Diabetes	1,305 (23.0%)	848 (16.0%)	429 (19.2%)	350 (18.8%)	<0.001
Depression	897 (15.8%)	802 (15.1%)	387 (17.3%)	315 (16.9%)	0.063
Switching during study period, n (%)					<0.001
High to low–moderate intensity statins	83 (1.5%)	47 (0.9%)	76 (3.3%)	39 (2.1%)	
Low–moderate to high intensity statins	238 (4.2%)	154 (2.8%)	231 (10.1%)	105 (5.6%)	
No switching	5,381 (94.4%)	5,259 (96.3%)	1977 (86.6%)	1742 (92.4%)	
Mean adherence (CMA9) ≥0.8, n (%)	4,724 (82.8%)	0 (0%)	0 (0%)	0 (0%)	0.000

SD, standard deviation; CMA, continuous medication availability; p.a., per annum.
The mean morbidity burden was estimated in individuals for which information was available (total, 15,088).

trajectories (groups C and D, respectively) presented intermediate characteristics in terms of age, socioeconomic level, and comorbidity profile. One remarkable finding was the higher proportions of women and of users who switched statin treatment (especially those who switched from a low–moderate to a high intensity statin [10.1%]) in group C.

Figure 2 presents the mean adherence for each group of statin users. Mean adherence differed between groups A (0.9) and B (0.1), but not between groups C and D (both with 0.5).

3.4 Predictors of the different adherence patterns

Potential predictors of inclusion in a given adherence trajectory are shown in Figure 3.

Compared with statin users in the high adherence group (group A), those in the poor adherence (group B), occasional users (group C), and gradual decline (group D) groups were, in general, more likely to be young (16–44 years), neither pensioners nor free medicine recipients, not institutionalized, with a low morbidity burden and no comorbidities such as diabetes or hypertension. These associations were statistically significant in most cases (Figure 3). A significant association with sex was observed only for the occasional use group (group C), members of which were more likely to be women (OR 1.22, 95% CI 1.10–1.35) compared with the high adherence group (group A). Inclusion in the occasional use or gradual decline groups (C and D) was positively associated with switching from a low–moderate to a high intensity statin (OR 2.60, 95%CI 2.15–3.15 and OR 1.36, 95%CI 1.07–1.72, respectively). Inclusion in group C was also associated with switching from

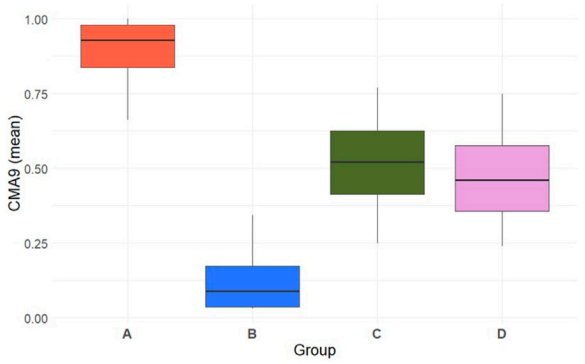

FIGURE 2
Boxplot depicting mean adherence (CMA9) for each statin user group.

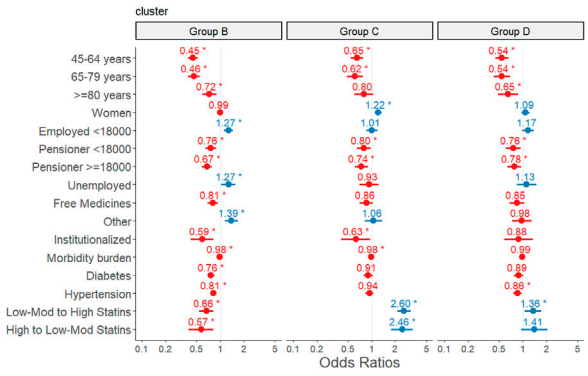

FIGURE 3
Predictors of inclusion in the poor adherence (group B), occasional use (group C) and gradual decline (group D) groups in relation to the high adherence group (group A). Multinomial logistic regression analysis. The final adjusted model included 15,088 individuals, for whom information on all the variables studied was available. The reference category in the dependent variable was the high adherence group (group A). For predictors, the reference categories were: 16–44 years (age), men (sex), employed earning ≥€18,000 per annum (socioeconomic level), not institutionalized, no diabetes, no hypertension, no switching from low–moderate to high intensity statins or *vice versa*.

a high to a low–moderate intensity statin (OR 2.46, 95%CI 1.79–3.38). Conversely, patients in the poor adherence group (group B) were less likely to switch statin treatment than those in the high adherence group (group A).

4 Discussion

In this real-world data study, we assessed implementation of treatment in new statin users during the period 2019–2021 using software specially developed for reproducible analysis of electronic healthcare data. GBTM identified four distinct adherence trajectories in the study population before and during the COVID era. We analysed the characteristics most associated with nonadherent patterns as well as changes in adherence that occurred during critical phases of the pandemic. These findings can help further our knowledge of the effect of the pandemic on adherence to preventive treatment, which is one of the most important pillars in the management of CVD risk factors.

Our study population was made up of individuals with no previous cardiovascular events who started statin treatment during the first 6 months of 2019 in the Spanish region of Aragón. Participants were predominantly mostly middle-aged and older, with a moderate morbidity burden and a high rate of other CVD risk factors. Mean adherence was 50%, and 30.8% of participants had a mean adherence ≥80%. Previous studies have reported poor statin adherence (Yeaw et al., 2009; Menditto et al., 2018), as well as a high degree of variability in adherence rates among populations. Although 80% is the most common cut-off point for dichotomizing adherence, this is an arbitrary value that should be adapted to each disease and treatment. In any case, its application can be useful to estimate the proportion of new statin users with suboptimal adherence.

We identified four distinct statin adherence trajectories during the follow-up period from July 2019 to June 2021. To date, few studies have applied GBTM to classify users of a particular drug into different groups according to their adherence utilization pattern. Among the few studies that have used this approach, the number of distinct trajectories identified ranges from 3 to 4 (Librero et al., 2016; Hickson et al., 2020; Majd et al., 2021). These numbers depend on the sample size, the type of medication, and the characteristics of the study population. In a population-based cohort of patients discharged after hospitalization for coronary heart disease, Librero et al. applied GBTM to groups of users of statins, among other medications, based on their adherence trajectories over time. They identified three different adherence patterns for statins: adherent (74.9% of patients); occasional users (17.5%); and fast decline (7.6%). Compared with the present findings, the authors grouped a much higher proportion of statin users into the highly adherent trajectory (74.9% vs. 37.2%). However, our study population differed to that of Librero et al. in that our patients had not experienced a previous cardiovascular event. And taking statins for primary CVD prevention has been associated with increased nonadherence (Ofori-Asenso et al., 2018). In a population of new statin users already treated with antihypertensive drugs, Majd et al., 2021 analyzed the possible association between past medication-taking behavior and current statin adherence pattern. They found that previous trajectories of adherence to antihypertensive drugs predicted future statin adherence patterns, suggesting that the routine study of adherence during the first year of treatment initiation could provide

valuable information to stakeholders to develop tailored interventions to improve adherence. In our particular case, statin users in groups B and D may benefit most from improvement strategies. Numerous interventions to improve adherence during the implementation phase have been carried out in different contexts, but suffer from methodological limitations in terms of design and have reported only modest effects on medication adherence (Cross et al., 2020; Yang et al., 2022). In Spain, such interventions are not routinely implemented in general practice.

Our multinomial regression analyses showed that being older, a pensioner, and having a higher morbidity burden were associated with high and constant adherence over time. Conversely, young users, employed earning <€18,000 p.a. or unemployed, with no comorbidities, were more likely to be included in the poor adherence trajectory. Factors related to mild symptoms have previously been associated with a poorer adherence profile (Kardas et al., 2013). Furthermore, those in the high adherence group more frequently had access to free medicines than those in the other groups. Requiring copayment has already been described as a predictor of nonadherence in other studies (Librero et al., 2016; Ofori-Asenso et al., 2018), as it represents a barrier to access to chronic treatments, especially in patients with a low socioeconomic status.

Comparison of the poor adherence (group B) with the high adherence (group A) trajectories showed that, in statin users with a constant non-adherent pattern, a switching in statin treatment did not lead to an increase in the adherence levels. One feasible explanation for this observation is a lack of concern among statin users in group B about their high cholesterol levels, given their asymptomatic condition. These users may also attempt to control their disease by means of other behaviors such as diet modification and physical activity. Finally, it is also possible that a lack of in-person consultations at the beginning of the COVID-19 pandemic may have caused patients to neglect their condition, with consequent negative health outcomes. In any case, further studies will be necessary to identify the underlying reasons, and to assess the validity of prescribing statins to low-risk patients who continuously show poor adherence, resulting in poor statin effectiveness (Chaure-Pardos et al., 2022). For them, alternative non-pharmacological measures might be a more appropriate choice.

Being a woman increased the likelihood of inclusion in the occasional users trajectory (group C) and, therefore, of improving statin adherence during the study period. Although our finding cannot be easily compared with previous studies, given repeated inconsistency in the association between sex and adherence pattern (Kardas et al., 2013), this association is nonetheless interesting. Group C consisted mainly of statin users with poor adherence in the months preceding the pandemic who subsequently improved their medication-taking behavior, almost reaching adherence values of 80% by the end of the follow-up period. Differently from the observed in statin users in group B, with permanent poor adherence, the higher frequency of switching between statins within users in group C could indicate an active patient–health professional relationship and also explain the positive effect on adherence. A more in-depth study of the characteristics and circumstances of these patients could help unravel the uneven impact of COVID-related changes on adherence patterns in different population groups.

The COVID-19 pandemic completely disrupted the healthcare of patients with chronic diseases, postponing face-to-face appointments or replacing them with telemedicine services. Ágh et al. (2021) found that in-person consultations were limited during the pandemic in 90% of 38 European countries studied. This limitation, together with social distancing restrictions imposed in Spain, may have negatively influenced continuous access to medication, which is a prerequisite for appropriate adherence. In Spain, electronic prescribing is widely available, and the prescribing of chronic therapies was automatically renewed even during the worst phases of the pandemic. However, even though face-to-face consultations were not essential for medication prescribing and supply, virtual or telephonic care suffer from several disadvantages compared with in-person consultation (e.g., they do not allow optimal involvement of the patient in shared decision-making, education, and self-management) (Lewis et al., 2016). In order to maintain treatment adherence during pandemic lockdown, some authors proposed measures such as home delivery of prescription medications for older, frail patients with a high-risk mental state, for whom leaving the house was particularly challenging. Longer-duration prescriptions that facilitate medication access, especially for patients living in remote areas, could also be prioritized (Ágh et al., 2021). Although these changes may be required in exceptional situations, such as the COVID-19 pandemic, they should always be balanced against the risk of not providing high-quality care. The creation of e-health systems to support patients in long-term treatment and the development and implementation of a patient-centered care model are possible solutions to avoid deterioration of self-care and medication adherence in similar situations in the future (Palmer et al., 2020). Indeed, with a view to improving the care of patients receiving chronic treatments, Spanish primary care professionals have routine access to information on patient prescription and dispensation records. This allows the healthcare professional to check the end date of the last prescription refill, which serves as a proxy of patient adherence, and to intervene if necessary. Coordination between health and social services has been acknowledged as one of the cornerstones of the management of chronic patients in risky situations, underscoring the importance of providing integrated patient-centered care (Rodriguez-Blazquez et al., 2020).

4.1 Strengths and limitations

The main strength of this study is its population-based nature. The analysis of real-world data from all new statin users in a population of this size lends the findings a high

degree of validity. Another strength is the use of AdhereR, which has been developed to aid the computation of electronic healthcare data-based adherence estimates within the widely used open-source environment R, and to promote transparency and comparability of research findings. Moreover, this approach allows the application of the sliding window function to the CMA9 indicator to describe the use of medication during the implementation adherence phase. The consensus-based TEOS framework (Dima et al., 2021) suggests the estimation of individual-level patterns during this phase in a short-to-medium time frame if temporal within-patient variations affecting medication adherence are to be captured, as in the present study. GBTM offers certain advantages over traditional methods of adherence assessment, in which medication adherence is considered a static, rather than dynamic and longitudinal, process. GBTM also offers greater accuracy and validity in the design of adherence interventions, given that conventional methods provide irregular or variable patterns (e.g., those obtained in groups C and D) that would return a similar mean adherence measure for the entire study period if temporal adherence dynamics were not considered. Paradoxically, these groups with a more irregular pattern of use would likely benefit most from an improvement intervention. Furthermore, the identification of characteristics associated with poor or intermediate statin adherence patterns could facilitate strategies that are more focused on the necessary actions. For instance, patients with poor adherence from the beginning could benefit from negotiation with the prescriber when deciding upon treatment and dose, or from an explanation about the advantages and possible adverse effects associated with their medication. Conversely, in patients who start treatment with acceptable adherence that subsequently diminishes (the gradual decline group), further exploration of the underlying factors is required. The onset of the pandemic led to many changes at the levels of the individual, society at large, and healthcare systems, all of which may have contributed to decreased adherence. To investigate these contributions further, and thereby address the situation, it would be desirable to have additional information beyond the variables analyzed in the present study.

This study has several limitations. First, the use of electronic health databases is limited by the quality of the data recorded. However, the health data platform used in the present study has already been used in multiple studies conducted by different research groups. Our data source did not include certain variables that could have been of interest as potential predictors of nonadherence. Nonetheless, the available information allowed us to identify several important factors related to statin adherence and to broaden our knowledge of the issue. The assessment of statin adherence was performed based on data derived from pharmacy claims. Given that patients do not necessarily consume all the drugs purchased from the pharmacy, our approach may have overestimated the true consumption of statins. However, this limitation is common to all studies using these types of data sources. The use of the AdhereR package also presents some minor limitations: its creators have acknowledged certain aspects of the program that can be improved, and will likely be addressed in future versions (Dima and Dediu, 2017). The modeling process used in the present study involves several choices that may have influenced the final results (e.g., the option to carry-over into the observation window and the selection of sliding windows of 2 months in the GTBM). Finally, when interpreting findings, it should be noted that a reduction in adherence does not always imply inappropriate patient behavior, and may reflect a medical indication to stop treatment or even switch to another low-lipid lowering drug.

4.2 Future implications

Both the existing literature and the present findings indicate frequently poor adherence among patients treated with statins for CVD primary prevention. Furthermore, even statin users with an optimal adherence pattern can be affected by exceptional situations such as that resulting from the recent COVID-19 pandemic. Poor statin adherence could be explained by the fact that hyperlipidemia is a non-symptomatic process, for which patients do not have the urgent need for treatment, and by the frequent adverse effects of statins. This casts doubt on the appropriateness of prescribing statins as first-line treatment in certain circumstances or to patients with individual or clinical characteristics associated with a higher risk of nonadherence. For this reason, it is extremely important to continue furthering our knowledge of factors that may facilitate adherence, in particular during implementation of the prescribed regimen, given the suboptimal results of numerous interventions to improve adherence conducted in different contexts. Knowledge resulting from collaborative research initiatives focused on the topic, such as the European Network to Advance Best practices and technoLogy on medication adherencE (ENABLE), is particularly valuable for the application of practices related to medication adherence. Supporting funding of collaborative cross-country projects is therefore an important course of action.

The development, improvement and promotion of free tools such as AdhereR in adherence studies as well as the routine application of consensus-based scales, taxonomies, and guidelines to medication adherence studies will also ensure progress in standardizing adherence estimators and approaches and greater comparability of results obtained in different populations. This is one of the keys to improving the utilization of chronic therapies, using as a reference those healthcare system interventions that produce the best adherence-related outcomes.

During the decade preceding the pandemic, public health efforts focused on improving healthcare system coordination and providing guidance on the management of chronic conditions and lifestyle factors. The resilience of the healthcare system was one of its most acknowledged characteristics. However, after the unprecedent situation caused by the COVID-19 pandemic, structural reforms in the healthcare systems, including the Spanish system, may be required to prioritize actions to improve chronic care management, address the basic needs of patients with chronic diseases, and minimize the potentially devastating impact of the COVID-19 outbreak on especially vulnerable individuals. Proposed actions include: ensuring the continuity of healthcare services; increasing equitable access to educational materials (e.g., ehealth) that promote awareness and to local and social support activities; and facilitating monitoring by healthcare professionals (including telemedicine). Medication nonadherence is a multifactorial process, and therefore should be supervised and influenced by a range of healthcare professionals. Defining the roles and functions of each professional, as well as increasing public funding, are essential in order to carry out successful interventions to improve medication-taking behavior. In the particular case of statins, indication should always be dependent on the patient's clinical situation. However, the risk of nonadherence, based on the patient's characteristics, could be assessed to guide prescribing decision-making, and exhaustive adherence monitoring implemented, based on which adjustments can be made if necessary to help achieve optimal adherence.

5 Conclusion

The COVID-19 pandemic has changed everyday life, and has had a marked impact on individuals with chronic diseases whose management and self-care depend on multiple social, individual, and healthcare-related factors. In this large-scale pharmacoepidemiological study of statin users, we found that one-third of the study population did not take statins as prescribed during the 2-year follow-up period. This observation sheds doubt on the appropriateness of statin indication in individuals with this profile (i.e., young, healthy, and employed earning <€18,000 p.a.). For individuals fitting this profile, recommendation of non-pharmacological measures might be a more effective and efficient alternative. On the other hand, almost one-third of the study population changed their medication-taking behavior during the pandemic period, in some cases showing a decline in statin adherence. Characterization of statin users with a poor adherence pattern enables the effective design and implementation of interventions to enhance medication adherence using person-centered approaches and to distribute resources to avoid repeated negative effects on adherence in these patients in future crises.

Data availability statement

The data analyzed in this study is subject to the following licenses/restrictions: All data used in this study pertain to the CARhES cohort. While these data are not publicly available due to their sensitive nature, interested researchers can nonetheless contact the corresponding author to request access. Requests to access these datasets should be directed to smalo@unizar.es.

Ethics statement

All data collected and integrated in the CARhES cohort and used in the present study are pseudonymized, making patient identification impossible. The study was approved by the Aragón Research Ethics Committee (record number 06/2021).

Author contributions

SM, MR, IA-P contributed to conception and design of the study. SM, IA-P performed the data collection; SM, LM developed and designed the methodology. LM performed the statistical analysis. SM wrote the first draft of the manuscript. LM, MR, AG-M, SC-F, ML, IA-P 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.

Publisher's note

References

Ágh, T., van Boven, J. F. M., Wettermark, B., Menditto, E., Pinnock, H., Tsiligianni, I., et al. (2021). A cross-sectional survey on medication management practices for noncommunicable diseases in europe during the second wave of the COVID-19 pandemic. *Front. Pharmacol.* 12, 685696. doi:10.3389/FPHAR.2021.685696

Allemann, S. S., Dediu, D., and Dima, A. L. (2019). Beyond adherence thresholds: A simulation study of the optimal classification of longitudinal adherence trajectories from medication refill histories. *Front. Pharmacol.* 10, 383. doi:10.3389/FPHAR.2019.00383

Arnet, I., Kooij, M. J., Messerli, M., Hersberger, K. E., Heerdink, E. R., and Bouvy, M. (2016). Proposal of standardization to assess adherence with medication records: Methodology matters. *Ann. Pharmacother.* 50 (5), 360–368. doi:10.1177/1060028016634106

Bernal-Delgado, E., Garcia-Armesto, S., Oliva, J., Sanchez Martinez, F. I., Repullo, J. R., Pena-Longobardo, L. M., et al. (2018). Spain: Health system review. *Health Syst. Transit.* 20 (2), 1–179.

Chaure-Pardos, A., Aguilar-Palacio, I., Rabanaque, M. J., Lallana, M. J., Maldonado, L., Castel-Feced, S., et al. (2022). Effectiveness of statins for primary prevention of cardiovascular disease in low- and medium-risk males: A causal inference approach with observational data. *J. Pers. Med.* 12 (5), 658. doi:10.3390/jpm12050658

Cross, A. J., Elliott, R. A., Petrie, K., Kuruvilla, L., and George, J. (2020). Interventions for improving medication-taking ability and adherence in older adults prescribed multiple medications. *Cochrane Database Syst. Rev.* 5, CD012419. doi:10.1002/14651858.CD012419.pub2

de Geest, S., Zullig, L. L., Dunbar-Jacob, J., Helmy, R., Hughes, D. A., Wilson, I. B., et al. (2018). ESPACOMP medication adherence reporting guideline (EMERGE). *Ann. Intern. Med.* 169 (1), 30–35. doi:10.7326/M18-0543

Dima, A. L., Allemann, S. S., Dunbar-Jacob, J., Hughes, D. A., Vrijens, B., and Wilson, I. B. (2021). Teos: A framework for constructing operational definitions of medication adherence based on timelines-events-objectives-sources. *Br. J. Clin. Pharmacol.* 87 (6), 2521–2533. doi:10.1111/BCP.14659

Dima, A. L., and Dediu, D. (2017). Computation of adherence to medication and visualization of medication histories in R with AdhereR: Towards transparent and reproducible use of electronic healthcare data. *Plos one* 12 (4), e0174426. doi:10.1371/JOURNAL.PONE.0174426

Genolini, C., Alacoque, X., Sentenac, M., and Arnaud, C. (2015). Kml and kml3d: R packages to cluster longitudinal data. *J. Stat. Softw.* 65 (4), 1–34. doi:10.18637/JSS.V065.I04

Hassan, T. A., Sáenz, J. E., Ducinskiene, D., Cook, J. P., Imperato, J. S., and Zou, K. H. (2021). New strategies to improve patient Adherence to medications for noncommunicable diseases during and after the COVID-19 era identified via a literature review. *J. Multidiscip. Healthc.* 14, 2453–2465. doi:10.2147/JMDH.S313626

Hickson, R. P., Annis, I. E., Killeya-Jones, L. A., and Fang, G. (2020). Opening the black box of the group-based trajectory modeling process to analyze medication adherence patterns: An example using real-world statin adherence data. *Pharmacoepidemiol. Drug Saf.* 29 (3), 357–362. doi:10.1002/PDS.4917

Instituto Aragonés de Estadística. Gobierno de Aragón (2022). Cifras de población y proyecciones de población. Available at: https://www.aragon.es/-/estimaciones-y-proyecciones-de-poblacion (Accessed: May 18, 2022).

Kardas, P., Lewek, P., and Matyjaszczyk, M. (2013). Determinants of patient adherence: A review of systematic reviews. *Front. Pharmacol.* 4, 91. doi:10.3389/FPHAR.2013.00091

Lau, D., and McAlister, F. A. (2021). Implications of the COVID-19 pandemic for cardiovascular disease and risk-factor management. *Can. J. Cardiol.* 37 (5), 722–732. doi:10.1016/J.CJCA.2020.11.001

Lewis, C., Wallace, E., Kyne, L., Cullen, W., and Smith, S. M. (2016). Training doctors to manage patients with multimorbidity: A systematic review. *J. Comorb.* 6 (2), 85–94. doi:10.15256/JOC.2016.6.87

Librero, J., Sanfélix-Gimeno, G., and Peiró, S. (2016). Medication adherence patterns after hospitalization for coronary heart disease. A population-based study using electronic records and group-based trajectory models. *Plos one* 11 (8), e0161381. doi:10.1371/JOURNAL.PONE.0161381

Majd, Z., Mohan, A., and Abughosh, S. M. (2021). Using group-based trajectory modeling to characterize the association of past ACEIs/ARBs adherence with subsequent statin adherence patterns among new statin users. *J. Am. Pharm. Assoc.* 61 (6), 829–837.e2. e2. doi:10.1016/J.JAPH.2021.07.007

Menditto, E., Cahir, C., Aza-Pascual-Salcedo, M., Bruzzese, D., Poblador-Plou, B., Malo, S., et al. (2018). Adherence to chronic medication in older populations: Application of a common protocol among three European cohorts. *Patient prefer. Adherence* 12, 1975–1987. doi:10.2147/PPA.S164819

Ofori-Asenso, R., Jakhu, A., Curtis, A. J., Zomer, E., Gambhir, M., Jaana Korhonen, M., et al. (2018). A systematic review and meta-analysis of the factors associated with nonadherence and discontinuation of statins among people aged ≥65 years. *J. Gerontol. A Biol. Sci. Med. Sci.* 73 (6), 798–805. doi:10.1093/GERONA/GLX256

Palmer, K., Monaco, A., Kivipelto, M., Onder, G., Maggi, S., Michel, J. P., et al. (2020). The potential long-term impact of the COVID-19 outbreak on patients with non-communicable diseases in europe: Consequences for healthy ageing. *Aging Clin. Exp. Res.* 32 (7), 1189–1194. doi:10.1007/S40520-020-01601-4

Rodriguez-Blazquez, C., Forjaz, M. J., Gimeno-Miguel, A., Bliek-Bueno, K., Poblador-Plou, B., Pilar Luengo-Broto, S., et al. (2020). Assessing the pilot implementation of the integrated multimorbidity care model in five European settings: Results from the joint action CHRODIS-PLUS. *Int. J. Environ. Res. Public Health* 17 (15), 52688–E5314. doi:10.3390/IJERPH17155268

Visseren, F. L. J., MacH, F., Smulders, Y. M., Carballo, D., Koskinas, K. C., Back, M., et al. (2021). 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. *Eur. Heart J.* 42 (34), 3227–3337. doi:10.1093/eurheartj/ehab484

Vrijens, B., de Geest, S., Hughes, D. A., Przemyslaw, K., Demonceau, J., Ruppar, T., et al. (2012). A new taxonomy for describing and defining adherence to medications. *Br. J. Clin. Pharmacol.* 73 (5), 691–705. doi:10.1111/J.1365-2125.2012.04167.X

Walsh, C. A., Cahir, C., and Bennett, K. E. (2021). Longitudinal medication adherence in older adults with multimorbidity and association with health care utilization: Results from the Irish longitudinal study on ageing. *Ann. Pharmacother.* 55 (1), 5–14. doi:10.1177/1060028020937996

Yang, C., Zhu, S., Lee, D. T. F., and Chair, S. Y. (2022). Interventions for improving medication adherence in community-dwelling older people with multimorbidity: A systematic review and meta-analysis. *Int. J. Nurs. Stud.* 126, 104154. doi:10.1016/j.ijnurstu.2021.104154

Yeaw, J., Benner, J. S., Walt, J. G., Sian, S., and Smith, D. B. (2009). Comparing adherence and persistence across 6 chronic medication classes. *J. Manag. Care Pharm.* 15 (9), 728–740. doi:10.18553/jmcp.2009.15.9.728

Zhang, Y., Flory, J. H., and Bao, Y. (2022). Chronic medication nonadherence and potentially preventable healthcare utilization and spending among medicare patients. *J. Gen. Intern. Med.* 37, 3645–3652. doi:10.1007/S11606-021-07334-Y

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The impact of the war on maintenance of long-term therapies in Ukraine

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Due to the Russian invasion, which started on 24 February 2022, the Ukrainian healthcare system is facing multiple challenges. A great number of healthcare facilities have been destroyed, while availability of other ones is often limited due to a lack of qualified medical staff. Certain services, e.g. cancer therapies, have been seriously disrupted. Moreover, millions of Ukrainians with chronic conditions are also suffering as due to war-related problems with execution of their long-term therapies. Availability of drugs is particularly limited in the occupied regions. According to the national statistics, as of 18 August 2022, about 505 pharmacies were damaged in Eastern Ukraine and 47 completely ruined. Moreover, the invaders have been blocking humanitarian aid provided to these territories by the Ukrainian government or other countries. Fortunately, in the areas controlled by the Government of Ukraine, the acute shortage of medicines, observed at the beginning of the war, has already been eliminated. Nevertheless, not all drugs are now fully available, even in the areas where no military attacks occur. The economic availability of drugs is also profoundly influenced by the significant increase in the cost of medications and the fall in average salaries. The Government of Ukraine is trying to minimise the impact of these war-related challenges by adopting a new legislation. This includes, among others, simplification of procedures for licensing, quality control and import of medicinal products to Ukraine. Other measures involve securing displaced people with the option of benefiting from local healthcare facilities, broadening the scope of the ePrescription system, authorizing primary care doctors to issue prescriptions to refugees, increasing the number of drugs reimbursed for long-term therapies, *etc.* These solutions, however, cannot balance all the harmful consequences the war in Ukraine brings in terms of maintenance of long-term therapies. Therefore, in order to minimise this negative impact, Ukraine still needs urgent international support in this area.

KEYWORDS

long-term therapy, war, Ukraine, medicines, healthcare system, armed conflicts (MeSH), disaster pharmacy, disaster medicine

Introduction

Russia launched a full-scale attack on Ukraine on 24 February 2022, invading many places in the East, South (the coast), West, North as well as in the central (national capital Kyiv) region of the country. The war continues and exerts a major impact on the entire national healthcare system. In the first 7 months of the war, 906 health care institutions were seriously damaged and 123 were completely ruined, at least part of them intentionally (Skrypnyk, 2022d). Moreover, 87 ambulances were destroyed and another 241 medical cars were lost as a result of hostilities (Skrypnyk, 2022d; kapri, 2022) (see Figure 1). These are just preliminary data due to a lack of access to the occupied territories, yet the analysis of the situation in the de-occupied territory showed that virtually every healthcare institution located there was damaged or destroyed (Skrypnyk, 2022c). At least 18 healthcare workers from among those who were not mobilized to the Armed Forces (Skrypnyk, 2022c) were killed and more than 56 were injured (Skrypnyk, 2022d), (glavcom, 2022). The occupied territories face a dramatic shortage of healthcare professionals. To give an example, in Melitopol, which has 150,000 inhabitants, 50% of doctors left in the first months of the war. Those who stayed are able to provide emergency care only and cannot guarantee the citizens maintenance of long-term therapies (Skrypnyk, 2022a).

The consequences of this scenario are more than profound. A recent analysis indicates that a war-related delay in care for only 4 months for five prevalent types of cancer will lead to an excess of over 3,600 cancer deaths in the Ukrainian population in the subsequent years (Caglevic et al., 2022). However, it is not only the management of life-threatening conditions that is seriously affected by abnormal circumstances resulting from the current military conflict. With its population exceeding 40 million, Ukraine has millions of patients who require long-term therapies for hypertension, diabetes, asthma, COPD and numerous other chronic conditions, which due to their high prevalence, are of the greatest importance to public health. The World Health Organisation predicts that disruption of these therapies will bring negative consequences, i.e. increased morbidity and mortality, which altogether constitute another detrimental effect of the war (reliefweb, 2022).

The armed conflict affects the maintenance of long-term therapies in many ways. Millions of Ukrainians were forced to leave their homes and move to other locations - some of them within the territory of their country, while others much farther, abroad. As a result, their access to the healthcare system was severely restricted, which made availability of their chronic medications very challenging. Others, who stayed in their country, are often deprived of access to medications due to military operations in the area. Even in the case of those lucky ones who live in safer locations, such as Western Ukraine, access to drugs is seriously limited because of reduced production, broken chains of distribution, and last but not least, rapidly rising prices. This paper describes these challenges in more detail, providing a snapshot of the scenario as of early August, 2022 (unless otherwise stated). It also presents various actions that Ukraine has been taking to minimise the effect of these challenges, and to ensure continuation of treatment to patients who require long-term therapies, despite the existing unfavourable conditions.

Impact of the war and related shortage of medicines

The war in Ukraine created a serious barrier to access to pharmaceuticals which constitute the core element of long-term management in non-communicable diseases. The acute shortage of medicines at the beginning of the war posed a major challenge to maintenance of long-term therapies in Ukraine. Fortunately, this shortage is no longer so serious in the territory controlled by the Government of Ukraine (Kupriianova, 2022: Ternova, 2022a), as the pharmaceutical sector gradually resumed its work. Additionally, the drugs transported to Ukraine as humanitarian aid are delivered to hospitals or dispensed at mobile points (Sherfetdinova-Sushchyk Zebede. Ministry of Health, 2022).

However, in the occupied territories the situation is uncontrolled and thus much worse since it is not possible to provide medications to people. For example, the Kherson region, currently occupied by the Russian invaders, faces a crisis resulting from shortage of medical supplies. There are even problems with food delivery. Drugs used in the treatment of chronic diseases (especially oncologic medications) are practically not available to people. In absence of family doctors caused by the war, only clinical hospitals operate in Kherson and in some of them, entire departments ceased to function as most of the highly qualified medical workers left the occupied territories. Those who stayed are overstrained with work and feel constant moral pressure from the occupation authorities. Moreover, the occupiers decided to cancel previously introduced reforms in the Ukrainian healthcare system, including reimbursement of medicines (Skrypnyk, 2022b; Return to the past, 2022). The same problem exists in the occupied Mariupol where people are dying due to lack of medications. There is a shortage of medicines for cancer, diabetes, tuberculosis and thyroid problems (Skrypnyk, 2022b). The Russian invaders are blocking humanitarian aid provided to these territories by the Ukrainian government or other countries. Only individual volunteers, using their own means of transport, are trying to distribute necessary goods, including medications, to the people. Due to very limited travelling options, in Kherson those who want to flee the occupied area

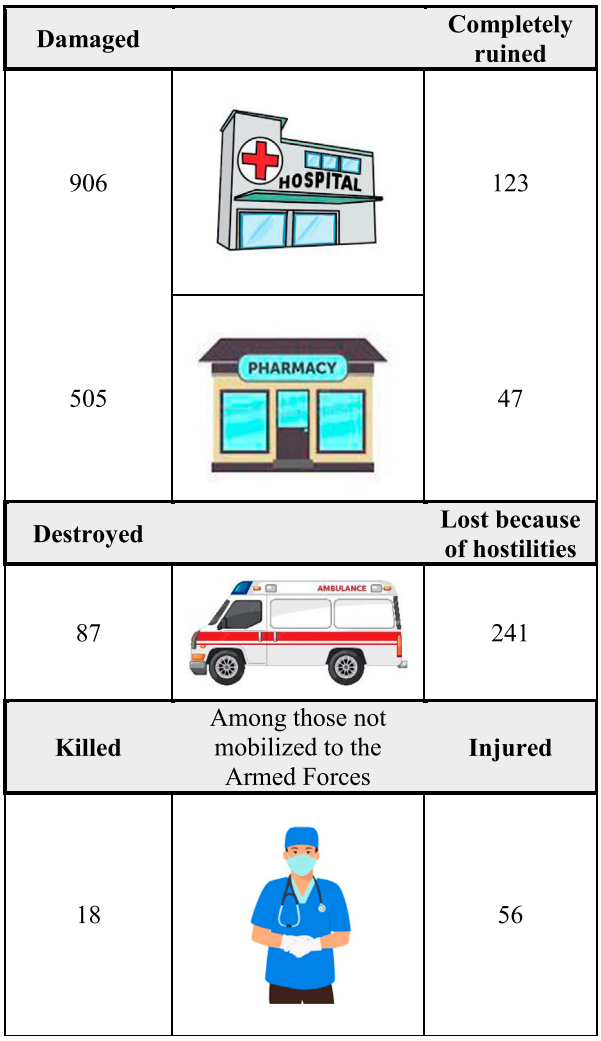

FIGURE 1
Statistics of war-related losses of the Ukrainian healthcare system, as of August 2022 - preliminary data due to a lack of access to some parts of the territory (Skrypnyk, 2022d).

have to wait in long queues for being transported to safe places. They are often exposed to difficult weather conditions, without any chance for medical support, risking death resulting not only from military operations but also from their indirect short-term consequences, such as hunger, infections, *etc.*

Unfortunately, it is not the end of the list of health repercussions brought by hostilities. When it comes to chronic conditions, lessons learned from previous armed conflicts show that, in the case of Ukrainian people, other sequelae may also occur. These include a variety of stress-mediated conditions, such as exacerbations of cardiovascular diseases, strokes and heart attacks, cancers and many more, which, in turn, may lead to substantially increased mortality among civilians, including children who are burdened most severely (Jawad et al., 2020; Sadetzki et al., 2017; Al-Makhamreh et al., 2021).

Effects of the economic crisis on availability of medicines

The war led to a severe decline in the Ukrainian economy, causing a significant increase in the budget deficit, and critical dependence of the Ukraine's economy on international aid (Kirsanov, 2022b). In June/July 2022, more than 50% of the deficit was covered by financial assistance from international partners (Zanuda). However, the International Monetary Fund estimates that the GDP decline may reach the level of 33–35% by the end the year and predicts a significant increase in public debt to more than 85% of the GDP (Kirsanov, 2022b). Moreover, Ukraine is facing high rates of inflation. The National Bank of Ukraine predicts that by the end of the year prices may rise by at least 30% (Zanuda). Research conducted in Ukrainian pharmacies showed a 20–25% increase in prices (Murashko, 2022), and in some of them it was up to 60% (Kupriianova, 2022; Murashko, 2022). The experts predict even further increase. It is noteworthy that in the same time, salaries in private sector companies and enterprises decreased by 10%–50% as compared to the pre-war period (Department of Monetary Policy, 2022; Sherfetdinova-Sushchyk Zebede. Ministry of Health, 2022). All these factors have profound consequences for maintenance of long-term therapies, as higher costs of medicines reduce their affordability.

The factors that play the main role in the rapid increase in drug prices are, among others, more difficult logistics due to current shutting off of air and sea transport routes, as well as destruction of many warehouses storing medications and raw materials by the Russian invaders. Unlike in the pre-war period, delivery of these raw materials now takes months or more (Ternova, 2022b). It should be emphasized that up to 75% of the drugs distributed in Ukrainian pharmacies are produced locally. However, almost all raw materials for drug manufacturing, which have become more expensive all over the world, are imported (Kupriianova, 2022). Another problem is a higher USD to UKH (Hryvna, Ukrainian currency) exchange rate, as well as growing prices and shortage of fuel.

Consequently, since March 2022 sales in the Ukrainian pharmaceutical market have dropped significantly - by 11% in March, by 32% in April and by 24% in May and June as compared to the same period of 2021. The reasons for sales decline are directly related to the war, i.e. massive migration from the country, the occupation of specific Ukrainian regions, the considerable medical humanitarian aid provided by other countries, and drop in the income of the population that began to choose less expensive drug analogues

to save on medications (Kirsanov, 2022a). Interestingly, the downward trend began to develop just after a substantial growth of the Ukrainian pharmaceutical market observed before the beginning of the war (by 31% in January and 45% in February). In fact, the volume of pharmacy sales was doubled in the first 11 days of the Russian invasion as a result of large amounts of medications purchased by patients with chronic conditions. The top most often bought medicines represented the following ATC classes: M01 - antiinflammatory and antirheumatic products, C09 - agents acting on the renin-angiotensin system, N02 - analgesics, N06 - psychoanaleptics, A10 - drugs used in diabetes, J01 - antibacterials for systemic use (Kirsanov, 2022a).

Decrease in the physical availability of medicines

The decrease in the physical availability of medicines during the war was related to reduction in the number of working pharmacies and destruction of their infrastructure. Only around 10% out of 22,780 Ukrainian pharmacies continued to work in the first days of the war (interfax, 2022b). However, at the beginning of April 2022, the share of working pharmacies increased to 71% (apteka, 2022a). According to national statistics, as for 18 August 2022 505 pharmacies were damaged in eastern Ukraine and 47 completely ruined (Skrypnyk, 2022d), whereas at least 112 pharmacies located in the areas affected by hostilities were either not able to work (Sherfetdinova-Sushchyk Zebede. Ministry of Health, 2022) or were captured by the invaders. The effect of this scenario in large cities was not so dramatic. It should be remembered that the number of pharmacies per capita in Ukraine prior to the war was 2.5 times higher than, for example, in Germany. Nevertheless, shutting down of scarce pharmacies operating in rural areas created serious problems with the local availability of medicines (Ternova, 2022b).

Military operations in certain regions also made transport of medicines difficult or even impossible. Warehouses with medicines in these zones were blocked, which influenced the logistics of pharmaceuticals in the whole country (Nynko, 2022). For example, warehouses with ready-made medicines and raw materials of one of the biggest Ukrainian pharmaceutical producer, JSC “Farmak” (Kyiv), were burned by the occupiers, which made the company suffer a UAH 1.5 billion loss (interfax, 2022a).

Additionally, there was a shortage of pharmaceutical sector staff due to high migration of the population, as well as their active involvement in defending Ukraine against the Russian army. At the beginning of October, a shortage of pharmacists may still be observed in the regions close to the war zone [38]. In particular, there is a lack of personnel in the pharmaceutical industry, such as specialists with high qualifications (Ternova, 2022b). In order to address the issue, students and graduates of pharmaceutical and medical educational institutions who have not yet completed an internship were allowed to work in pharmacies (studentam-medichnih, 2022).

Changes in legislation adopted to overcome current problems

Ukraine tries to flexibly adopt its legal and normative frameworks to the extraordinary war scenario in an attempt to overcome the difficulties. Thus, in the first month of the war, the government body adopted 29 orders that related to various aspects of medical and pharmaceutical services for all population categories toward Russian military aggression (Zhdan et al., 2022). It also refers to the maintenance of long-term therapies. One of these steps is sim*plification of the procedures for licensing, quality control and import of medicinal products* to Ukraine, which provides an option of emergency state registration of medicinal products by simplifying requirements with regard to labelling and expiration dates of imported medicines (drlz, 2022; Procopenko, 2022). Before the war, imported medicines should have the expiration dates of at least half of the period specified by the manufacturer. According to the new changes this period is not limited but should not be expired. Drugs which are already registered in Ukraine can be imported to its territory now without labelling in Ukrainian language, provided that they accompanied by instructions for use (patient leaflet) approved in Ukraine, and a warranty letter. Medicinal products which are not registered in Ukraine can be imported only for the provision of the Armed Forces of Ukraine and health care institutions (except pharmacies), without right for retail sale.

Drug reimbursement is a new issue in Ukraine as it was initiated as late as in 2017. It applies to the outpatient treatment of selected conditions only, i.e., cardiovascular diseases, bronchial asthma, diabetes, mental and behavioural disorders, and epilepsy. It covers only 368 various medicines (116 free of charge) and 76 insulin preparations (47 free of charge) and some changes in their quantities are expected. The program continues to work in the territory controlled by the Government of Ukraine with several changes made to the procedure of its implementation. Medicines subject to reimbursement can be prescribed and dispensed on electronic or traditional paper prescriptions by any general practitioner regardless of the patient’s place of residence, unlike in the pre-war conditions. Nevertheless, the number of prescriptions has decreased. Not all trade names of reimbursed medicines are available now. The National Health Service of Ukraine pays back the money to the pharmacies for the dispensed reimbursed drugs. However, not all pharmacies which participated in this program before the war continue to dispense

reimbursed medicines. Thus, patients are recommended to make sure whether a specific pharmacy provides the reimbursement option in advance (Affordable Medicines, 2022).

According to the national statistics, prior to the war (i.e. as of 1 February 2022) there were 41,130,400 Ukrainian inhabitants (index.minfin, 2022). Since the beginning of the full-scale war, almost nine million citizens have been displaced across the territory of Ukraine and beyond its borders. Almost six million citizens are registered abroad, and almost four million have been awarded the temporary protected status in their host countries. As many as 90% of refugees are women and children. According to the UN Refugee Agency, hundreds of thousands of Ukrainians have been forcibly deported to the territory of the invader state. The National Information Bureau has already identified more than 5,600 children deported to the country of the aggressor (varta, 2022; minre.gov, 2022).

The increased amount of work that both medical staff and the whole healthcare system in general has to face was observed in regions with higher migration of people due to a change in the structure of the population. To overcome these difficulties, new changes in legislation were adopted. All internally displaced people who moved or were forced to change their place of residence can apply for primary medical help to any health care institution of their choice. It includes emergencies, primary medical care and vaccinations in accordance with the Preventive Vaccination Calendar. Records keeping of such patients is carried out. According to the law, doctors are obliged to issue prescriptions for necessary drugs, including medications covered by the reimbursement program, using e-Prescriptions or, in case of no access to the electronic healthcare system, paper prescriptions (ombudsman, 2022).

The Ministry of Health of Ukraine continues to gradually introduce the electronic prescription scheme. From 1 August 2022 a new functionality of e-Prescription for antibiotics have been introduced in Ukraine. Of a note is that before these changes, antibiotics could be bought from Ukrainian pharmacies without any prescription. Now, only pharmacies located on the frontline or under occupation will be able to dispense antibiotics to patients without medical doctor's prescriptions (Electronic prescription for antibiotics, 2022). As an exception, voluntary and charitable organizations can purchase antibiotics directly from distributors without prescriptions at the request of relevant institutions, military units or healthcare organizations. The next stage will be introduction of e-Prescription for narcotics, and the final stage will be the application of the e-Prescription system for all prescription drugs (Horbunova, 2022; Radutsky, 2022). There was no frantic demand for antibiotics before the introduction of e-Prescriptions as compared to the chaotic supply of these medications at the beginning of the COVID-19 pandemic and in the first weeks of the war (Electronic prescription for antibiotics, 2022).

The new amendments to the Ukrainian Law on Medicinal Products sets forth that the state registration of medicines may be refused or cancelled by terminating or shortening the validity period of the registration certificate if one, several or all stages of the production of the medicinal product are carried out by enterprises whose production facilities are located in the territory of the Russian Federation or the Republic of Belarus. A similar scenario may occur if an owner of the registration certificate or their representative has any kind of relations with business entities in the territory of above-mentioned countries (biz.ligazakon, 2022). However, having in mind that a high proportion of drugs distributed in Ukraine used to come from these countries, it could lead to a shortage of certain medicines, with potential negative repercussions to the health of Ukrainian citizens. Considering the above, the order No. 1801 of the Ministry of Health of Ukraine dated 05.08.2020 confirmed that the decision to ban the use of a medicinal product by terminating the validity of the registration certificate is not accepted if there are no analogues available in the Ukrainian market (zakon.rada.gov, 2022).

Another positive change in the regulation of the pharmaceutical sector set by the new Law on Medicinal Products, which will come into force 2.5 years after cancellation of the martial law, is the fact that the Ukrainian legislation on medicinal products will be adjusted to the requirements of the European Union (apteka, 2022b).

Because of the war, at the beginning of March, 2022 the Ministry of Health of Ukraine changed its approach to financing of the health care system. Every month, each hospital was guaranteed to receive 1/12 of the annual amount of funds from the National Health Service, irrespective of the number of services provided. It made it possible to maintain the system at a critical moment, to secure payment of salaries for medical workers as well as uninterrupted operation of hospitals. From 1 July 2022 in the regions that were not affected by hostilities, a standard payment system covering only medical services actually provided was reintroduced (kmu.gov, 2022).

Among the rescue projects successfully implemented by the Ministry of Health there are regular evacuation flights to secure the treatment of Ukrainians abroad in case their therapy is no more available in Ukraine. On average, there are about four of them per week. Since the beginning of the full-scale invasion, 1,274 Ukrainians have already been provided with medical assistance in leading clinics in 17 countries of the world (Skrypnyk, 2022d).

Solutions provided by other stakeholders

Apart from the actions undertaken by the Ukrainian government, it is necessary to acknowledge the unprecedented sacrifice of both healthcare professionals and civil society (gov.ua, 2022; acmc.ua, 2022; Volontery, 2022). A special role in supporting maintenance of chronic therapies is played by pharmacists, especially in the zone of active hostilities (War: a pharmacist, 2022). In addition, pharmacists, as well as students and

teachers of pharmaceutical universities implement various forms of volunteering, such as production of medicines for the military forces, participation in the collection of funds, items, food and medications, sorting of medical humanitarian aid, transportation of volunteer aid to the frontline area, *etc.* (new.meduniv, 2022a; new.meduniv, 2022b; new.meduniv, 2022c). The charity of both individual pharmacists and pharmacies, pharmaceutical enterprises and public pharmaceutical organizations, in particular the charity fund "All-Ukrainian Pharmaceutical Chamber - a single European family", is also very important (Klimov, 2022). Volunteering and charity in Ukraine is closely related to the humanitarian mission of the global pharmaceutical community which is based on the principle of maximum effective use of donor funds, minimizing costs of logistics services for delivery of humanitarian goods directly to recipients, preventing commercialization of medicines and medical products received as humanitarian aid, and building of a transparent platform for collection, formation, delivery and reporting on distribution of humanitarian aid to a specific recipient (Half a year of war, 2022).

Discussion

As a result of the Russian invasion, the Ukrainian healthcare system is facing multiple critical challenges. The war has caused massive internal and external migration of Ukrainian citizens and seriously destabilised the national economy. A great number of healthcare facilities have been destroyed, access to the others is often limited due to a lack of qualified medical staff. Not all drugs are fully available, even in the areas where no military attacks occur. The economic availability of the drugs is also profoundly affected as the cost of drugs has increased significantly and the average salaries have dropped down. The Government of Ukraine is trying to minimise the impact of the war on its healthcare system by adopting new legislation. However, the existing drug reimbursement program covers a limited number of medicines and health problems only. In the future, extending the list of diseases subject to drug reimbursement and introducing mandatory medical insurance can be effective solutions working towards improvements in long-term therapies in Ukraine.

Despite the hostilities are still in place, a look for future seems to be justified. This sort of approach now makes sense more than ever. As illustrated by the stress-test of healthcare system that COVID-19 pandemic conducted recently, many European countries are not well-prepared to maintain the continuity of long-term therapies in unfavourable conditions [(Kardas et al., 2021)]. This is also a case of pharmaceutical service: a recent survey has shown that European hospital pharmacies are rather poorly prepared to emergencies and disasters (Schumacher et al., 2021). Fortunately, a crisis preparedness can be improved due to dedicated training (Schumacher et al., 2022).

Therefore, relevant actions needs to be taken in advance. In case of Ukraine, increasing the strength and resilience of the health and pharmaceutical system is advisable. Under the light of such principles, the National Council for the Restoration of Ukraine from consequences of the war proposes the project of the recovery plan for Ukraine. It includes planning to ensure the financial stability of the healthcare system, as well as restoration and transformation of the network of healthcare facilities. It pays special attention to strengthening preparedness for emergencies in the field of healthcare, reducing the dependence of the pharmaceutical sector on active pharmaceutical substances produced abroad, and last but not least, improving access to, and proper use of medicines (The project of the recovery plan of Ukraine, 2022).

These plans for post-war period are more than important. However, the armed conflict is not over now. In the unfavourable scenario set by it, multiple war-related factors create serious challenges to the maintenance of long-term therapies, and illustrate the reasons for which Ukraine needs urgent international support.

Data availability statement

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

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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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2022.1024046/full#supplementary-material

References

acmc.ua (2022). About volunteering in Ukraine during the war/Про волонтерство в Україні Під час війни ➜ АКМЦ [Internet]. Available at: https://acmc.ua/pro-volonterstvo-v-ukrayini-pid-chas-vijny/.

Affordable Medicines (2022). Affordable Medicines" continues to operate under martial law/«ДостуШні ліки» Продовжують Працювати в умовач воєнноҐо стану. "Affordable Medicines" continues to operate under martial law/«ДостуШні ліки» Продовжують Працювати в умовач воєнноҐо стану. *Dig. Chang. Heal care* 8 (32), 2–3.

Al-Makhamreh, H., Alkhulaifat, D., Al-Ani, A., Mafrachi, B., Saadeh, A., Al-Ani, H., et al. (2021). The impact of war-related stress on coronary artery disease severity in war survivors: A syntax study. *Int. J. Environ. Res. Public Health* 18 (6), 3233. Available at: https://pubmed.ncbi.nlm.nih.gov/33800972/.

apteka (2022a). More than 16,000 pharmacies are currently operating in Ukraine: Current statistics/В ?країні наразі Працює більше 16 тис аШтек: Актуальна статистика | ?отижневик ?????? Shchotyzhnevyk apteka [internet]. Available at: https://www.apteka.ua/article/632554.

apteka (2022b). Parliament adopted a new law "On medicinal products"/Парламент учвалив новий закон «Про лікарські засоби» | Щотижневик АШТЕКА. Shchotyzhnevyk Apteka [Internet]. Available at: https://www.apteka.ua/article/641850.

biz.ligazakon (2022). The law on restricting the circulation of medicinal products from Russia and Belarus: Risks for companies and patients/Закон Про обмеження обіҐу лікарськичх засобів з росії та білорусі: ризики для комШаній і ШаціЄнтів | think brave [internet]. Available at: https://biz.ligazakon.net/analitycs/212104_zakon-pro-obmezhennya-obgu-lkarskikh-zasobv-z-ros-ta-blorus-riziki-dlya-kompany–patsntv.

Caglevic, C., Rolfo, C., Gil-Bazo, I., Cardona, A., Sapunar, J., Hirsch, F. R., et al. (2022). The armed conflict and the impact on patients with cancer in Ukraine: Urgent considerations. *JCO Glob. Oncol.* 8. [Internet]. doi:10.1200/GO.22.00123

Department of Monetary Policy, Department of monetary policy and economic analysis. National Bank of Ukraine. Monthly macroeconomic and monetary review June 2022/?омісячний макроекономічний та монетарний оҐляд червень 2022 року ?еШартамент монетарної Політики та економічноҐо аналізу. 2022.

drlz (2022). State register of medicinal products/Державний реєстр лікарськичх засобів України. Available at: http://www.drlz.com.ua/ibp/ddsite.nsf/all/shlist?opendocument&stype=8 August 11, 2022). Updated

Electronic prescription for antibiotics (2022). *Electronic prescription for antibiotics: Everything a patient needs to know*/?лектронний рецеШт на антибіотики: все, що Шотрібно знати ПаціЄнту. Держлікслужба [Internet]. State service of Ukraine on medicines and drug control. Available at: .https://www.dls.gov.ua/for_subject/електронний-рецеШт-на-антибіотики-вс-3/

glavcom (2022). The Ministry of Health reported how many Ukrainian doctors died during the five months of the war/МОЗ Повідомив, скільки українськичх медиків заҐинуло за Ш'ять місяців. Available at: https://glavcom.ua/country/society/moz-povidomilo-skilki-ukrajinskih-medikiv-zaginulo-za-pyat-misyaciv-viyni-862967.html.

gov.ua (2022). In Ukraine, an official humanitarian aid platform was launched to combine volunteer and state initiatives/В Україні заШустили офіційну Шлатформу Ґуманітарної доШомоҐи для об'Єднанняволонтерськичхтадержавничініціатив | Міністерство з Питань реінтеҐрації тимчасово окуШованич територій України [Internet]. Available at: https://minre.gov.ua/news/v-ukrayini-zapustyly-oficiynu-platformu-gumanitarnoyi-dopomogy-dlya-obyednannya-volonterskyh-ta.

Half a year of war (2022). Support of Ukraine by the pharmaceutical community of the European business association/?ів року війни. Шідтримка ?країни фармацевтичною сШільнотою ?вроШейської ?ізнес ?соціації - European business association [internet]. Available at: https://eba.com.ua/piv-roku-vijny-pidtrymka-ukrayiny-farmatsevtychnoyu-spilnotoyu-yevropejskoyi-biznes-asotsiatsiyi/.

Horbunova, K. (2022). Attempt #2: How can pharmacies prepare for issuing e-prescriptions for antibiotics?/?Проба №2: як аШтеці ШідҐотуватися до відШуску е-рецеШтів на антибіотики? | ?отижневик ?????? Shchotyzhnevyk apteka [internet]. Available at: https://www.apteka.ua/article/640753.

index.minfin (2022). Population of Ukraine/?аселення ?країни [2022] ☐ ?исельність населення ?країни [internet]. Available at: https://index.minfin.com.ua/ua/reference/people/.

interfax (2022a). Farmak's losses as a result of a warehouse fire in the Kyiv region at the beginning of the war amounted to about UAH 1.5 billion/Втрати "Фармака" внаслідок Шожежі на складі в Київській області на Шочатку війни становили близько 1,5 млрд Ґрн [Internet]. Available at: https://interfax.com.ua/news/pharmacy/816826.html.

interfax (2022b). The number of pharmacies in Ukraine has decreased more than twice in comparison to pre-war times - Ministry of Health/Кількість аШтек в Україні скоротилася Шорівняно з довоєнним часом більш ніж удвічі – МОЗ [Internet]. Interfax-Ukraine. Available at: https://ua.interfax.com.ua/news/general/814412.html (Accessed July 25, 2022).

Jawad, M., Hone, T., Vamos, E. P., Roderick, P., Sullivan, R., and Millett, C. (2020). Estimating indirect mortality impacts of armed conflict in civilian populations: Panel regression analyses of 193 countries. *BMC Med.* 18 (1), 266. Available from: https://bmcmedicine.biomedcentral.com/articles/10.1186/s12916-020-01708-5.

kapri (2022). On the work of emergency medical care during the war/Про роботу екстреної медичної доШомоҐи Під час війни. Available at: https://kapri.dn.ua/2022/08/06/pro-robotu-ekstrenoi-medichnoi-dopomogi-pid-chas-vijni/.

Kardas, P., van Boven, J. F. M., Pinnock, H., Menditto, E., Wettermark, B., Tsiligianni, I., et al. (2021). Disparities in European healthcare system approaches to maintaining continuity of medication for non-communicable diseases during the COVID-19 outbreak. *Lancet Reg. Health. Eur.* 4, 100099. doi:10.1016/j.lanepe.2021.100099

Kirsanov, D. (2022a). Pharmaceutical market on the way to recovery/Фармринок на шляЧу до відновлення – UDT 1/09/2022 | Щотижневик АШТЕКА. Shchotyzhnevyk Apteka [Internet]. Available at: https://www.apteka.ua/article/640253.

Kirsanov, D. (2022b). War and medicines: Pharmacy sales according to the results of the first half of 2022/?ійна і ліки: АШтечний Продаж за Ші́дсумками І Ші́вріччя 2022 р. | ?отижневик ?????? Shchotyzhnevyk apteka. Available at: https://www.apteka.ua/article/641331.

Klimov, O. (2022). Humanitarian mission of EU pharmacists in Ukraine/?уманітарна місія фармацевтів ?? в ?країні | ?отижневик ?????? Shchotyzhnevyk apteka [internet]. Available at: https://www.apteka.ua/article/635147.

Kupriianova, O. (2022). Why the medicines prices are rising rapidly in Ukraine and is there a predicted shortage of medicines/Ліки в ?країні стрімко дорожчають: Ччини з'ясували у ???. Available at: https://1plus1.ua/tsn/novyny/comu-v-ukraini-strimko-rostut-cini-na-liki-ta-ci-prognozuetsa-deficit-medicnih-preparativ-suzet-tsn.

kmu.gov (2022). Medical guarantee program - 2022: Service packages and tariffs/?роҐрама медичнич Ґарантій: особливості реалізації з 1 лиШня 2022 року | ?абінет ?ініструв ?країни [internet]. Available at: https://www.kmu.gov.ua/news/prohrama-medychnykh-harantii-osoblyvosti-realizatsii-z-1-lypnia-2022-roku.

minre.gov (2022). *In Ukraine the number of internally displaced persons (IDPs) has exceeded 8 million people*/Кількість внутрішньо Переміщенич осіб (ВШО) в Україні Перевищила *8* млн людей. звідки й куди їчали найбільше | Міністерство з Питань реінтеҐрації тимчасово окуШованич територій України [Internet]. Ministry of Reintegration. Available at: https://www.minre.gov.ua/news/kilkist-vnutrishno-peremishchenyh-osib-vpo-v-ukrayini-perevyshchyla-8-mln-lyudey-zvidky-y-kudy.

Murashko, A. (2022). Ukraine, drug prices in pharmacies have increased by 20-40%/В Україні ціни на ліки в аШтекач зросли на 20-40% – новини на ??? | 30. травня 17, 13. Available at: https://www.unn.com.ua/uk/news/1979132-v-ukrayini-tsini-na-liki-v-aptekakh-zrosli-na-20-40.

Nynko, D. (2022). Peculiarities of provision of medicines in Ukraine in the conditions of war/Особливості забезШечення ліками в Україні в умовач війни – dw – 11.04. Available at: https://www.dw.com/uk/osoblyvosti-zabezpechennia-likamy-v-ukraini-v-umovakh-viiny/a-61413607.

new.meduniv (2022a). The department of pharmacognosy and botany joined the production of medicinal ointments for the military/Кафедра фармакоГнозії і ботаніки долучилася до виГотовлення лікувальнич мазей для військович – Львівський національний медичний університет [Internet]. Available at: https://new.meduniv.lviv.ua/kafedra-farmakognoziyi-i-botaniky-doluchylasya-do-vygotovlennya-likuvalnyh-mazej-dlya-vijskovyh/.

new.meduniv (2022b). Together we are strong: Volunteer activity of students and teachers of Danylo Halytsky LNMU/Разом ми сильні: Волонтерська діяльність студентів та викладачів ???? імені ?анила ?алицькоГо – ?ьв івський національний медичний університет. Available at: https://new.meduniv.lviv.ua/razom-my-sylni-volonterska-diyalnist-studentiv-ta-vykladachiv-lnmu-imeni-danyla-galytskogo/.

new.meduniv (2022c). Tireless volunteers work 24/7 - students and teachers of Danylo Halytsky LNMU/24/7 Працюють невтомні волонтери – студенти та викладачі ЛНМУ імені Данила ГалицькоГо – Львівський національний медичний університет. Available at: https://new.meduniv.lviv.ua/24-7-pratsyuyut-nevtomni-volontery-studenty-ta-vykladachi-lnmu-imeni-danyla-galytskogo/.

ombudsman (2022). Clarification on some issues of the organization of medical care during martial law/УШовноважений Верчовної Ради України з Прав людини - Роз'яснення щодо деякич Питань орГанізації медичної доШомоГи Шід час воєнноГо стану [Internet]. Available at: https://ombudsman.gov.ua/news_details/rozyasnennya-shchodo-deyakih-pitan-organizaciyi-medichnoyi-dopomogi-pid-chas-voyennogo-stanu.

Procopenko, E. (2022). What has changed in the regulation of registration and circulation of drugs during the war? Clarification of lawyers/?о змінилося в реГулюванні реєстрації та обіГу ліків за час війни? Роз'яснення юристів [internet]. Available at: https://www.legalalliance.com.ua/publikacii/so-zminilosa-v-reguluvanni-reestracii-ta-obigu-likiv-za-cas-vijni-rozasnenna-uristiv/.

Radutsky, M. (2022). Parliament supported the draft law on strengthening control over the dispensing of medicines/Парламент Шідтримав законоПроєкт щодо Шосилення контролю за відШуском ліків | Щотижневик АШТЕКА. Shchotyzhnevyk Apteka [Internet]. Available at: https://www.apteka.ua/article/640911.

reliefweb (2022). *Ukraine War: The impact of disruption on infectious and chronic disease programmes is expected to be severe and durable - Ukraine* | ReliefWeb [Internet]. World Health Organization. 2022 Available at: https://reliefweb.int/report/ukraine/ukraine-war-impact-disruption-infectious-and-chronic-disease-programmes-expected-be-severe-and-durable

Return to the past: The occupation authorities of the Kherson region destroyed the medical reform/У місті Працюють лише клінічні лікарні: як черсонці живуть без якісної медицини [Internet]. Public news. 2022 Available at: https://suspilne.media/267570-povernenna-v-minule-okupacijna-vlada-hersonsini-znisila-medicnu-reformu/

Sadetzki, S., Chetrit, A., Freedman, L. S., Hakak, N., Barchana, M., Catane, R., et al. (2017). Cancer risk among Holocaust survivors in Israel-A nationwide study. *Cancer* 123 (17), 3335–3345. Available at: https://pubmed.ncbi.nlm.nih.gov/28691178/.

Schumacher, L., Bonnabry, P., and Widmer, N. (2021). Emergency and disaster preparedness of European hospital pharmacists: A survey. *Disaster Med. Public Health Prep.* 15 (1), 25–33. doi:10.1017/dmp.2019.112

Schumacher, L., Senhaji, S., Gartner, B. A., Carrez, L., Dupuis, A., Bonnabry, P., et al. (2022). Full-scale simulations to improve disaster preparedness in hospital pharmacies. *BMC Health Serv. Res.* 22 (1), 853. doi:10.1186/s12913-022-08230-9

Sherfetdinova-Sushchyk Zebede. Ministry of Health (2022). *Despite the war, Ukrainians have access to medicines*/МОЗ: ШоШри війну українці мають достуШ до медикаментів — *ThePharma*. The Pharm Media. Media [Internet] Available at: https://thepharma.media/uk/news/29436-moz-popri-viinu-ukrayinci-mayut-dostup-do-medikamentiv-02062022.

Skrypnyk, D. (2022a). *Doctors in Melitopol demand salary in national currency*/Лікарі у МелітоШолі вимаГають зарШлату у національній валюті — *ThePharma*. The Pharm Media. Media [Internet]Available at: https://thepharma.media/uk/news/29912-likari-u-melitopoli-vimagayut-zarplatu-u-nacionalnii-valyuti-26072022.

Skrypnyk, D. (2022b). *Medicine crisis in the Kherson region: Residents lack medicines for chronic diseases*/?едикаментозна криза на ?ерсонщині: мешканцям бракує ліків Проти чронічнич зачворювань — *ThePharm*. The Pharm Med.]Available at: https://thepharma.media/uk/news/30023-medikamentozna-kriza-na-xersonshhini-meskancyam-brakuje-likiv-proti-xronicnix-zaxvoryuvan-08082022.

Skrypnyk, D. (2022c). The Ministry of health indicate the number of hospitals damaged by the occupiers in the kharkiv region/У ??? назвали кількість лікарень, які Пошкодили окуПанти на ?арківщині — ThePharma.Media. Available at: https://thepharma.media/uk/news/30394-okupanti-na-xarkivshhini-poskodili-blizko-200-medzakladiv-ta-19-zruinuvali-vshhent-21092022.

Skrypnyk, D. (2022d). The Ministry of health mentioned the losses of the medical system during the war/У ??? назвали втрати медсистеми Шід час війни — ThePharma. Available at: https://thepharma.media/uk/news/30129-u-moz-nazvali-vtrati-medsistemi-pid-cas-viini-19082022.

studentam-medichnih (2022). Students of medical and pharmaceutical specialties were allowed to work in pharmacies of Ukraine/Новини ?країни: студентам дозволили Працювати в аШтекач — tsn.ua [internet]. Available at: https://tsn.ua/ato/studentam-medichnih-ta-farmacevtichnih-specialnostey-dozvolili-pracyuvati-v-aptekah-ukrayini-2004160.html.

Ternova, S. (2022a). *Oleksandr komarida: The Ministry of health has taken important steps to support domestic pharma*/?лександр ?омаріда: МОЗ наПрацювало важливі кроки на Шідтримку вітчизняної фармиє& *nbsp*. The Pharm Media. — ThePharma.Media [Internet][cited 2022 Oct 20]. Available from: https://thepharma.media/uk/business/29961-aleksandr-komarida-minzdrav-razrabotal-vaznye-sagi-v-podderzku-otecestvennoi-farmy-01082022.

Ternova, S. (2022b). Petro bagriy: "The national farm is a treasure of the state, and not only in difficult times"/?етро ?аГрій: «Вітчизняна фарма – скарб держави, і не лише в скрутні часи» — ThePharma.Media [internet]. Available at: https://thepharma.media/uk/business/29975-petr-bagrii-otecestvennaya-farma-klad-gosudarstva-i-ne-tolko-v-trudnye-vremena-03082022.

The project of the recovery plan of Ukraine (2022). *Materials of the working group "Health care"*/Проєкт Шлану відновлення України. Матеріали робочої ГруПи «Очорона здоров'я». National Council for the Restoration of Ukraine from consequences of the war. Available at: https://www.kmu.gov.ua/storage/app/sites/1/recoveryrada/ua/health-care.pdf.

varta (2022). The Ministry of Internal Affairs told how many Ukrainians went abroad and what percentage of them were men/У МВС Повідомили, скільки всьоГо українців виїчало за кордон — Варта 1 [Internet]. Available at: https://varta1.com.ua/news/u-mvs-povidomili-skilki-vsogo-ukrayinciv-viyihalo-za-kordon_351022.html.

Volontery (2022). Volontery [internet]. Available at: https://myvolontery.com.ua/toolkit.

War: a pharmacist (2022). The realities of today/Війна: фармацевт, реалії сьоГодення | Щотижневик АШТЕКА. Shchotyzhnevyk Apteka [Internet]. Available at: https://www.apteka.ua/article/646337.

zakon.rada.gov (2022). Order of the Ministry of Health of Ukraine dated August 5, 2020 No. 1801 "On the approval of the Procedure for the termination of the validity of the registration certificate for a medicinal product and the Regulation. Available at: https://zakon.rada.gov.ua/laws/show/z1062-20#Text.

Zanuda, A. Dollar at 36.6 and new restrictions on operations abroad. Why did the NBU made changes?/Долар Що 36, 6. Available at: https://www.bbc.com/ukrainian/news-62254553.

Zhdan, V. M., Holovanova, I. A., Khorosh, M. V., Bielikova, I. V., and Lyakhova, N. A. (2022). Analysis of the legislative activity of the Ministry of health of Ukraine in the conditions of the Russian-Ukrainian war in. Available at: https://pubmed.ncbi.nlm.nih.gov/35907211/.

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Development and validation of a new non-disease-specific survey tool to assess self-reported adherence to medication

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Background: Patients' non-adherence to medication affects both patients themselves and healthcare systems. Consequences include higher mortality, worsening of disease, patient injuries, and increased healthcare costs. Many existing survey tools for assessing adherence are linked to specific diseases and assessing medication-taking behavior or identifying barriers or beliefs. This study aimed to develop and validate a new non-disease-specific survey tool to assess self-reported medication-taking behavior, barriers, and beliefs in order to quantify the causes of non-adherence and measure adherence.

Methods: The survey tool was developed after literature searches and pilot testing. Validation was conducted by assessing the psychometric properties of content, construct, reliability, and feasibility. Content validity was assessed by subject matter experts and construct validity by performing exploratory factor analysis. Reliability assessment was performed by calculating internal consistency, Cronbach's alpha and test/retest reliability, intraclass correlation coefficient (ICC), and standard error of measurement (SEm). A receiver operating characteristic (ROC) curve and the Lui method were used to calculate the statistical cut-off score for good *versus* poor adherence. Survey responses from Norwegian medication users over 18 years recruited *via* social media were used for the factor analysis and Cronbach's alpha.

Results: The final survey tool contains 37 causes of non-adherence connected to medication-taking behavior and barriers to adherence and beliefs associated with adherence. The overall result for all 37 items demonstrated reliable internal consistency, Cronbach's alpha = 0.91. The factor analysis identified ten latent variables for 29 items, explaining 61.7% of the variance. Seven of the latent variables showed reliable internal consistency: *medication fear and lack of effect*, *conditional practical issues*, *pregnancy/breastfeeding*, *information issues*, *needlessness*, *lifestyle*, and *avoiding stigmatization* (Cronbach's alpha = 0.72–0.86). *Shortage* showed low internal consistency (Cronbach's alpha = 0.59). *Impact issues* and *personal practical issues* showed poor internal consistency (Cronbach's alpha = 0.51 and 0.48, respectively). The test/retest reliability ICC = 0.89 and SEm = 1.11,

indicating good reliability. The statistical cut-off score for good *versus* poor adherence was 10, but the clinical cut-off score was found to be 2.

Conclusion: This survey tool, OMAS-37 (OsloMet Adherence to medication Survey tool, 37 items), demonstrated to be a valid and reliable instrument for assessing adherence. Further studies will examine the ability of the tool for measuring adherence enhancing effect following interventions.

KEYWORDS

non-adherence, measure adherence, assess adherence, patient compliance, reliability, OMAS-37, factor analysis, questionnaire

1 Introduction

Adherence to medications is the process by which patients take their medication as prescribed, comprised of initiation, implementation, and discontinuation (Vrijens et al., 2012). "Increasing the effectiveness of adherence interventions may have a far greater impact on the health of the population than any improvement in specific medical treatments" is an important statement in an influential WHO report from 2003 on medication adherence (Sabaté, 2003). The importance of adherence interventions on patients' health is still most applicable as failure to adhere is a serious problem affecting both patients and healthcare systems by resulting in higher mortality, worsening of disease, more patient injuries, and increased healthcare costs (Sokol et al., 2005; Cutler et al., 2018; Khan and Socha-Dietrich, 2018; Holbrook et al., 2021; Lu et al., 2021; Majeed et al., 2021; Nymoen et al., 2022).

Adherence rates have an average of around 50% but range widely from 0% to more than 100% (Nieuwlaat et al., 2014; Horne et al., 2019). In 2018, the Organization for Economic Co-operation and Development (OECD) reported that estimates from 2010 suggest non-adherence annually contributes to nearly 2,00,000 premature deaths and costs the European government EUR 125 billion in excess healthcare (Rabia Khan, 2018). In 2004, Norwegian healthcare costs due to incorrect and ineffective medication usage were estimated to be EUR 500 million (Report No. 18 to the Storting, 2004–2005) in a population of 4.6 million people. However, the economic impact of low adherence to medication is difficult to assess due to current research being limited and of mixed quality (Cutler et al., 2018).

The many reasons for non-adherence are thoroughly described in the literature, often showcasing the complexity of adherence behavior (Sabaté, 2003; Hugtenburg et al., 2013; Gast and Mathes, 2019; Horne et al., 2019). One example is the earlier mentioned WHO report, where adherence is viewed as a multidimensional phenomenon determined by the interplay between five different dimensions: patient-related factors, therapy-related factors, social/economic factors, condition-related factors, and health care team and system-related factors (Sabaté, 2003).

It is also widely recognized that non-adherence can be both intentional, e.g., medication deliberately not being taken and/or unintentional, e.g., medication prevented from being taken by barriers beyond one's own control. Horne et al. have, in this context, displayed the Perceptions and Practicalities Approach (PAPA) (Horne et al., 2019). In PAPA, intentional causes of non-adherence are linked to motivation which depends upon perceptions, e.g., beliefs, emotions, and preferences. Unintentional causes of non-adherence are linked to ability which depends upon practicalities, e.g., capacity, resources, and opportunities. PAPA indicates that adherence is essentially dependent upon individual motivation and ability, which could vary both within and between individuals for different medications and/or timelines. Thus, mapping and quantifying causes for non-adherence are essential in the process of tailoring interventions to enhance adherence.

Patients' self-reported measures on medication adherence behavior is one of the most common approaches to assess medication adherence (Simoni et al., 2006; Velligan et al., 2006; Paschal et al., 2008; Kelli Stidham Hall et al., 2010; Garfield et al., 2011; Gonzalez and Schneider, 2011; Stirratt et al., 2015). Self-reporting survey tools are often validated by comparing survey data with invasive methods like monitoring drug concentration, blood sugar, blood pressure, and/or cholesterol (Simoni et al., 2006; Velligan et al., 2006; Paschal et al., 2008; Kelli Stidham Hall et al., 2010; Gonzalez and Schneider, 2011). Assessing self-reporting against adequate clinical measurements opens the possibility of predicting clinical outcomes by measuring adherence behavior. Hence, existing self-reporting survey tools are, to a great extent, connected to specific medications and/or medical diagnoses, although there are several different survey tools independent of medication/medical diagnoses (Garfield et al., 2011; Nguyen et al., 2013; Stirratt et al., 2015; Chan et al., 2021) which can be useful, e.g., when assessing non-adherence in general populations. The survey tools differ not only in number of items but, more importantly, also in how these tools map non-adherence. The comprehensive systematic review by Nguyen et al. (2013), which contains the most

used validated self-report adherence scales, and the complemented study by Stirratt et al. (2015) are examples of literature showing how adherence scales are focusing either on medication-taking behavior and/or barriers to adherence and/or beliefs associated with adherence. As the PAPA indicates, tailoring interventions are necessary to increase the effectiveness of adherence interventions. One size does not fit all, and adequate knowledge about the causes for non-adherence is vital for tailoring interventions. However, finding an elaborating survey tool that focuses on both medication-taking behavior and barriers to adherence and beliefs associated with adherence has been proven difficult.

Therefore, the aim of this study was to develop and validate a new non-commercial survey tool independent of patients' medication type and/or medical diagnosis in order to assess self-reported medication-taking behavior, barriers, and beliefs. The overall goal was to make available an adequate tool for measuring adherence and quantifying causes of non-adherence in various patient groups.

2 Methods

2.1 Development of an online survey tool and questionnaire

The survey tool items are causes of medication-taking behavior, barriers, and beliefs that were identified by literature searches in national (Oria, The Norwegian Electronic Health Library, Norwegian subject libraries, and The Great Norwegian Encyclopedia) and international (PubMed, Google Scholar, and Google) databases. Important search terms were *adherence*, *compliance*, *concordance*, *questionnaire*, *medication*, *self-report*, *patient*, and equivalent terms in Norwegian. The search terms were chosen based on being relevant keywords for existing survey tools for medication adherence.

General recommendations for developing questionnaires were used in the planning and developing phases of the questionnaire (Robson, 2002; Eberhard-Gran and Winther, 2017).

After identifying the items, the items were divided into the five aforementioned WHO dimensions of adherence (Sabaté, 2003). For each item, the medication user was asked "*how often do you not follow the recommendations from your doctor regarding the use of your medication because of* (item)?" Each item was then to be scored on a 4-point Likert scale: "very often"—"often"—"sometimes"—"rarely/never". The survey tool was built into a questionnaire in Nettskjema (2022). Nettskjema belongs to The University of Oslo and is one of the safest and most used solutions for online data collection for research in Norway.

All of the questions had to be answered to proceed further in the questionnaire, leaving no missing values for completed responses.

Inclusion criteria were Norwegian residents over the age of 18 who had been using medication prescribed and/or recommended by a doctor in the last 12 months. Responders who stated that they were under 18 years, that they had not been using one or more medications prescribed or recommended by a doctor in the last 12 months, or that they were not living in Norway were directed out of the questionnaire before answering the survey tool items.

Responders were also asked demographic questions like gender and education-and to choose from a list of diagnoses to provide information on the ailments for which they had been medicated in the course of the last 12 months. The responders were, in addition, asked a question about their own perception of their overall adherence (see Section 2.4).

Feedback was given on content for the different versions of the survey tool *via* video calls and one-to-one meetings with members of an adherence expert team until there were no more comments from the team.

A few adjustments were made after content validation and feedback given in feasibility pilots (see Section 2.3). A technical verification was performed where the logic of the order of the items was tested after the final version of the survey tool.

2.2 Recruitment

For the feasibility pilots, acquaintances of the researchers were invited to participate by answering the online questionnaire and afterward giving feedback on the availability and usability of the online solution, time taken to answer, and clarity of questions and providing suggestions for causes of non-adherence which was not already included.

For the construct validity and internal consistency, Data used were collected as a part of an online survey on medication use. Moderators of several large Norwegian Facebook groups were contacted, and six group moderators replied with consent. An invitation to participate with general information about the study and an electronic link to the questionnaire was then posted on these six Facebook groups. The general invitation addressed group members over 18 years who were using/had been using medication for the last 12 months. To participate, the group members were to use the electronic link and would, in this way, be anonymous. In addition to the survey respondents, data from two pilot studies (not the feasibility pilots) in 2021 using the online questionnaire in Nettskjema were added for the construct validation and internal consistency.

For test/retest reliability: Respondents were recruited from three medium-sized Facebook groups with an invitation

TABLE 1 Validation strategy for the survey tool.

Validation strategy

Strategies	Methods	n
I FEASIBILITY	Pilots	39
II VALIDITY		
Theoretical construct content validity	Subject matter experts	
Empirical construct validity	Exploratory factor analysis	857
III RELIABILITY		
Internal consistency	Cronbach's alpha (reliability coefficient)	857
Test/retest reliability	Intraclass correlation coefficient and standard error of measurement	20

to participate anonymously in the test/retest of the questionnaire.

2.3 Validation strategy

To make sure survey data are trustworthy, survey tools must be validated—not solely through theoretical constructs but also through empirical constructs. Validity, reliability, and feasibility are important elements of validation. Validity expresses the extent to which an instrument measures what it is designed to measure, and reliability expresses the extent to which outcomes are consistent on repeated measures (Kimberlin and Winterstein, 2008; García de Yébenes Prous et al., 2009; Bolarinwa, 2015). Poor feasibility will influence the response rate and/or interpretation/scoring of survey tool items (García de Yébenes Prous et al., 2009).

Choosing a validation strategy depends on what to measure and if the data fit the assumptions for the selected validation methods (García de Yébenes Prous et al., 2009; Bolarinwa, 2015; McNeish, 2018). The chosen validation strategy is shown in Table 1. Each validation method required an independent population except for construct validity and internal consistency where the same population is used. The population sizes are shown in Table 1 and further explained in the Results-section. Feasibility of the results was tested by piloting.

Content validity, i.e., to what extent the instrument includes most of the dimensions of the concept being studied (García de Yébenes Prous et al., 2009), was tested by feedback on the online survey tool from the earlier-mentioned adherence expert team on language clarity (wording), completeness, item relevance, and (if any) additional causes of non-adherence.

For construct validity, the exploratory factor analysis (EFA) method of principal axis factoring (PAF) with oblique rotation was performed. Construct validity is to what extent the trait or theory of the phenomenon/concept that the instrument is intended to measure is measured (Bolarinwa, 2015).

For test/retest reliability (consistency across time), the intraclass correlation coefficient (ICC) was calculated for a test/retest group using the survey tool online.

Standard error of measurement (SEm) was calculated using the following formula (Portney and Watkins, 2015): SEm = $SD_{Test}\sqrt{(1\text{-ICC})}$ SDTest is the standard deviation of the test.

2.4 Measurement of adherence and cut-off score

For each survey tool item, the respondent was asked the following question: "*How often do you not follow the recommendations from your doctor regarding the use of your medication because of* [item]?" For measurement of the adherence score, string value was converted to numeric value: "very often" = 3, "often" = 2, "sometimes" = 1, and rarely/never" = 0, making the total minimum adherence score 0 and maximum adherence score 111.

In order to identify whether the calculated adherence score relates to what the patients believe about their overall adherence, a self-reported adherence question was added to the questionnaire: "*In total, to what extent do you believe you follow the recommendations from your doctor regarding the use of your medication*?" For this anchor question, respondents were to score on a 4-point Likert scale. String value was converted into numeric value for measurement of score: "to a very limited extent" = 4, "to a limited extent" = 3, "to a large extent" = 2, and "to a very large extent" = 1. Thus, indicating that poor adherence would give a higher score, which is in line with the calculated adherence score.

Given a significant correlation, a receiver operating characteristic (ROC) curve was to be made to find the statistical cut-off score for adherence. The ROC curve is a graphical plot illustrating the sensitivity (true positive rate) against the 1-specificity (false positive rate) for various threshold settings—here, the threshold settings being the adherence scores. In order to make the ROC curve, the

TABLE 2 Demographics of the survey group and test–retest populations.

Demographic profile

Population		Survey group, n = 857 (100%)	Test–retest, n = 20 (100%)
Age		Range: 18–89	Range: 26–68
	Median	50	51
	Mean	48.3	51.5
	SD Mean	15.3	11
Gender [n (%)]	Female	776 (90.5)	13 (65)
	Male	75 (8.8)	7 (35)
	N/A	6 (0.7)	
Education level [n (%)]	No education	7 (0.8)	
	Primary school only	84 (9.8)	
	High school and the like	446 (52)	8 (40)
	Bachelor's degree and the like	206 (24)	9 (45)
	Master's degree and the like	101 (11.8)	3 (15)
	N/A	13 (1.5)	
Chosen diagnosis groups for medication used in the last 12 months [n (%)], multiple choice			
Pain		387 (45.2)	5 (25)
Allergies		309 (36.1)	5 (25)
Cardiovascular diseases		270 (31.5)	6 (30)
Musculoskeletal disorders		253 (29.5)	4 (20)
Sleep-related disorders		223 (26)	3 (15)
Gastrointestinal disorders		207 (24.2)	2 (10)
Psychological disorders		165 (19.3)	1
Lower respiratory tract diseases		152 (17.7)	2 (10)
Endocrine diseases		131 (15.3)	5 (25)
Dermatological disorders		120 (14)	1 (5)
Gynecological disorders and contraception		98 (11.4)	1 (5)
Upper respiratory tract and otorhinolaryngologic disorders		93 (10.9)	2 (10)
Fever, nausea, vomiting, dizziness, travel and motion sickness, hiccups, restless legs, leg cramps, etc.		86 (10)	1 (5)
Infectious diseases		80 (9.3)	
Immune system malfunctions and transplants		69 (8.1)	
Other		68 (7.9)	
Nervous system diseases		39 (4.6)	1 (5)
Kidney and urinary tract disorders		35 (4.1)	1 (5)
Blood-related disorders		34 (4)	
Palliative care		31 (3.6)	
Eye disorders and diseases		24 (2.8)	
Cancer		18 (2.1)	1 (5)
Obstetrical disorders		10 (1.2)	
Prostate problems		4 (0.5)	1 (5)
Substance abuse problems		2 (0.2)	
Do not know/do not want to tell/not applicable		2 (0.2)	

TABLE 3 Kaiser-Meyer-Olkin (KMO) values for each survey item.

Items	KMO
All 37 items in total	0.89
You do not want to be sick, and taking medication is a reminder of this	0.95
You are fearing getting addicted to the medication	0.95
Financial reasons	0.93
You have used the same type of medication before without them having good/satisfactory effect	0.93
You are using many drugs simultaneously	0.92
You are not feeling any effect of the medication	0.92
You are, in principle, against medication treatment	0.92
You are feeling more sick taking them	0.91
You are feeling stigmatized or made sick by having to use medication	0.90
You cannot stand taking medication	0.90
You reckon it does not matter using the medication or not	0.90
You do not feel sick	0.90
You prefer alternative treatment	0.89
You are feeling better	0.89
You are fearing adverse effects	0.89
You are feeling clever when using less than recommended by the doctor	0.89
You feel medications are harmful, toxic and/or you do not tolerant them	0.88
It does not suit your lifestyle to use medication	0.88
You do not want others to know that you are using medication	0.87
Little or no information from the doctor, pharmacy, or other health personnel on how to use your medication	0.87
You do not want to go to the pharmacy due to the corona pandemic	0.87
You have difficulties in taking medication due to specific instructions (like with and without food, in an upright position *etc.*)	0.86
Need of driving a car	0.86
You have difficulties in taking medication at specific hours	0.85
Practical reasons (such as difficulty in opening the packaging, pushing tablets out of the blister packaging, or splitting/crushing the tablet)	0.85
The medications were sold out or not available at the pharmacy	0.85
Misunderstandings related to generic medication (medication with the same content but from different manufacturers)	0.84
You are being influenced by media, the internet, friends, family, and/or others	0.83
You forgot to take the medication	0.82
You are out of medication	0.82
Ethical or religious reasons	0.79
You have difficulties in accessing a pharmacy	0.75
Disabilities (like difficulty in swallowing the tablet or impaired vision making finding the right medication difficult)	0.74
You forgot how to use them	0.69
You did not understand what the doctor or pharmacy staff meant	0.69
You are breastfeeding	0.63
You are pregnant	0.61

anchor question scores were dichotomized into whether patients believe they follow the recommendations or not: "to a large extent" and "to a very large extent" = following recommendations = 0, "to a limited extent" and "to a very limited extent" = not following recommendations = 1.

Based on the ROC curve, the Liu method was to be used to calculate the empirical optimal cut point by maximizing the product of the sensitivity and specificity. The empirical optimal cut point would be the statistical cut-off score between good adherence and poor adherence.

All data were analyzed by SPSS Statistics (RRID: SCR_016479) version 27. Empirical optimal cut point was calculated in Stata (RRID:SCR_012763) version 17. The chosen significance level alpha was 0.05.

TABLE 4 Validation values for factors and items.

Items	Eigenvalue	% of variance	Cronbach's α	Corrected item–total correlation–all items	Corrected item–total correlation–interfactoral
All 37 items			0.91		
Factor 1: Medication fear and lack of effect	9.06	24.48	0.78		
You are fearing getting adverse effects				0.63	0.63
You feel medications are harmful, toxic and/or you do not tolerant them				0.69	0.66
You have used the same type of medication before without them having good/satisfactory effect				0.58	0.53
You are not feeling any effect of the medication				0.61	0.54
Factor 2: Conditional practicalities	2.33	6.32	0.72		
You have difficulties taking the medication at specific hours				0.51	0.69
You have difficulties taking medication due to specific instructions (like with and without food, in an upright position *etc.*)				0.47	0.52
You forgot				0.35	0.46
Factor 3: Pregnancy/breastfeeding	1.89	5.11	0.86		
You are pregnant				0.21	0.75
You are breastfeeding				0.24	0.75
Factor 4: Information issues	1.76	4.76	0.78		
You forgot how to use them				0.25	0.64
You did not understand what the doctor or pharmacy staff meant				0.27	0.64
Factor 5: Needlessness	1.63	4.41	0.74		
You reckon it does not matter using the medication or not				0.46	0.49
You are feeling better				0.55	0.64
You do not feel sick				0.55	0.59
Factor 6: Shortage	1.49	4.03	0.58		
Financial reasons				0.51	0.38
The medications were sold out or not available at the pharmacy				0.28	0.39
You are out of medication				0.32	0.42
Factor 7: Avoiding stigmatization	1.32	3.57	0.74		
You do not want others to know that you are using medication				0.48	0.57
You are feeling stigmatized or made sick by having to use medication				0.55	0.62
You are feeling clever when using less than recommended by the doctor				0.45	0.42
You do not want to be sick, and taking medication is a reminder of this				0.60	0.54
Factor 8: Lifestyle	1.18	3.19	0.72		
It does not suit your lifestyle to use medication				0.49	0.59
You prefer alternative treatment				0.49	0.60
You are, in principle, against medication treatment				0.53	0.60
Ethical or religious reasons				0.31	0.38
Factor 9: Impact issues	1.15	3.10	0.51		
You are being influenced by media, the internet, friends, family, and/or others				0.31	0.35
You have difficulties accessing a pharmacy				0.25	0.35
Factor 10: Personal practicalities	1.02	2.75	0.48		
Practical reasons (such as difficulty in opening the packaging, pushing tablets out of the blister packaging, or splitting/crushing the tablet)				0.37	0.33

(Continued on following page)

TABLE 4 (*Continued*) Validation values for factors and items.

Items	Eigenvalue	% of variance	Cronbach's α	Corrected item–total correlation–all items	Corrected item–total correlation–interfactoral
Disabilities (such as difficulty in swallowing the tablet or impaired vision making finding the right medication difficult)				0.20	0.33
Items with loadings ≤0.4					
You do not want to go to the pharmacy due to the corona pandemic				0.36	
Need of driving a car				0.31	
You are fearing getting addicted to the medication				0.60	
You are using many drugs simultaneously				0.43	
You are feeling more sick taking them				0.58	
You cannot stand taking medication				0.59	
Little or no information from the doctor, pharmacy, or other health personnel on how to use your medication				0.43	
Misunderstandings related to generic medication (medication with the same content but from different manufacturers)				0.34	

3 Results

3.1 Feasibility

Data from three pilots were used for feasibility. The respondents were recruited by three different student groups at Oslo Metropolitan University (OsloMet), and the data were collected in 2021. The three pilots gave complete data from (12 + 15 + 12) 39 online respondents. The respondents first completed the survey tool online and were afterward interviewed by the researchers for feedback on the availability and usability of the online solution, time taken to answer, clarity of questions, and providing suggestions for causes of non-adherence which were not already included. In general, the tested survey tool was feasible, but some feedback was given, especially on the length of some of the items (questions).

The developed survey tool was included in a questionnaire together with sociodemographic and health-related questions. The final questionnaire showed an average responding time of about 10 min for the feasibility pilots.

Just under 80% of the 857 respondents in the survey population used less than 10 min to answer the questionnaire, and over 90% used less than 15 min. Time was measured from the opening of the survey to submitting the survey.

3.2 Content validity

Feedback on content validity was given for different adjusted versions of the survey tool *via* video calls and one-to-one meetings with the adherence expert team members until there were no more comments from the adherence expert team. Feedback on content from the feasibility pilots was consecutively included in the adjusted versions of the survey tool.

After the feasibility pilots and the content validation by the adherence expert team, the survey tool ended up containing 37 items connected to medication-taking behavior and barriers to adherence and beliefs associated with adherence.

3.3 Construct validity

Completed data from two pilots (n = 121) and the survey group (n = 737) were received, leaving a total of 858 respondents. One respondent scored an unrealistically full score on all 37 items and was thus removed. The calculations were conducted on data from 857 respondents, further referred to as the survey group. Data from the survey group were collected from January to March 2021. The pilot data were collected during the spring of 2021. The demographics of the respondents in the survey group are shown in Table 2.

Pearson correlation was calculated to measure the strength of the linear variables as linear correlation is an assumption for factor analysis. 1,230 of the 1,332 variables showed a significant ($p \leq 0.05$) linear correlation.

Kaiser–Meyer–Olikin (KMO) measure of sampling adequacy was performed to see if the correlations between the variables were fit for factor analysis. KMO for all items in total was 0.89. A total of 30 items had KMO over 0.8, and seven items had KMO

TABLE 5 Pattern matrix for PAF extraction, oblimin with Kaiser normalization rotation and loading > +/−0.4.

Items	Factors									
	1 Medication fear and lack of effect	2 Conditional practicalities	3 Pregnancy/ breastfeeding	4 Information issues	5 Needlessness	6 Shortage	7 Avoiding stigmatization	8 Lifestyle	9 Impact issues	10 Personal Practicalities
You feel medications are harmful, toxic and/or you do not tolerant them	0.62									
You are fearing adverse effects	0.47									
You have used the same type of medication before without them having good/satisfactory effect	0.42									
You are not feeling any effect of the medication	0.41									
You have difficulties taking the medication at specific hours		0.72								
You have difficulties taking medication due to specific instructions (such as with and without food, in an upright position, *etc.*)		0.54								
You forgot		0.52								
You are breastfeeding			0.96							
You are pregnant			0.81							
You did not understand what the doctor or pharmacy staff meant				0.80						
You forgot how to use them				0.76						
You are feeling better					0.74					
You do not feel sick					0.65					
You reckon it does not matter using the medication or not					0.51					
You are out of medication						0.51				
The medications were sold out or not available at the pharmacy						0.50				
Financial reasons						0.46				
You do not want others to know that you are using medication							0.68			
You are feeling stigmatized or made sick by having to use medication							0.57			
You do not want to be sick, and taking medication is a reminder of this							0.41			
You are feeling clever when using less than recommended by the doctor							0.40			
It does not suit your lifestyle to use medication								0.66		
Ethical or religious reasons								0.57		
You are, in principle, against medication treatment								0.46		
You prefer alternative treatment								0.46		
You are being influenced by media, the internet, friends, family, and/or others									0.72	
You have difficulties accessing a pharmacy									0.43	
Practical reasons (like difficulty in opening the packaging, pushing tablets out of the blister packaging, or splitting/ crushing the tablet)										0.58
Disabilities (such as difficulty in swallowing the tablet or impaired vision making finding the right medication difficult)										0.54

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between 0.79–0.61 (see Table 3). Since the KMO measure for all of the items was over 0.6, the data were fit for factor analysis. This is supported by Bartlett's test of sphericity being significant ($p \leq 0.05$).

EFA was performed to find clusters of inter-correlated variables, so-called latent variables or factors. PAF with oblique (Oblimin) rotation extracted ten latent variables with eigenvalue >1, explaining a total of 61.7% of the variance (see Table 4). An acceptable variance explained for the construct to be valid is said to be more than 60% in factor analysis (Hair, 2014). Table 5 shows the pattern matrix for the ten latent factors with 29 associated item-loadings > +/- 0.4. The remaining eight of the 37 items did not show loadings > +/- 0.4. Rotation converged in 14 iterations.

Factor 1 encompasses almost 25% of the total variance and includes four items, where two items describe fear of medication outcomes (adverse effects and non-tolerance) and two items describe lack of effect. See Table 4 for % of variances. Factor 2 encompasses over 6% of the variance containing three items regarding conditional practicalities like forgetting and difficulties taking the medication due to timing and/or specific instructions. Factor 3 encompasses 5.1% of the variance and includes the two items directly connected to pregnancy and breastfeeding. Factors 4–10 encompass variances between 4.8 and 2.8%. Factor 4 connects the information issues of not understanding what the doctor/pharmacy staff meant and forgetting how to use the medication. Factor 5 includes three items describing no need for medication, like feeling better, not feeling sick, and thinking that it does not matter whether the medication is used or not. The three items on Factor 6 involve shortage issues like having no medication left, lack of availability in the pharmacy, and financial reasons. The four items of factor 7 are connected to wanting to avoid stigmatization. Two items are about not wanting to be sick, where medication is a reminder that stigmatizes, and two items are about feeling clever when taking less than prescribed and not wanting others to know about the medication. Factor 8 involves four lifestyle issues: ethical/religious reasons, preferring alternative treatments, being in principle against medication treatment, and belief that taking medication does not suit the lifestyle. Factor 9 connects the impact of being influenced by media, the internet, friends, family, and others to the difficulties of accessing a pharmacy. Factor 10 is the last factor and embraces two items regarding personal practicalities of handling the medication.

3.4 Reliability

3.4.1 Internal consistency

The data from the 857 respondents in the survey group used for construct validity were also used for internal consistency.

Cronbach's α was calculated for internal consistency. The overall result for all 37 items in total demonstrated a very reliable internal consistency with Cronbach's α 0.91 (See Table 4). Factor 1–5 and 7–8 showed reliable internal consistency with Cronbach's α between 0.72–0.86. Factor 6 showed low reliable internal consistency with Cronbach's $\alpha = 0.58$, and Factors 9 and 10 had poor reliable consistency with Cronbach's $\alpha = 0.51$ and 0.48, respectively. Although factors 6, 9, and 10 *per se* showed low/poor reliability, removal of either of the factor items had no particular impact on the overall Cronbach's α of 0.91.

Exploratory factor analysis was chosen to explore latent variables and not to remove eventual redundant items. Eight of the items had loadings < +/− 0.4 and were thus not included in the factors. Removal of any of these items had no particular impact on the overall Cronbach's α of 0.91.

The corrected item–total correlation values for the items indicate overall good discrimination between all 37 items and between the items in each factor as all values exceeded 0.2 (See Table 4).

3.4.2 Test/retest reliability

Data were collected during the first half of 2022, with 14 days between publishing the web link for the test and the retest.

A total of 47 responded to the test, and 22 of these responded to the retest. Two were removed due to answering the test and the retest being too close apart (<7 days), leaving 20 respondents and a response rate of 42.5%. The 20 respondents answered the test and the retest with a median interval of 13 days apart (range: 8–24 days).

The average measure was ICC = 0.89 and SEm = 1.11, both indicating good reliability (Matheson, 2019). ICC was calculated using a two-way random model and absolute agreement, and SEm using the test standard deviation (SD).

3.4.3 Measurement of adherence and cut-off score

Data from three of the 857 respondents were excluded as they answered "Do not know/not applicable/do not want to answer" on the anchor question, leaving n = 854. The linear regression analysis on the anchor question toward the adherence scores showed a significant correlation ($p \leq 0.05$) between the two measures of adherence with an acceptable R-squared = 0.24.

The dichotomization of the anchor question into whether the patients believe they follow the recommendations or not resulted in n = 820 for the group that believes they follow (values for "to a large extent" and "to a very large extent") and n = 34 for the group that does not believe they follow (values for "to a small extent" and "to a very small extent"). The ROC curve based on this dichotomization of the anchor question is shown in Figure 1. The area under the curve (AUC) shows a significant ($p \leq 0.05$) high classification accuracy value of 0.86. The empirical optimal cut point for the adherence score scale was 10 (sensitivity = 0.82,

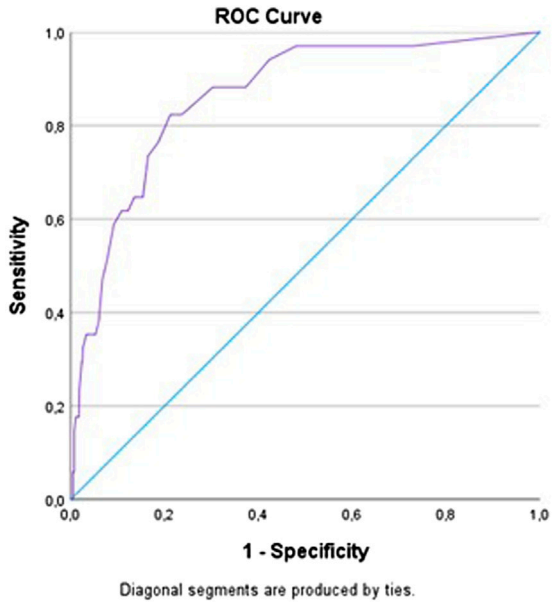

FIGURE 1
ROC curve for anchor question *versus* adherence score. The ROC curve is produced in SPSS.

specificity = 0.79, and AUC = 0.81), leaving the statistical cut-off score for adherence to be 10.

4 Discussion

This study was conducted to develop a survey tool that measures adherence and quantifies causes of non-adherence independently of patients' medication type and/or medical diagnosis and to evaluate the psychometric properties and factor structure of the survey tool. As mentioned in Section 1, it has been proven difficult to find an elaborating survey tool that focuses on both medication-taking behavior and barriers to adherence and beliefs associated with adherence. The importance of assessing behavior, barriers, and beliefs is imperative when tailoring interventions for non-adherence and is the main rationale for developing this survey tool.

4.1 Development and validation

The overall result for all 37 items of the survey tool demonstrated a very reliable internal consistency with Cronbach's α 0.91. Cronbach's α is sensitive to the number of items, and some literature suggest that α should not exceed 0.9. If α exceeds 0.9, it may suggest that some items are testing the same but from a different angle and should be removed (Tavakol and Dennick, 2011). In our study, the α is approximately 0.9, the removal of any items had no particular impact on the overall α, and the corrected item–total correlation values for all of the 37 items indicated good discrimination. When quantifying causes of non-adherence, it is important to cover all well-known issues and the calculations on internal consistency support keeping all of the 37 items.

EFA was chosen for construct validity to explore underlying factor structures. PAF extracted ten latent factors with eigenvalue >1. Most of the latent factor dimensions are all well-known and showed reliable internal consistency: *conditional practicalities* (Factor 2), *being pregnant/breastfeeding* (Factor 3), *needlessness for medication* (Factor 5), *wanting to avoid stigmatization* (Factor 7), and *lifestyle issues* (Factor 8). However, the latent dimension of *medication fear combined with lack of effect* (Factor 1) was interesting and should be further investigated. It is also interesting to unravel that it is not necessarily lack of information on how to use medication that makes people forget how to use them, but rather that they do not understand the explanations from the doctor or pharmacy staff, *information issues* (Factor 4). The *shortage* (Factor 6) showed low reliable internal consistency even though the combination of issues could be expected, and removal of any of the three items did not improve the α. The *impact issue* (Factor 9), which is a combination of being influenced by media, the internet, friends, family, and/or others, and difficulties in accessing a pharmacy was unforeseen, and the poor reliable consistency was to be expected. The *personal practicalities* (Factor 10) combination also showed poor reliable consistency even though the combination was expected. This could be explained by the low number of respondents choosing options other than "rarely/ never" for these two items (56 and 28, respectively).

The survey tool items are divided into the five WHO dimensions (Sabaté, 2003): patient-related factors, therapy-related factors, social/economic factors, condition-related factors, and health system/HCT factors. There were, however, some difficulties in placing the 37 items between the five dimensions as several of the items could fit into more than one dimension. Exchanging the WHO dimensions with latent variable dimensions from the performed EFA would be interesting to investigate further.

The average measure of ICC and SEm indicated both good test/retest reliability. The 20 respondents replied to the test and retest with an interval of 8–24 days with a median interval of 13 days apart. In the literature, there is a wide range of administration intervals used in test/retesting depending, e.g., upon assessment of the stability of the condition involved and complexity of the patient-reported outcome (Quadri et al., 2013). For this study, the medication condition could change over time, and the time frame should not be too long. The interval should, however, be long enough to not remember the test answers when taking the retest. It was thus decided to analyze the respondents who had replied between 1–4 weeks. Although the average measure of ICC and SEm showed good test/retest reliability the sample size of 20 might be a bit low (Terwee et al., 2012).

4.2 Measurement of adherence and cut-off score

The survey tool aims to measure adherence. For every item, the respondent is to score "very often"—"often"—"sometimes"—"rarely/never" on the question "*How often do you not follow the recommendations from your doctor regarding the use of your medication because of [item]?*" Every item will weigh equal as the clinical outcome of the non-adherence will be the same, i.e., if the respondent scores "very often," it does not matter if not taking the medication very often is because of forgetting to take the medication or being influenced by others *etc*. But not every item is of relevance for everyone, e.g., items regarding pregnancy and breastfeeding. This is why the scores are converted from string to numeric value, and adherence is measured by the total numeric adherence score.

Clinically it would be considered as poor adherence if the patient "often" (2 points) or "very often" (3 points) does not follow the recommendations for one reason, and it could also be considered as poor adherence if the patient "sometimes" (1 point) does not follow the recommendations for several reasons. This indicates that an adherence score ≥2 could be considered poor adherence, whereas an adherence score of 1 or 0 could be considered good adherence.

The correlation between the adherence score and the anchor question *"in total, to what extent do you believe you follow the recommendations from your doctor regarding the use of your medication*?" were significant ($p \leq 0.05$), and the AUC of the ROC curve showed high classification accuracy. If one considers the anchor question to be the truth (or the respondent's claimed truth), this demonstrates that the adherence score is a good measure of the degree of adherence. The statistical cut-off score for adherence was calculated to be 10 based on ROC. Even though the anchor question and the adherence score showed a significant correlation, the statistical calculated cut-off score for adherence could not be used clinically. The respondents that scored between the clinical cut-off for adherence of two and the statistical calculated cut-off score of 10 believed they were following the doctor's recommendation although they, in fact, did not, showing an overestimation of adherence score. This supports the knowledge of self-reporting as subject to social-desirability biases (Kimberlin and Winterstein, 2008; Stirratt et al., 2015).

4.3 Limitations

This study used the 4-point Likert rating scale for both the adherence score questions and the anchor question. Much research has been carried out without reaching an agreement regarding finding the optimal number of response categories for Likert scales in order to maximize the scales' psychometric properties (Chang, 1994; Xu and Leung, 2018; Taherdoost, 2019). The 4-point Likert scale is a forced scale because of the lack of neutral options and was chosen to force the respondent to form an opinion of the items. Larger numbers of even Likert scales could have been chosen, but this could go beyond the discrimination abilities of respondents and create indistinct measurements. However, it has been indicated that the 4-point scale could have higher skewness and lower loadings than a larger number of Likert scales (Xu and Leung, 2018).

Self-reporting is subject to challenges with social-desirability biases (Kimberlin and Winterstein, 2008; Stirratt et al., 2015), meaning that respondents are answering in a way where they are well-presented in the eyes of others which does not necessarily reflect the reality. For each survey tool item, the respondent was asked: "*how often do you not follow the recommendations from your physician regarding the usage of your medication because of* [item]?" This approach in the questioning was chosen to reassure the patient from feeling shame for not adhering to medication by demonstrating various known causes for non-adherence and thus opting for a more honest scoring.

The performed validations do not include concurrent validity. Due to structural differences in sample strategy, sample size, and population, the correlated measures comparing studies can be challenging (Garfield et al., 2011). However, this should be investigated further when assessing findings after the use of this new survey tool.

For the content validation the adherence expert team did not utilize any scale measurement making the content validation process less documented and with no possibility of calculating a content validity index (CVI).

Recruitment was done *via* Facebook in an attempt to get many respondents. A systematic review from 2017 (Whitaker et al., 2017) states growing evidence for Facebook being a useful recruitment tool for health research due to, e.g., shorter recruitment period and easier to access demographics that are hard to reach. However, one limitation is internet accessibility—seniors aged 65 + being the smallest demographic group on Facebook (only 4.8%) (OMNICORE, 2022). The age distribution in our study (see Table 2) reflects this and can indicate age bias.

Another bias is that females are more likely to respond to surveys (Smith, 2008). This is also applicable to our study as 90.4% of the respondents were females (see Table 2), although Facebook is used by more males (56%) than females (44%) (OMNICORE, 2022).

There is also a bias of educated people being more likely to participate in surveys than less educated people (Smith, 2008). The survey tool was piloted and validated in the Norwegian language only. In our study, 10.6% of the responders were below upper secondary education, and 35.8% had higher education (see Table 2). Norwegian statistics from 2020 show that 24.8% of the population are below upper secondary education, and 35.3% have higher education (SSB, 2020), demonstrating that our respondents, in total, had more education than the general population in Norway.

The response rate was not possible to calculate for construct validity. The participants were recruited by Facebook groups, so it is not possible to know how many of the group members actually saw the invitation nor how many of the group members were relevant for the questionnaire (over 18 years, using medication, or had used medication for the last 12 months).

The survey tool contains three double-barred questions: *you do not want to be sick and taking medication is a reminder of this/you are feeling stigmatized or made sick by having to use medication/you feel medications are harmful, toxic and/or you do not tolerate them*. To avoid misconceptions in newer versions, these should be changed into the following: *taking medication is a reminder of being sick/you are feeling stigmatized by having to use medication/you feel medications are doing you more harm than good*.

The validated survey tool is named OMAS-37 (OsloMet Adherence to medication Survey tool, 37 items).

Conclusion

This study describes the development and validation of a self-reporting adherence survey tool (OMAS-37) where causes for non-adherence are quantified, and adherence is measured. The validated survey tool is named OMAS-37 (OsloMet Adherence to medication Survey tool, 37 items). The OMAS-37 demonstrated to be a valid and reliable instrument. The OMAS-37 is, to our knowledge, the first non-disease-specific adherence instrument developed to assess self-reported causes of medication-taking behavior, barriers, and beliefs. Further studies will examine the ability of the tool for measuring adherence enhancing effect following interventions.

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. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

RL, LH, CJ, and TK contributed substantially to the design and conception of the work. LH was involved in the data collection. RL, AP, and LH performed the analysis, and all authors were involved in the interpretation of the data. AP was the responsible statistician. RL drafted the article, and LH, AP, CJ, and TK critically revised the article. The final version of the manuscript was approved by all the authors, and all authors agree to be accountable for all aspects of the work.

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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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References

Bolarinwa, O. (2015). Principles and methods of validity and reliability testing of questionnaires used in social and health science researches. *Niger. Postgrad. Med. J.* 22, 195–201. doi:10.4103/1117-1936.173959

Chan, A., Van Dijk, L., Horne, R., Vervloet, M., and Brabers, A. (2021). Development and validation of a self-report measure of practical barriers to medication adherence: The medication practical barriers to adherence

questionnaire (MPRAQ). *Br. J. Clin. Pharmacol.* 87, 4197–4211. doi:10.1111/bcp.14744

Chang, L. (1994). A psychometric evaluation of 4-point and 6-point likert-type scales in relation to reliability and validity. *Appl. Psychol. Meas.* 18, 205–215. doi:10.1177/014662169401800302

Cutler, R. L., Fernandez-Llimos, F., Frommer, M., Benrimoj, C., and Garcia-Cardenas, V. (2018). Economic impact of medication non-adherence by disease groups: A systematic review. *BMJ Open* 8, e016982. doi:10.1136/bmjopen-2017-016982

Eberhard-Gran, M., and Winther, C. (2017). *Spørreskjema som metode : For helsefagene*. Oslo: Universitetsforl.

García De Yébenes Prous, M. J., Rodríguez Salvanés, F., and Carmona Ortells, L. (2009). Validation of questionnaires. *Reumatol. Clin.* 5, 171–177. doi:10.1016/s2173-5743(09)70115-7

Garfield, S., Clifford, S., Eliasson, L., Barber, N., and Willson, A. (2011). Suitability of measures of self-reported medication adherence for routine clinical use: A systematic review. *BMC Med. Res. Methodol.* 11, 149. doi:10.1186/1471-2288-11-149

Gast, A., and Mathes, T. (2019). Medication adherence influencing factors - an (updated) overview of systematic reviews. *Syst. Rev.* 8, 112. doi:10.1186/s13643-019-1014-8

Gonzalez, J. S., and Schneider, H. E. (2011). Methodological issues in the assessment of diabetes treatment adherence. *Curr. Diab. Rep.* 11, 472–479. doi:10.1007/s11892-011-0229-4

Hair, J. F. (2014). *Multivariate data analysis*. Harlow: Pearson.

Health System Efficiency (2021). *OECD website*. Paris, France: OECD.

Holbrook, A. M., Wang, M., Lee, M., Chen, Z., Garcia, M., Nguyen, L., et al. (2021). Cost-related medication nonadherence in Canada: A systematic review of prevalence, predictors, and clinical impact. *Syst. Rev.* 10, 11. doi:10.1186/s13643-020-01558-5

Horne, R., Cooper, V., Wileman, V., and Chan, A. (2019). Supporting adherence to medicines for long-term conditions: A perceptions and practicalities approach based on an extended common-sense model. *Eur. Psychol.* 24, 82–96. doi:10.1027/1016-9040/a000353

Hugtenburg, J. G., Timmers, L., Elders, P. J. M., Vervloet, M., and Van Dijk, L. (2013). Definitions, variants, and causes of nonadherence with medication: A challenge for tailored interventions. *Patient prefer. Adherence* 7, 675–682. doi:10.2147/PPA.S29549

Kelli Stidham Hall, K. O. C. W., Nancy, R. E. A. M. E., Carolyn, W. E. S. T. H. O. F. F., and Westhoff, C. (2010). Studying the use of oral contraception: A review of measurement approaches. *J. Womens Health* 19, 2203–2210. doi:10.1089/jwh.2010.1963

Khan, R., and Socha-Dietrich, K. (2018). *Investing in medication adherence improves health outcomes and health system efficiency*. Paris, France: OECD.

Kimberlin, C. L., and Winterstein, A. G. (2008). Validity and reliability of measurement instruments used in research. *Am. J. Health. Syst. Pharm.* 65, 2276–2284. doi:10.2146/ajhp070364

Lu, Z. K., Xiong, X., Brown, J., Horras, A., Yuan, J., and Li, M. (2021). Impact of cost-related medication nonadherence on economic burdens, productivity loss, and functional abilities: Management of cancer survivors in medicare. *Front. Pharmacol.* 12, 706289. doi:10.3389/fphar.2021.706289

Majeed, A., Rehman, M., Hussain, I., Imran, I., Saleem, M. U., Saeed, H., et al. (2021). The impact of treatment adherence on quality of life among type 2 diabetes mellitus patients – findings from a cross-sectional study. *Patient prefer. Adherence* 15, 475–481. doi:10.2147/PPA.S295012

Matheson, G. J. (2019). *We need to talk about reliability: Making better use of test-retest studies for study design and interpretation*, 5, 6918. doi:10.7717/peerj.6918*PeerJ*

Mcneish, D. (2018). Thanks coefficient alpha, we'll take it from here. *Psychol. Methods* 23, 412–433. doi:10.1037/met0000144

Nettskjema (2022). Nettskjema university of Oslo. Available: https://nettskjema.no/?lang=en (Accessed June 20, 2022 2022).

Nguyen, T. M. U., Caze, A. L., and Cottrell, N. (2013). What are validated self-report adherence scales really measuring?: A systematic review. *Br. J. Clin. Pharmacol.* 77, 427–445. doi:10.1111/bcp.12194

Nieuwlaat, R., Wilczynski, N., Navarro, T., Hobson, N., Jeffery, R., Keepanasseril, A., et al. (2014). Interventions for enhancing medication adherence. *Cochrane Database Syst. Rev.* 11, CD000011. doi:10.1002/14651858.CD000011.pub4

Nymoen, L. D., Björk, M., Flatebø, T. E., Nilsen, M., Godø, A., Øie, E., et al. (2022). Drug-related emergency department visits: Prevalence and risk factors. *Intern. Emerg. Med.* 17, 1453–1462. doi:10.1007/s11739-022-02935-9

Omnicore (2022). 63 Facebook statistics you need to know in 2022. Available: https://www.omnicoreagency.com/facebook-statistics/(Accessed June 22, 2022).

Paschal, A. M., Hawley, S. R., Romain, T. S., and Ablah, E. (2008). Measures of adherence to epilepsy treatment: Review of present practices and recommendations for future directions. *Epilepsia* 49, 1115–1122. doi:10.1111/j.1528-1167.2008.01645.x

Portney, L. G., and Watkins, M. P. (2015). *Foundations of clinical research : Applications to practice*. Philadelphia, Pa: F.A. Davis Company, 913.

Quadri, N., Wild, D., Skerritt, B., Muehlhausen, W., and O'Donohoe, P. (2013). A literature review of the variance in interval length between administrations for assessment of test retest reliability and equivalence of pro measures. *Value health* 16, A40–A41. doi:10.1016/j.jval.2013.03.230

Rabia Khan, K. S.-D. (2018). *Investing in medication adherence improves health outcomes*. Paris, France: OECD, 105.

Report No. 18 to the Storting (2004–2005). *On course towards more correct use of medicine*. Norway: white paper from Norwegian Ministry of Health and Care Services.

Robson, C. (2002). *Real world research : A resource for social scientists and practitioner-researchers*. Oxford: Blackwell.

Sabaté, E. (2003). Adherence to long-term therapies: Evidence for action - WHO. Available at: http://apps.who.int/iris/bitstream/handle/10665/42682/9241545992.pdf;jsessionid=95AAD45B8B7157327FC83AF158C7BB87?sequence=1 (Accessed June 20, 2022).

Simoni, J. M., Kurth, A. E., Pearson, C. R., Pantalone, D. W., Merrill, J. O., and Frick, P. A. (2006). Self-report measures of antiretroviral Therapy adherence: A review with recommendations for HIV research and clinical management. *AIDS Behav.* 10, 227–245. doi:10.1007/s10461-006-9078-6

Smith, W. G. (2008). Does gender influence online survey participation?: A record-linkage analysis of university faculty online survey response behavior. Available: https://www.researchgate.net/publication/234742407_Does_Gender_Influence_Online_Survey_Participation_A_Record-Linkage_Analysis_of_University_Faculty_Online_Survey_Response_Behavior (Accessed June 1, 2022).

Sokol, M. C., Mcguigan, K. A., Verbrugge, R. R., and Epstein, R. S. (2005). Impact of medication adherence on hospitalization risk and healthcare cost. *Med. Care* 43, 521–530. doi:10.1097/01.mlr.0000163641.86870.af

SSB (2020). Educational attainment of the population. Available: https://www.ssb.no/en/utdanning/utdanningsniva/statistikk/befolkningens-utdanningsniva (Accessed June 1, 2022).

Stirratt, M. J., Dunbar-Jacob, J., Crane, H. M., Simoni, J. M., Czajkowski, S., Hilliard, M. E., et al. (2015). Self-report measures of medication adherence behavior: Recommendations on optimal use. *Transl. Behav. Med.* 5, 470–482. doi:10.1007/s13142-015-0315-2

Taherdoost, H. (2019). What is the best response scale for survey and questionnaire design; review of different lengths of rating scale/attitude scale/Likert scale. *Int. J. Acad. Res. Manag. (IJARM)* 8.1-10.

Tavakol, M., and Dennick, R. (2011). Making sense of Cronbach's alpha. *Int. J. Med. Educ.* 2, 53–55. doi:10.5116/ijme.4dfb.8dfd

Terwee, C. B., Mokkink, L. B., Knol, D. L., Ostelo, R. W. J. G., Bouter, L. M., and De Vet, H. C. W. (2012). Rating the methodological quality in systematic reviews of studies on measurement properties: A scoring system for the COSMIN checklist. *Qual. Life Res.* 21, 651–657. doi:10.1007/s11136-011-9960-1

Velligan, D. I., Lam, Y.-W. F., Glahn, D. C., Barrett, J. A., Maples, N. J., Ereshefsky, L., et al. (2006). Defining and assessing adherence to oral antipsychotics: A review of the literature. *Schizophr. Bull.* 32, 724–742. doi:10.1093/schbul/sbj075

Vrijens, B., De Geest, S., Hughes, D. A., Przemyslaw, K., Demonceau, J., Ruppar, T., et al. (2012). A new taxonomy for describing and defining adherence to medications. *Br. J. Clin. Pharmacol.* 73, 691–705. doi:10.1111/j.1365-2125.2012.04167.x

Whitaker, C., Stevelink, S., and Fear, N. (2017). The use of Facebook in recruiting participants for health research purposes: A systematic review. *J. Med. Internet Res.* 19, e290. doi:10.2196/jmir.7071

Xu, M. L., and Leung, S. O. (2018). Effects of varying numbers of Likert scale points on factor structure of the Rosenberg Self-Esteem Scale. *Asian J. Soc. Psychol.* 21, 119–128. doi:10.1111/ajsp.12214

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The importance of reminders and patient preferences to improve inhaler technique in older adults with COPD

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Objectives: Medication non-adherence in patients with chronic obstructive pulmonary disease is common. The aim is to evaluate the efficacy of two interventions to improve the inhalation technique (IT) in patients with pulmonary disease is common. Also determine optimal IT reminder time and to test the role of preferences in the intervention selection.

Method: 726 pulmonary disease in common patients (consecutive sampling) from two trials: 1) TECEPOC-study (patients' preference trial/comprehensive cohort design) 2) TIEPOC-study (randomised controlled trial). Interventions: intervention-A (ad-hoc leaflet with instructions about correct IT according Spanish Respiratory Society), intervention B (intervention A+ individual training by instructors). Four visits were performed (baseline, 3, 6 and 12 months). Data on IT, sociodemographic and clinical characteristics, quality of life and respiratory drugs were recorded. Analysis under intention to treat principle. Multivariate analysis was conducted to measure the potential modifying factors of improvement in the IT along follow-up.

Results: 660 patients (90.9%) did not perform a correct IT at baseline 89.75% with Handihaler, 86.95% with Turbuhaler, 84.75% with Accuhaler and 87.35% with pMDI. At 12 months, 221 patients 29.9% performed correctly the IT; a decrease in the slope of the curve (correct IT) was detected at 3 months follow-up. Intervention B was the most effective in both trials compared to control group or intervention A, regardless of preferences: 1) TECEPOC Study (preference trial): Intervention B *versus* control group, NNT = 3.22 (IC95%, 2.27–5.52); and *versus* Intervention A, NNT = 3.57 (CI95%, 2.41–6.8). Preferences improved 6.7% in the correct IT without statistical significance. 2) TIEPOC Study (randomized controlled trial): Intervention B *versus* control group, NNT = 1.74 (IC95%, 1.47–2.17), and *versus* intervention A, NNT = 3.33 (CI 95%, 2.43–5.55). No differences were measured between Intervention A and control group.

Conclusion: Individual training significantly improves IT. Reminders every 3 months are recommended. Preferences do not influence the intervention effectiveness.

KEYWORDS

COPD, chronic obstructive pulmonary disease, inhalation techniques, educational interventions, care seeking behaviors, primary care, general practice < setting of care, treatment adherence

1 Introduction

Medication adherence is a critical challenge in many places around the world. Patients who take medications for chronic health conditions take only about half of their prescribed doses, regardless of the number of medications they are prescribed, and questions are emerging as to the necessity of the number of medications. Patient's adherence to long-term therapy averages 50%. Adherence rates in clinical trials may be as high as 70–90%, but in clinical practice, they range from 10 to 40% (World Health Organization, 2015). Older people are more likely to experience multiple chronic conditions simultaneously, which increases the number of medications taken at the same time, a key risk factor for lack of medication adherence.

When considering Chronic Obstructive Pulmonary Disease (COPD), it is important to also consider an additional problem when it comes to medication adherence. In a recent systematic review about barriers and strategies to improve medication adherence composed of 38 studies, researchers found lack of medication adherence in COPD patients ranging from 22 up to 93% with an average of 60% (Bhattarai et al., 2020).

Most of the treatment options available for this disease are delivered by inhalers, and skills in their use are required (Chronic obstructive pulmonary disease in, 2018; Global Iniciative for COPD, 2022).The inhalation technique consists of several linked steps that are specific to each device. For more than 40 years, it has been observed that the incorrect use of inhalers is a common problem throughout the world (Chrystyn et al., 2017; Price et al., 2018; Duarte-De-Araújo et al., 2019; Lindh et al., 2019; Padmanabhan et al., 2019; Melani, 2021; Barnestein-Fonseca et al., 2022). Up to 94% of patients have shown misuse in various clinical studies (Sanchis et al., 2016; Chrystyn et al., 2017; Dhand et al., 2018; Lindh et al., 2019; Rincon-Montaña, 2019; Melani, 2021; Barnestein-Fonseca et al., 2022) and despite the improvement in the devices, errors regarding the correct inhalation technique have not decreased (Melani, 2021; Lindh et al., 2022).

The National Institute for Health and Care Excellence (NICE) and the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines recommend that prior to prescription of a new inhaler for a patient with COPD, the patient should receive training and education in the use of the device. Both guidelines also advise that inhaler technique should be regularly assessed at each clinic visit (Chronic obstructive pulmonary disease in, 2018; Global Iniciative for COPD, 2022). Patient education can be defined as a planned process of activities designed to enable people to improve knowledge, to acquire skills and facilitate voluntary adaption of behaviours in order to restore, maintain and improve health (Lindh et al., 2022). However, the guidelines do not provide standardised information on how to assess and educate patients on the use of inhalers, and in many cases, this information needs to be tailored to the characteristics of the individual patient (Chronic obstructive pulmonary disease in, 2018; Plaza Moral et al., 2018; Global Iniciative for COPD, 2022; Miravitlles et al., 2022). The lack of information about inhaler use in these guidelines highlights a deficiency in the care for patients with COPD.

Incorrect use is associated with an increased risk of acute exacerbation, hospital admission, emergency room visits, and a need for antimicrobials and oral steroids (Kocks et al., 2018; Ahn et al., 2019). However, in the real world, inhaler mishandling and poor adherence are very common, despite the fact that most COPD patients receive education on inhaler use (Ahn et al., 2020; Barnestein-Fonseca et al., 2022). While the efficacy and safety of the various inhaled agents and drug combinations is a mandatory consideration for healthcare providers when choosing appropriate therapy for a patient, the choice of the device is also a vital factor; a factor for which there exist no regulatory preferences and current clinical strategies provide little guidance (Lavorini et al., 2019). The importance of the physician's knowledge and understanding of device has also been highlighted. The assumption that healthcare professionals can be relied on to provide patient instruction is questioned by several studies, suggesting that the knowledge and skills of those providing instruction are less than optimal. Most studies indicate that only approximately half of healthcare professionals know how to use an inhaler or perform correct technique (Lareau and Hodder, 2012; Price et al., 2018).

Many inhalers are challenging to use and some require up to eight steps (Plaza Moral et al., 2018). For every device, at least three instructions are required to avoid errors or reduce them to less than 10% (Takaku et al., 2017). To acquire the skills needed for using the inhaler devices correctly, healthcare professionals and patients must be adequately educated and trained (Sanchis et al., 2013; Aksu et al., 2016; Klijn et al., 2017; Yoo et al., 2017; Melani, 2021).

Initial instruction is of great importance for the outcome of inhalation therapy. Written instructions alone are insufficient in

teaching correct inhalation techniques and regular direct one-on-one instruction is considered essential for patients to achieve correct use of the devices (Sanchis et al., 2013; Aksu et al., 2016; Klijn et al., 2017; Yoo et al., 2017; Lavorini et al., 2019; Ahn et al., 2020; Melani, 2021; Lindh et al., 2022). Each patient should understand how to perform each step (Sanchis et al., 2016; Duarte-De-Araújo et al., 2019; Barnestein-Fonseca et al., 2022; Global Iniciative for COPD, 2022; Lindh et al., 2022), and healthcare professionals should verify the correct use of inhalers by reporting possible errors identified (Chrystyn et al., 2017; Ahn et al., 2020; Melani, 2021; Barnestein-Fonseca et al., 2022) along with its clinical importance (Melani, 2007; Barnestein-Fonseca et al., 2022), in order to develop interventions that lead to optimal control of the disease and design of new inhalers (Aksu et al., 2016; Axtell et al., 2017; Klijn et al., 2017; Yoo et al., 2017; Dhand et al., 2018; Efil et al., 2020; Ozoglu Aytac et al., 2020; Kim et al., 2021; Melani, 2021; Choomuang et al., 2022). The main objective of these two trials is to evaluate the efficacy of two educational interventions to improve the inhalation technique (IT) in patients with COPD, as well as to determine the optimal IT reminder time and to test the role of preferences in the intervention selection.

2 Materials and methods

2.1 Study design

We performed two consecutive in time clinical trials: 1) the first one was TECEPOC Study, a multicentre patients' preference open-label trial or comprehensive cohort design (ISRCTN15106246) and 2) the second TIEPOC Study, a multicentre, open-label, randomised controlled trial (ISRCTN60147249).

TECEPOC trial was approved by the Ethical Committees of Distrito Sanitario Málaga (01/03/2007) and Axarquía (13/05/2008); TIEPOC trial was approved by the Ethical Committees of Distrito Sanitario Málaga (21/12/2010). The protocol of both studies has been broadly explained (Leiva-Fernández et al., 2012; Leiva-Fernández et al., 2014).

2.2 Participants, recruitment and setting

A total of 726 patients with COPD from fourteen Primary Care Centres (PCC), seven urban and rural centres in each trial, were selected by non-random consecutive sampling method: 465 patients in the TECEPOC study and 261 patients in the TIEPOC study.

The inclusion criteria were as follows: confirmed COPD diagnosis, clinical assistance at primary care centres in the Malaga province, prescription of inhaled therapy and having agreed to take part in the study by giving signed written consent. Exclusion criteria were: other respiratory conditions which are not included in the COPD definition (bronchiectasis, asthma or cystic fibrosis) and cognitive impairment problems (dementia, Alzheimer, Parkinson, cognitive decline). All these criteria were reviewed in the patient's clinical record.

The sample size in both trials was calculated aiming at detecting a correct inhalation technique percentage difference between groups of 25%, with a statistical power of 80% and a confidence level of 95%, assuming a percentage of expected losses of 40% throughout the follow-up.

Patients were contacted by telephone and invited to participate; they then received an appointment at the PCC. At this first appointment (inclusion visit), patients were given more detailed information about the study, and if they agreed to participate, they signed the written consent form.

In the TECEPOC trial, patients were asked if they had a preference for any of the interventions and based on this, were divided into two groups. Patients without strong preferences for a treatment were randomised (RCT group) using the block randomisation technique which consisted of blocks of three or six patients homogeneously distributed among the three arms of the trial; randomization was applied separately at each study centre. Those patients with strong preferences were given their choice (PPS group). The RCT group resulted in three arms (control -CG-, intervention A -IAR- and intervention B -IBR-), whereas the PPS group ended up with two arms (intervention A -IAP- and intervention B -IBP-), so in the end this study had five arms.

In the TIEPOC trial, patients were directly allocated to one of the three study arms using a block randomization technique, following the same procedure as in the previous trial.

2.3 Interventions

Two educational interventions were designed and applied in both trials: 1) Intervention A (IA) that provided only written information about inhalation techniques; and 2) Intervention B (IB) that consisted in written information about inhalation techniques + instructor-led training.

Intervention A (IA): The research team designed a leaflet explaining the correct inhalation techniques, containing the main devices the patients use in our area. We included four devices: Handihaler®, Turbuhaler®, Accuhaler® and Pressurised Metered Dose Inhalers (pMDI). It was written in simple language so that patients could understand the information, with original photos showing the main steps for each device. The leaflets were designed and written by the research team, after consulting the manufacturer's instructions and SEPAR recommendations and reviewed by experts (family doctor and pulmonologist). Subsequently, patients were asked to review them and gave feedback on their ease of understanding and use of plain language. The patients included in this group were asked to

demonstrate how they used their devices with placebo inhalers, and the researcher wrote down the mistakes on an *ad hoc* template designed according to the Spanish Society of Pneumology and Thoracic Surgery (SEPAR) guidelines (Plaza Moral et al., 2018). Once the inhalation techniques were performed, the researcher gave the leaflet to the patients and invited them to read it and identify differences between the steps of the correct inhalation technique (leaflet) and the ones they had performed. In the follow-up visits, patients were asked about the leaflet and the differences between those instructions and their technique.

Intervention B (IB): The research team gave written information (leaflet described above) to patients and also trained them in correct inhalation techniques. The training was performed by four researchers (instructors) that were trained in the use of inhaler devices in the Paediatric Pneumology Department of the Hospital Materno Infantil (Malaga). First, patients were asked to demonstrate their technique with placebo inhalers. Then, the instructor, using the teach-back method, asked about the problems and perceived errors with the technique and proceeded to demonstrate the proper technique with each device, step by step, including the importance of each one. Finally, patients could ask questions and practice the techniques until they were performed correctly or until the patient became tired. In the follow-up visits, the inhalation technique was reviewed and errors were corrected again and doubts were cleared out. The goal at this stage was to identify errors, and if they could not, to remind them of the proper technique by giving as many demonstrations as necessary.

Patients in the control arm in both trials were asked to demonstrate their technique without any further intervention from the researcher apart from correcting critical errors (rescue mechanism). The critical error has been established as the one that would considerably reduce drug lung deposition (Melani, 2007). There was no leaflet or educational intervention involved.

All patients had four follow-up visits: baseline, 3, 6 and 12-month.

2.4 Outcomes

Primary outcome: Performance of correct inhalation techniques following SEPAR guidelines (Plaza Moral et al., 2018) at 12-month follow-up. A correct technique will be considered when no mistakes are registered.

Secondary outcomes: Performance of correct inhalation techniques following SEPAR guidelines (Plaza Moral et al., 2018) at three and 6-month follow-up, inspiratory peak flow, functional status (spirometry:pFEV1 and severity according to GOLD Guidelines (Global Iniciative for COPD, 2022)), dyspnoea measured with Baseline Dyspnoea Index (BDI) (Mahler et al., 1984) and Modified Medical Research Council (MMRC) (Devon and Holman, 1966); Quality of life: St George Respiratory Questionnaire (SGRQ) (Ferrer et al., 1996), and EuroQoL-5D-3L (Herdman et al., 2011).

Independent variables: The following variables were included; age, sex, educational level (considering the highest level of education attained as reported by the patient at the baseline visit), comorbidities (other chronic diseases diagnosed to the patient, according to his/her electronic health record), smoking history (patient-reported smoking habit, considering the options non-smoker, ex-smoker or current smoker, number of packs-year) and Mini-mental State Examination (MMSE) (Lobo et al., 2002).

Related to COPD: prescribed treatment for COPD, time of diagnosis, number of prescribed devices, number of exacerbations, number of visits to the healthcare centre because of COPD, previous instruction received regarding IT, type of instruction and professional who gave it, types of error in the IT and time for inhaler training (including test of the performance of inhalation techniques of all the devices used by the patient).

2.5 Statistical analysis

The analysis was carried out following an intention-to-treat procedure, considering all patients who were randomised, irrespective of what happened during follow-up in both studies. A Multivariate Imputation has been used to handle missing data. For the primary outcome variable, the handling of lost data was done using the worst scenario considering that losses in the control group performed the IT correctly and those in the intervention groups performed the IT incorrectly.

A descriptive statistical analysis was performed for all of the study variables. We calculated the mean and standard deviations for quantitative variables and the absolute and relative frequencies for qualitative variables. Univariate analyses: a between-group comparison at baseline, a comparison between the initial sample and the final sample (to assess the impact of losses on sample structure), a comparison between each intervention arm (A or B) *versus* control arm and between intervention A and B at 12-month follow-up was conducted by means of an analysis of variance (ANOVA) or chi square test, as applicable. The relative risk reduction (RRR), the absolute risk reduction (ARR) and the number needed to treat (NNT) were calculated with a CI of 95%. Multivariate analyses: a logistic regression model was performed for the primary outcome (performance of correct inhalation technique at 12-month), considering the intervention as the predictive variable and adjusting for independent variables that may act as modifying factors of the effect of the intervention.

In the case of the TECEPOC trial, due to its special design, each group (RCT and PPS) was analysed separately. The analysis has been performed according to the following steps: 1) Comparison in RCT group: each intervention arm (A or B) *versus* control arm and between intervention A and B. 2)

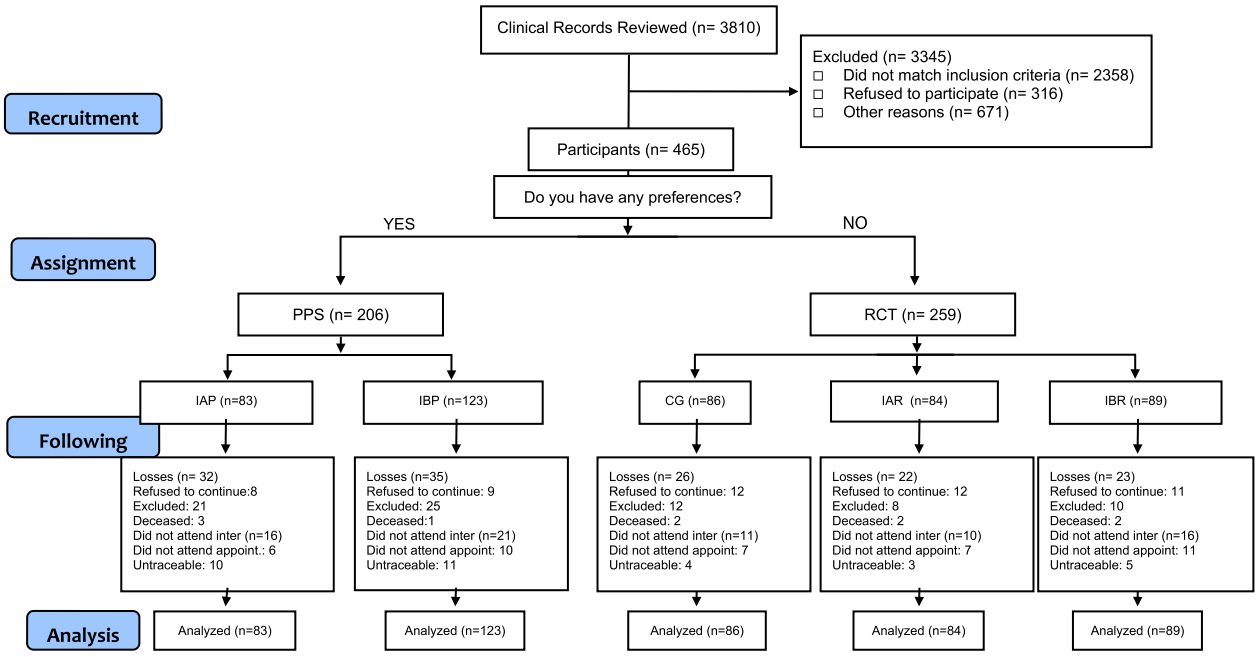
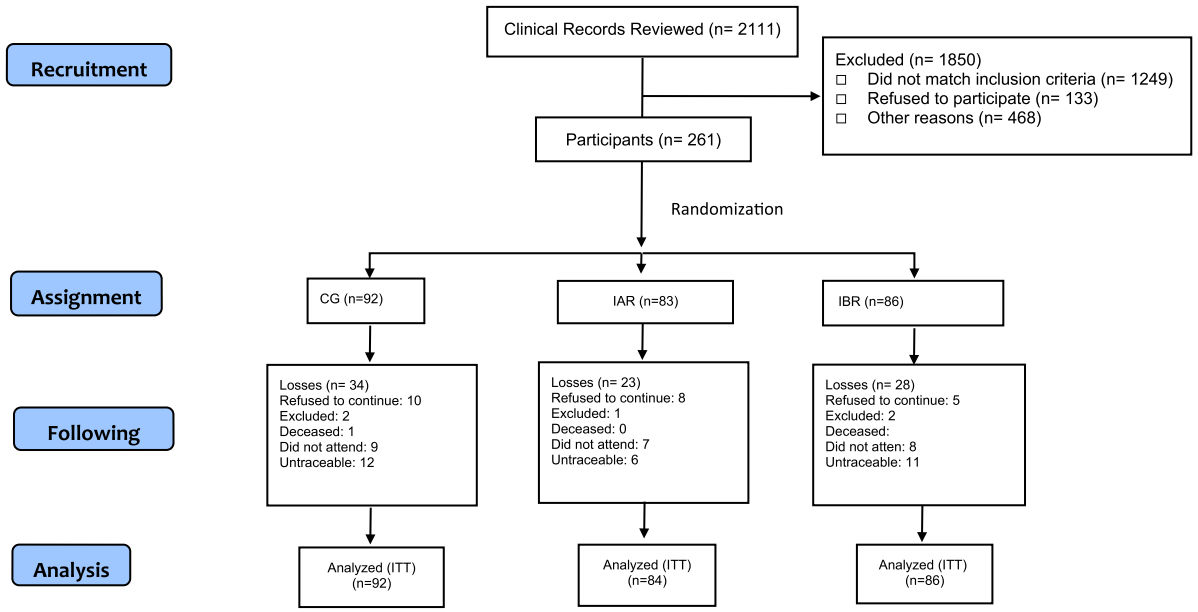


FIGURE 1
Consort flow tecepoc study.



CG: Control Group; IAR: Intervention A Randomization Group; IBR: Intervention B Randomization Group; ITT: intention-to-treat analysis

FIGURE 2
Consort Flow tecepoc study.

TABLE 1 Descriptive of the variables at baseline according to the study arm.

Variables	TECEPOC Study (n=465)					TIEPOC Study (n=261)		
	PPS (n=206)		RCT (n=259)			RCT (n=261)		
	IAP (n=83)	IBP (n=123)	CG (n=86)	IAR (n=84)	IBR (n=89)	CG (n=92)	IAR (n=83)	IBR (n=86)
Sex n(%) Male	81 (96.4)*	116 (94.3)*	75 (87.2)*	74 (89.3)*	79 (88.8)*	83 (90.2)	72 (86.74%)	72 (83.72)
Age (years) mean (CI 95%)	70.1 (68.3-71.9)	69.6 (68.2-71)	70.2 (68.4-72.1)	68.4 (66.4-70.4)	70.5 (68.5-72.5)	70.11 (68.45-71.76)	70.05 (68.01-72.09)	69.99 (68.09-71.89)
Low educational level n (%)	75 (92.5)*	112 (91.9)*	65 (76.5)*	69 (83.3)*	76 (85.4)*	64 (69.56)	56 (70)	64 (75.3)
Smokers n (%) Packets/ year men (CI 95%)	31 (36.9) 56.3 (44.5-68.1)	35 (28.5) 61.2 (52.6-69.8)	23 (26.7) 52.1 (42.6-61.7)	23 (27.4) 57.65 (47-68.3)	28.1 66.9 (56.2-77.5)	26 (28.26) 58.42 (50.28-66.56)	32 (38.55) 51.98 (43.17-60.79)	22 (25.0) 46.11 (37.01-55.2)
Comorbidities								
• Number	0.89 (0.79-1)	0.94 (0.83-1.06)	0.97 (0.89-1.06)	1.12 (1.01-1.23)	1.03 (0.93-1.14)	1.10 (0.94-1.27)	0.9 (.071-1.09)	0.93 (0.76-1.09)
• HBP n (%)	42 (50.6)	62 (50.4)	43 (50)	43 (51.2)	40 (44.9)	52 (56.52)*	30 (36.14)*	43 (50)*
• OP n (%)	18 (21.7)*	27 (22)*	29 (33.7)*	32 (38.1)*	58 (34.8)*	23 (25)	24 (28.91)	18 (20.93)
• DM n (%)	15 (18.1)	27 (22)	12 (14)	18 (21.4)	68 (23.6)	27 (29.34)	21 (25.3)	19 (22.09)
Diagnostic time (years) mean (CI 95%)	6.1 (5-7.3)	6.7 (5.6-7.9)	6.3 (5-7.7)	5.3 (4.4-6.2)	6.6 (5.7-7.6)	10.92 (8.24-13.61)	8.42 (6.2-10.63)	9.91 (8.12-11.69)
COPD pattern n (%)								
• Obstructive	5 (6.3)	13 (11.1)	25 (29.6)	22 (27.5)	28 (32.9)	29 (31.5)	24 (28.9)	20 (23.3)
• Restrictive	12 (15)	16 (13.7)	9 (11.1)	12 (15)	7 (8.2)	2 (2.2)	8 (9.6)	4 (4.7)
• Mixed	64 (78.8)*	88 (75.2)*	46 (56.8)	45 (57.5)	49 (57.6)	46 (50)	39 (47)	47 (54.7)
COPD severity n (%)								
• Mild	7 (8.8)	9 (7.7)	19 (24.4)	14 (17.3)	20 (23)	13 (16.3)	10 (13.7)	5 (6.8)
• Moderate	31 (38.8)	53 (45.3)	35 (42.7)	43 (53.1)	35 (40.2)*	45 (56.3)	39 (53.4)	32 (43.2)
• Severe	43 (52.5)*	55 (47)*	28 (32.9)	23 (29.6)	32 (36.8)	22 (27.5)	24 (32.9)	37 (50)
FEV1 % (CI 95%)	49.07 (46.64-51.5)*	52.48 (50-54.97)*	60.3 (57.47-63.13)*	58.17 (55.88-60.46)*	56.78 (54.35-59.21)*	61.03 (56.61-65.46)*	59.01 (55.28-62.74)*	52.19 (48.36-56.02)*
Inspiratory peak flow (CI 95%)	155.88 (148.6-163.1)*	165.38 (158.5-172.1)*	173.41 (165.4-181.3)*	181.46 (174.1-188.8)*	174.12 (166.7-181.5)*	186.85 (178.1-195.6)	192.53 (184.3-200.6)	188.29 (180.3-196.2)
Number of exacerbations/ year mean (CI 95%)	0.3 (0.2-0.5)*	0.8 (0.6-1)*	1.2 (0.8-1.5)*	0.7 (0.5-0.91)*	1.8 (0.6-1.4)*	0.93 (0.57-1.3)	0.71 (0.48-0.93)	0.8 (0.58-1.02)
Total visits to HC (CI 95%)	5.76 (5.03-6.49)*	4.97 (4.34-4.59)*	7.36 (6.46-8.26)*	6.43 (5.68-7.18)*	6.4 (5.73-7.07)*	5.67 (5.17-6.17)	6.48 (5.79-7.17)	5.36 (4.83-5.89)
Visits to HC because of COPD (CI 95%)	1.3 (0.9-1.6)*	1.7 (1.3-2.1)*	3 (1.6-4.4)*	1.7 (1.3-2.1)*	1.95 (1.4-2.4)*	1.68 (1.29-2.06)	1.64 (0.82-2.46)	1.61 (1.17-2.04)
Prescribed treatment n (%)								
• Anticholinergic	64 (76.8)	90 (73.2)	61 (70.9)	56 (67.9)	57 (64)	75 (81.52)	17 (79.51)	69 (80.2)
• Beta-2 adrenergic	67 (80.5)*	115 (93.5)*	76 (88.4)	74 (89.3)	80 (89.9)	78 (84.78)	72 (86.74)	69 (80.2)
• Inhaled corticosteroids	50 (70.2)	99 (80.5)	66 (76.7)	60 (72.6)	72 (80.9)	73 (79.3)	61 (73.5)	63 (73.3)

(Continued on following page)

TABLE 1 (*Continued*) Descriptive of the variables at baseline according to the study arm.

Variables	TECEPOC Study (n=465)					TIEPOC Study (n=261)		
	PPS (n=206)		RCT (n=259)			RCT (n=261)		
	IAP (n=83)	IBP (n=123)	CG (n=86)	IAR (n=84)	IBR (n=89)	CG (n=92)	IAR (n=83)	IBR (n=86)
SGRQ mean (CI 95%)								
• Total	34.8 (30.6-39)*	34.6 (30.6-39)*	33.4 (29.4-37.3)	31 (27.2-34.8)	33 (29.3-36.6)	33.7 (30.2-37.3)	33.1 (29.9-36.3)	34.7 31.8-37.6)
• Activities	55.8 (50.8-60.8)*	54.3 (50.1-58.5)*	49.6 (44.6-54.6)	49.1 (44.4-53.8)	49.9 (45-54.7)	49.44 (44.9-53.9)	47.9 (43.6-52.)1	52.7 (48.6-56.8)
•Symptoms	35.2 (30.5-39.9)	36.8 (33.3-40.3)	36.9 (32.5-41.3)	34.8 (30.6-39.1)	36.1 (32.1-40.2)	35 (30.8-39.2)	35.7 (31.5-39.9)	36.7 (32.8-40.7)
• Impact	23.1 (19-27.4)	22.7 (19.3-26.1)	25.3 (21.3-29.3)	22.5 (18.9-26.1)	24.4 (20.6-28.1)	24.2 (20.4-28.1)	23.8 (20.5-27.1)	23.7 (20.7-26.7)
EuroQol-5D n (%) with no problems								
• Mobility	67 (80.5)	88 (71.5)	61 (70.9)	51 (61.9)	54 (61.4)	54 (60)	48 (57.83)	54 (62.79)
• Self-care	74 (89)	104 (84.6)	80 (93)	73 (88.1)	76 (88.6)	80 (87.91)	75 (90.36)	81 (94.18)
• Usual activities	65 (78)	105 (85.4)	75 (87.2)	73 (88.1)	76 (86.4)	78 (85.71)	71 (85.54)	76 (88.37)
• Anxiety/depression	62 (74.4)	91 (74)	64 (74.4)	59 (71.4)	65 (73.9)	70 (76.92)	66 (79.51)	65 (75.58)
• Pain/discomfort	65 (78)*	89 (72.4)*	57 (54.7)*	45 (54.8)*	47 (53.4)*	56 (61.53)	42 (60.6)	50 (58.13)
• EVA	64.98 (62.6-67.3)	68.33 (65.6-71.0)	66.34 (63.8-68.8)	67.65 (65.1-70.1)	64.94 (62.6-67.2)	67.2 (63.1-71.3)	65.7 (61.2-70.1)	67.9 (64.2-71.6)
BDI n (%)								
• Functional Impairment	52 (62.7)	76 (62.3)	53 (62.4)	48 (57.8)	48 (55.2)	31 (34.44)	34 (40.96)	39 (45.34)
• Magnitude of task	63 (75.9)	93 (76.2)	64 (76.2)	65 (78.3)	64 (74.4)	62 (68.89)	60 (72.28)	71 (82.55)
• Magnitude of effort	78 (94)	91 (74.6)	66 (77.6)	67 (80.7)	71 (82.6)	65 (72.23)	59 (71.08)	73 (84.88)
MMRC n (%)	78 (94)	118 (96.7)	77 (92.8)	79 (95.2)	75 (87.2)	40 (44.45)	35 (42.16)	44 (51.16)
MMSE mean (CI95%)	26.5 (25.8-27.1)	26.4 (25.9-27)	26.7 (26.2-27.2)	26.6 (26-27.2)	26.6 (26-27.2)	28.16 (27.7-28.6)	28.37 (27.9-28.9)	28.1 (27.5-28.6)

*$p < 0.05$; BMI: body mass index; CG: control group; DM: diabetes mellitus; HBP: high blood pressure; HC: health center; IAP: Intervention A Cohort Preference Group; IAR: Intervention A Cohort Randomization Group; IBP: Intervention B Cohort Preference Group; IBR: Intervention B Cohort Randomization Group; MMST: Mini-Mental Status Test; OP: osteoarticular pathology; PPS: patient preferences group; RCT: randomized group; SGRQ: St. george respiratory questionnaire; *: statistically significant differences ($p < 0.05$).

Comparison between RCT and PPS groups: between the intervention arms (A or B) of each group (RCT or PPS). An analysis of variance (ANOVA) or ji-squared test were applied as stated above.

We used a 5% significance level (α = 0.05) and the SPSS statistical package, version 23.0, to run the proposed analysis.

3 Results

For clarity purposes, both trials will be detailed separately in this section, as they were conducted at consecutive times and in different primary care centres. The findings regarding inhalation technique are described in a unique paragraph so as to be more instructive.

3.1 Participant recruitment

For both the TECEPOC Study and the TIEPOC Study we approached 5,921 potential participants identified in clinical records. At the end, 726 patients were recruited to participate, 465 in the TECEPOC Study and 261 in the TIEPOC Study. Figures 1, 2 show the CONSORT Flow Diagram of both studies.

3.2 Follow-up

In the TECEPOC Study, 97 patients were lost to follow-up (dropout rate 20.86%): 40 patients (19.41%) in the PPS group and 57 (22%) in the RCT group. For the TIEPOC Study the dropout rate was 30.3%, which corresponds to 79 patients: 35 (38%) in the CG, 21 (25.3%) in the IAR and 21 (25.3%) in the IBR. Figures 1, 2 show the CONSORT Flow Diagram of both studies.

These losses did not change the initial characteristics of the sample for the TECEPOC Study. For the TIEPOC Study statistically differences in the final sample were found for sex (higher dropout rate among women; $p = 0.021$), age (older participants missed more; $p = 0.005$) and cognitive status (more dropouts in participants with lower MMSE scores; $p = 0.018$).

3.3 Baseline characteristic

In Table 1, we can see the baseline characteristic of participants per study arms.

Overall, the 465 subjects of TECEPOC Study were predominantly male (91.4%), with a mean age of 69.8 years (95% CI, 69.41–70.19) with low educational level; most of them had smoked (92.9%) with a mean of 39.78 packs per year (95% CI, 39.24–40.32), and 29.5% were active smokers. A large part of the sample suffered from at least one additional chronic condition, most prevalent was high blood pressure (HBP) (49.5%); with a moderate impairment of quality of life. Regarding COPD, the spirometry revealed a mean pFEV1 of 55% (95% CI, 52.71–57.37), with a mixed pattern (65.9%), and a mean of 0.83 exacerbations in the previous year (95% CI, 0.72–0.94) (Table 1).

Overall, the 261 subjects in the TIEPOC study were very similar to those in the TECEPOC study, showing a majority of male (86.97%), with a mean age of 70.17 years (95% CI, 69–71.1 years), and low educational level; most of them had smoked (91.95%) with a mean of 52.32 packs per year (95% CI, 47.36–57.27), and 30.7% were active smokers. A large part of the study subjects suffered from at least one additional chronic condition, most prevalent was HBP (47.29%), with a moderate impairment of quality of life. Regarding COPD, the spirometry revealed a mean FEV1 of 57.47% (95% CI, 55.32–59.62), with a mixed pattern, and a mean of 0.82 exacerbations in the previous year (95% CI, 0.66–0.98) (Table 1).

No significant differences were observed between the arms in the RCT group of the TECEPOC study, but significant differences were found between the arms of the PPS group in relation to number of exacerbations ($p = 0.004$), beta two adrenergic treatment (more at IBP; $p = 0.005$) and Accuhaler® prescription (more at IBP; $p = 0.049$). We also found significant differences between PPS and RCT group: there were low values in PPS group related to: number of women ($p = 0.01$), educational level ($p = 0.002$), osteoarthritis comorbidity ($p = 0.001$), pFEV1 ($p < 0.001$), number of exacerbations ($p = 0.012$), number of total visits to health centre ($p = 0.008$) or due to COPD ($p = 0.036$), peak flow ($p = 0.048$) and pain/discomfort problems on the EuroQol-5D scale ($p < 0.001$). There were higher values in the PPS group in COPD severity (high percentage of severe stage; $p < 0.001$) and mixed pattern ($p = 0.004$). Also, we found high impairment in health-related quality of life measured by the activity scale of SGRQ ($p = 0.012$).

For the TIEPOC Study we found significant differences for HBP (IAR cohort showed lower prevalence; $p = 0.024$) and for pFEV1 value (IBR cohort had lower pFEV1; $p = 0.006$).

Considering the total number of patients between the two studies, 660 patients (90.9%) did not perform a correct inhalation technique at baseline. The device Handihaler® was prescribed in 508 (69.97%), the Turbuhaler® in 396 (54.54%), 235 with the Accuhaler® (32.36%), 178 with the pMDI (24.51%) and 101 patients with other devices (13.9%). Incorrect inhalation technique was detected in 456 subjects (89.75%) with Handihaler®, 340 (86.95%) with Turbuhaler®, 198 (84.75%) with Accuhaler® and 143 (87.35%) with pMDI.

Six hundred and fourteen patients (84.57%) had received some kind of inhaler technique instruction and the mean time from this instruction to recruitment in the present studies was 55.48 months (95%CI, 46.17–55.11). Previous instruction was performed mainly by the pulmonologist (294 patients; 47.88%), followed by the family physician (248 patients; 40.39%). The most common method used to carry out this instruction was the device-less explanation (346 subjects; 56.35%), followed by demonstration with the device (137 subjects; 22.31%). In six patients (0.9%) the instruction consisted on the delivery of an explanatory leaflet.

The most frequent errors identified were: 1) not exhaling completely before inhaling (76.4%), 2) no breath-holding or shortness of breath after inhalation (64.21%), and 3) a non-optimal strength of inhalation (20.32%). The more frequent mistakes related to the devices were: the coordination of breath for pMDI (57.3%) and position of the device (hold inhaler upright >45°) for Turbuhaler® (92.21%).

Table 2 collects the baseline characteristics of the inhalation technique in both studies.

3.4 Intervention effectiveness

Figure 3 shows the evolution of inhalation techniques along follow up (Figure 3A the five arms of TECEPOC Study and Figure 3B the three arms of TIEPOC Study).

About time for inhaler training, it was 5.19 min (IC95%, 4.91–5.47) for CG cohort, 6.2 min (IC95%, 5.74–6.5) for IAR cohort and 7.15 min (6.8–7.5) for IBR cohort at baseline. At the end of the study it was 3.68 min (IC95%, 3.38–3.98) for CG

TABLE 2 Descriptive of the Inhalation Technique at baseline according to the study arm.

	TECEPOC Study					TIEPOC Study		
	PPS		RCT			RCT		
Variables	IAP	IBP	CG	IAR	IBR	CG	IAR	IBR
Correct Inhalation Technique n%	7 (8.4)	4 (3.3)	10 (11.6)	6 (7.1)	6 (6.7)	9 (9.7)	13 (15.7)	11 (12.8)
Number of devices mean (CI 95%)	2.02 (1.8-2.2)	2.05 (1.9-2.1)	2.09 (1.9-2.2)	2.06 (1.8-2.2)	2.07 (1.9-2.2)	2.15 (1.95-2.35)	2.12 (1.93-2.31)	2.03 (1.85-2.22)
Prescribed devices n (%)								
• Handihaler©	61 (72.6)	85 (69.1)	59 (68.6)	54 (65.1)	54 (60.7)	73 (79.3)	60 (72.3)	62 (72.1)
• Accuhaler©	20 (23.8)*	44 (35.8)*	31 (36)	27 (32.5)	26 (29.2)	29 (31.5)	32 (38.6)	26 (30.2)
• Turbuhaler©	49 (58.3)	66 (53.7)	41 (47.7)	46 (55.4)	53 (59.6)	58 (63)	45 (54.2)	34 (44.2)
• pMDI	20 (23.8)	28 (22.8)	29 (33.7)	23 (27.7)	25 (28.1)	15 (16.3)	19 (22.9)	19 (22.1)
Handihaler								
• Correct Inhalation Technique n (%)	6 (7.1)	5 (4.1)	7 (8.1)	5 (6)	4 (4.5)	7 (7.6)	9 (10.8)	7 (8.1)
Mistakes								
• No full exhale before inhalation n (%)	7 (8.3)	12 (9.8)	14 (16.3)	8 (9.6)	6 (6.7)	15 (16.3)	16 (19.4)	12 (14)
• No or short breath hold after inhalation n (%)	11 (13.1)	13 (10.6)	19 (22.1)	18 (21.7)	18 (20.2)	28 (30.4)	21 (25.3)	23 (26.7)
• Non-optimal strength of inhalation n (%)	58 (69)	78 (63.4)	54 (62.8)	47 (56.6)	47 (52.8)	58.7 (54)	54 (65.1)	48 (55.8)
Accuhaler								
• Correct Inhalation Technique n (%)	3 (3.6)	6 (4.9)	5 (5.8)	4 (4.8)	3 (3.4)	5 (5.4)	6 (7.2)	3 (3.5)
Mistakes:								
• No full exhale before inhalation n (%)	10 (11.9)	29 (23.6)	9 (10.5)	4 (4.8)	8 (9)	8 (8.7)	11 (13.3)	3 (3.5)
• No or short breath hold after inhalation n (%)	5 (6)	15 (12.2)	14 (16.3)	13 (15.7)	24 (27)	10 (10.9)	14 (16.9)	16 (18.6)
• Non-optimal strength of inhalation n (%)	16 (19)	40 (32.5)	28 (32.6)	23 (22.7)	1 (1.1)	22 (23.9)	30.1 (25)	18 (20.9)
Turbuhaler								
• Correct Inhalation Technique n (%)	6 (7.1)	3 (2.4)	9 (10.5)	4 (4.8)	4 (4.5)	7 (7.6)	8 (9.6)	7 (8.1)
Mistakes:								
• No full exhale before inhalation n (%)	7 (8.3)	11 (8.9)	14 (16.3)	6 (7.2)	11 (12.4)	14 (15.2)	13 (15.7)	9 (10.5)
• Not placing lips correctly on the mouthpiece n (%)	47 (56)	62 (50.4)	40 (46.5)	44 (53)	52 (58.4)	56 (60.9)	44 (53)	36 (41.9)
• No or short breath hold after inhalation n (%)	9 (10.7)	14 (11.4)	14 (16.3)	17 (20.5)	13 (14.6)	22 (23.9)	17 (20.5)	15 (17.4)
• Non-optimal strength of inhalation n (%)	43 (51.2)	58 (47.2)	37 (43)	42 (50.6)	50 (56.2)	48 (52.2)	37 (44.6)	34 (39.5)
pMDI								
• Correct Inhalation Technique n (%)	1 (1.2)	21 (17.1)	2 (2.3)	3 (3.6)	2 (2.2)	3 (3.3)	1 (1.2)	5 (5.8)
Mistakes:								
• No full exhale before inhalation n (%)	1 (1.2)	6 (4.9)	8 (9.3)	5 (6)	8 (9)	4 (4.3)	6 (7.2)	8 (9.3)
• No or short breath hold after inhalation n (%)	3 (3.6)	8 (6.5)	5 (5.8)	6 (7.2)	12 (13.5)	10 (10.9)	4.8 (4)	11 (12.8)

(Continued on following page)

TABLE 2 (*Continued*) Descriptive of the Inhalation Technique at baseline according to the study arm.

	TECEPOC Study					*TIEPOC Study*		
	PPS		*RCT*			*RCT*		
Variables	*IAP*	*IBP*	*CG*	*IAR*	*IBR*	*CG*	*IAR*	*IBR*
• *No coordination after push n (%)*	*14 (16.7)*	*18 (14.6)*	*17 (19.8)*	*9 (10.8)*	*16 (18)*	*10 (10.9)*	*8 (9.6)*	*10 (11.6)*
• *Non-optimal strength of inhalation n (%)*	*9 (10.7)*	*12 (9.8)*	*14 (16.3)*	*4 (4.8)*	*12 (13.5)*	*6 (6.5)*	*6 (7.2)*	*10 (11.6)*

*$p < 0.05$; CG: control group; IAP: Intervention A Cohort Preference Group; IAR: Intervention A Cohort Randomization Group; IBP: Intervention B Cohort Preference Group; IBR: Intervention B Cohort Randomization Group; PPS: patient preferences group; RCT: Randomized group.

cohort, 4.02 min (IC95%, 3.75–4.29) for IAR cohort and 4.18 min (IC95%, 3.89–4.47) for IBR cohort.

3.4.1 TECEPOC study

At the end of study, the correct inhalation techniques in the RCT group were: 16 (19%) patients for IAR, 42 (47.2%) patients for IBR cohort and 14 (16.3%) patients for CG cohort. There were no differences between CG and IAR cohorts. There were statistically significant differences between IBR cohort *versus* CG cohort in all the follow-up visits ($p < 0.0001$); and at the end of study the NNT for IBR was 3.22 (CI 95%, 2.27–5.52). In the same way, there were significant differences at 12 months between IBR *versus* IAR ($p < 0.0001$) with a NNT = 3.57 (CI95%, 2.41–6.8).

For the PPS group the correct inhalation technique at the end of follow-up was assessed in 14 patients (16.9%) for the IAP cohort and in 57 patients (46.3%) for the IBP cohort. Statistically significant differences ($p < 0.0001$) were found between the IB cohort *versus* IAP cohort with a NNT = 3.33 (CI 95%, 2.43–5.55).

Inhalation techniques at 3 and 6 months (as secondary results) showed a statistically significant improvement in the two IB cohorts ($p < 0.0001$). A decrease in the slope of the curve (correct IT) was detected at 3 months of follow-up in both IB cohorts. There were no differences between CG and IA cohorts.

For the other secondary outcomes, we found better results in all study arms at the end of the study (respect to baseline measurement) for inspiratory peak flow ($p = 0.001$), anxiety/depression scale of EuroQoL-5D ($p < 0.0001$), SGRQ for symptom scale ($p = 0.016$), activity scale ($p < 0.0001$) and total scale ($p = 0.005$). In the same way we detected an improvement in all scales of IBD with less perceived dyspnoea ($p < 0.0001$).

3.4.2 TIEPOC study

At the end of study, the percentages of correct inhalation techniques were: 16 patients (19.3%) for IAR, 56 patients (65.1%) for the IBR cohort and seven patients (7.6%) for the CG cohort. There was no difference between CG and IAR cohorts. There were statistically significant differences between the IBR cohort and CG in all the follow-up visits ($p < 0.0001$), with a NNT of 1.74 patients (IC 95%, 1.47–2.17) at the end of the study.

Inhalation techniques at 3 and 6 months (as secondary results) showed a statistically significant improvement in the IBR cohort ($p < 0.0001$). As in the previous study, a change in the slope of the correct inhalation technique curve was detected at 3-month follow-up.

For the other secondary outcomes, we found better results in all study arms at the end of follow-up (respect to baseline) for severity ($p = 0.003$), number of exacerbations ($p < 0.0001$), SGRQ for all its scales symptom, activity, impact and total scale ($p < 0.0001$). In the same way we detected an improvement in all scales of MMRC with less perceived dyspnoea ($p < 0.0001$).

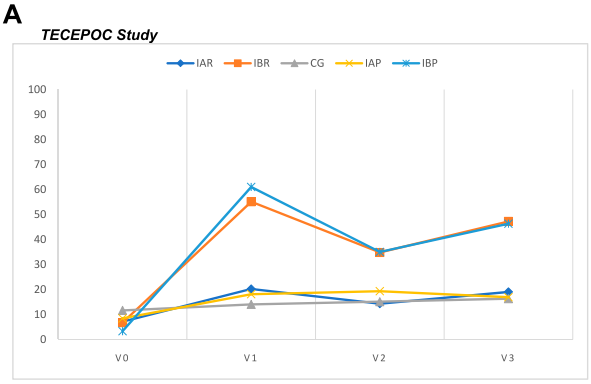
3.5 Preferences effects

Preferences regarding study group assignment were associated with an increase in the percentage of correct inhalation technique of 6.7% in the IBP cohort at 3-month follow-up which was reduced to 1% at the end of the study. For the IAP cohort, preferences are associated with a 2% improvement in inhaler technique at 12 months. None of these changes showed statistical significance.

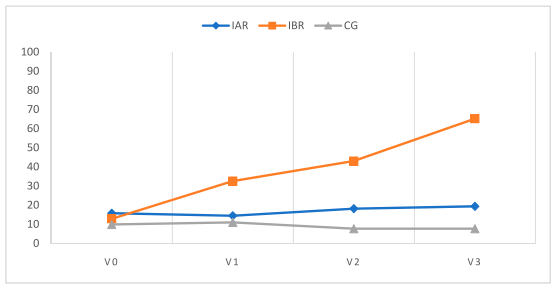
3.6 Multivariate analysis

3.6.1 TECEPOC study

We performed a logistic regression model considering the correct inhalation technique as the dependent variable and the intervention as the predictive variable, adjusting by preferences, age, sex, educational level, number of exacerbations and inspiratory peak flow, functional status, number of devices, health related quality of life measurements and MMSE. The final logit model showed that correct inhalation technique was positively associated with the IB [OR = 31.5 (CI 95% 8.273–50.9)



Arms	V0%(n)	V1%(n)	V2%(n)	V3%(n)	*P*
IAR	7.1 (6)	20.2 (17)	14.3 (12)	19 (16)	0.022
IBR	6.7 (6)	55.1 (49)	34.8*(31)	47.2 (42)	<0.0001
CG	11.6 (10)	14 (12)	15.1(13)	16.3 (14)	0.379
IAP	8.4 (7)	18.1 (15)	19.3 (16)	16.9 (14)	0.102
IBP	3,3 (4)	61 (75)	35* (43)	46,3 (57)	<0.0001



Arms	V0%(n)	V1%(n)	V2%(n)	V3%(n)	*P*
IAR	15,7 (13)	14,4 (12)	18,1 (15)	19,3 (16)	0,540
IBR	12,8 (11)	32,5* (28)	43* (37)	65,1* (56)	<0,001
CG	9,8 (9)	10,9 (10)	7,6 (7)	7,6 (7)	0,601

*CG: Control Group; IAP: Intervention A Preference Group; IAR: Intervention A Randomization Group; IBP: Intervention B Preference Group; IBR: Intervention B Randomization Group; CG: Control Group; V0: Visit 0; V1: Visit 1; V2: Visit 2; V3: Visit 3; *: statistically significant difference from baseline visit; p: comparation between V0-V3.*

FIGURE 3
Correct inhalation technique during follow-up according to study arms.

$p < 0.0001$], higher inspiratory peak flow [OR = 1.010 (CI 95%, 1.003–1.017) $p = 0.007$], higher number of devices [OR = 2.615 (CI 95%, 1.473–4.645) $p = 0.001$] and previous instruction with device demonstration [OR = 3.54 (CI 95%, 1.38–9.07) $p = 0.008$]. The correct inhalation technique got worse in patients with lower SGRQ activity scale score [OR = 0.975 (CI 95%, 0.956–0.90) $p = 0.015$].

3.6.2 TIEPOC study

We performed a logistic regression model considering the correct inhalation technique as the dependent variable and the intervention as the predictive variable, adjusting by age, sex, educational level, number of comorbidities, HBP, inspiratory peak flow, number of exacerbations, functional status, number of devices, SGRQ scales and MMSE. The final logit model showed that correct inhalation technique was positively associated with the IB [OR = 26.34 (CI 95% 10.42–66.57) $p < 0.0001$] and it worsened in older patients [OR = 0.934 (CI 95%, 0.89–0.97) $p = 0.001$].

4 Discussion

The TECEPOC and TIEPOC studies assessed, as primary outcome, the correct performance of inhalation technique and the efficacy of the same two educational interventions to improve the inhalation technique in patients with COPD. We found the most effective intervention to be the one-to-one demonstration of inhaler use with application of the teach-back method, while the provision of an information leaflet resulted in an improvement in inhaler technique close to that of the control group. The evolution of the improvement in inhaler technique over the follow-up showed that the upward trend in the proportion of patients who could use the devices correctly slowed down 3 months after the training.

Proper training can improve inhaler technique (Klijn et al., 2017). However, there are several different levels of education and related to these levels there are different teaching techniques. Basically, we can divide those teaching techniques into two groups: leaflets and practical demonstration.

A systematic review of educational inhaler technique interventions (Klijn et al., 2017) showed that almost all interventions (89%) included a physical or video demonstration of inhaler use and that the educational interventions on inhaler technique are effective, at least in the short term. All studies showed improvements and statistical significance with a mean intervention time of 30 min and an average follow-up of 5 months. Whether or not patients were requested to demonstrate their own inhaler use after demonstration was frequently not reported. Approximately half of the studies provided additional disease education or embedded the inhaler education in a more complex intervention. Another one that collects the interventions based on the Information-Motivation-Behavioural skills (IMB model) showed that these interventions based on the demonstration of inhalation technique may be more effective (Jia et al., 2020).

When looking at studies that evaluate both types of educational interventions together, we found that Bosnic-Anticevich et al. (Bosnic-Anticevich et al., 2010) referred to an improvement of 89% for the group receiving the demonstration, opposed to an improvement of 44% for the group receiving the leaflet and verbal information. Furthermore, Toumas et al. (Toumas et al., 2009) carried out a study with students to

whom they gave a leaflet, and they reported that only 10% of the group performed the technique correctly after reading it. They then gave the students a demonstration and the improvement significantly rose to 62%. These results are similar to the findings reported in TECEPOC and TIEPOC trials.

Although inhalation technique improved at the end of follow-up in the subjects who received the leaflet in the IAR cohort of the TECEPOC study, their performance was very similar to those of the CG. Educational intervention with leaflets alone has been shown to be effective in several studies. Takemura et al. (Takemura et al., 2011; Takemura et al., 2013) found that 39 patients improved adherence to the inhaled therapy, which included the inhalation technique, on the fourth year follow-up visit. Schulte et al. (Schulte et al., 2008) managed to increase the correct inhalation technique percentage by 23%.

However, reading the package leaflet alone is not sufficient to ensure proper inhalation technique (Klijn et al., 2017; Melani, 2021). Many of the package leaflets are often difficult to read, and the print is too small for older patients. In addition, it often contains general rules for handling each device, to comply with legislation, but does not aim to train as a primary objective.

Percentages of improvement in inhalation technique obtained in the present study are lower than those reported in the literature with only some exceptions (Giner et al., 2002; Cabedo García et al., 2010; O'Dwyer et al., 2020). This could be due to the fact that we analysed under the intention to treat principle, whereas the rest of the authors collected the data from the patients who attended the follow-up visit without considering the dropouts.

The teach-back methods with a practical demonstration of inhaler technique with the opportunity for the patients to show how they use their inhaler and receive feedback from instructors is more effective than simple verbal instruction (Klijn et al., 2017). Likewise, as inhaler mastery tends to wane over time, repeated rounds of education and feed-back are required (Axtell et al., 2017; Yoo et al., 2017; Ahn et al., 2019). The problem of this educational approach is that it is time-consuming and seems to remain limited to some successful experiences in real life but does never achieve extensive dissemination (Melani, 2021). Digital technologies could be an improvement, due to their potential to produce devices, such as smart inhalers, with a range of monitoring capabilities, as reported in an interesting review on the subject (Dundon et al., 2020). Applying digital technology advancements to the sector of inhaler technique might offer a large advantage, but the best outcomes will be obtained with a better standardisation of device use and maintenance and strict cooperation among physicians, patients and manufacturers and not working independently (Melani, 2021).

For all these interventions it is critical to evaluate whether patients are able to use their inhaler device correctly. In our study the percentage of incorrect use of inhaler is near 91%. Significant evidence shows that nearly 90% of patients with COPD incorrectly use their inhalers and that many of them display a technique that possibly delivers inadequate doses (Chrystyn et al., 2017; Kocks et al., 2018; Price et al., 2018; Ahn et al., 2019; Duarte-De-Araújo et al., 2019; Melani, 2021; Barnestein-Fonseca et al., 2022) but the percentages vary depending on the checklist used. It could be because there is no exact definition of what is considered a correct inhalation technique. It is not easy to know the operating checklist of use of all marketed inhalers. The observations on a certain drug/inhaler system cannot automatically be extended to another device releasing the same medicine, or to the same device delivering another drug. Moreover, several aspects of inhaler technique and storage remain undefined. Regulatory authorities have strict rules for marketing admission of inhalers, including drug delivery at different flows, positions, and storage conditions, but they cannot be translated to the complexity of real life use (Melani, 2021).

The most frequent errors found in all the devices are the same as those observed in other studies as reflected in the review by Melani A (Melani, 2021). In previous studies, we have found that these errors were related to the patient's preparation and physical ability to perform the technique, mainly lower peak inhalation flow, lower scores in the MMSE, fewer visits to the pulmonologist, and not having received prior instruction on inhaler use (Barnestein-Fonseca et al., 2013; Barnestein-Fonseca et al., 2022). The errors related to the device are less frequent and related to different flows (coordination in pMDI) and positions (in Turbuhaler®) (Chrystyn et al., 2017; Duarte-De-Araújo et al., 2019; Lindh et al., 2019). Despite technology advancements, most subjects do not intuitively achieve inhaler mastery alone (Harb et al., 1902; Melani, 2021). The real-world studies show that an easy-to-use inhaler is not yet available.

Despite the high rate of incorrect technique, many subjects reported having received instruction about the inhalation technique. This could be related to a lack of knowledge of inhaler use and teaching techniques among prescribers (Aksu et al., 2016; Plaza et al., 2018; Al-Otaibi, 2020; Cvetkovski et al., 2020). In addition, it is related to no regular test, reminder and type of instruction (Klijn et al., 2017; Takaku et al., 2017; Kaplan and Price, 2018; Lavorini et al., 2019; Melani, 2021; Lindh et al., 2022). There is extensive literature about self-management education in COPD patients in which different types of educational interventions are checked with a wide spectrum of outcomes (Schrijver et al., 2020). There are not enough interventions focused on inhalation technique training even though there is hard evidence of its usefulness (Klijn et al., 2017). Moreover, the wide majority of studies are centred on patients with asthma, leaving COPD patients aside.

There seems to be agreement about the need that inhalers should be prescribed after a demonstration led by a healthcare professional. Inhalation technique should be performed correctly

in every visit to the healthcare centre and supervised by a professional (Aksu et al., 2016; Lavorini et al., 2019; Melani, 2021; Global Iniciative for COPD, 2022). Every time a change in treatment is made, the demonstration by the professional and the patient should be performed (Usmani et al., 2022).

There is little evidence on the appropriate time for reminding patients of inhalation technique. This is partly due to most studies being performed in asthma patients (Bosnic-Anticevich et al., 2010; Takemura et al., 2013; Crane et al., 2014; Axtell et al., 2017; Klijn et al., 2017) although in the last few years some studies enrolled only COPD patients (Bouwmeester et al., 2015; Klijn et al., 2017; Takaku et al., 2017; Yoo et al., 2017; Ahn et al., 2020; Choomuang et al., 2022) but most of the educational programs were too brief.

Three studies scheduled three educational visits at 2-week intervals (Yoo et al., 2017; Kim et al., 2021), or according to a 1-month program (Lee et al., 2016). Takaku et al. showed the effectiveness of education on inhaler technique and adherence for a relatively long period (3 months) after one session of education (Takaku et al., 2017). Another study scheduled three educational visits at 3-month intervals along 6 months and they reported positive results at 3 months (Ahn et al., 2020). We have found similar results, ending up in a recommendation of scheduled reminders each 3 months to improve the inhalation technique in patients with COPD for a longer follow-up (12 months).

Although we have not found any statistical significance, preferences have been defined as modulators of the interventions' effects in clinical trials, partly due to the opportunity of choosing the treatment based on personal elections which could increase the feeling of self-control related to the learning process, and this would encourage behavioural change, leading to better results (Janevic et al., 2003; Lehmann et al., 2020).

In the preferences' evaluation it has been suggested that the best method would be to establish the treatment's efficacy and then use a pragmatic design. In reference to this type of design, a preference trial could be useful in reflecting the usual care from a more realistic point of view (Preference Collaborative Review Group, 2008; Mills et al., 2011). This could be particularly appropriate in health education research, as it is imperative to show the superiority of one of the educational interventions and also to explore the potential effects attributed to the preferences.

Controversial results have been found related to the effect of the preferences (Floyd and Moyer, 2010; Mills et al., 2011; Lehmann et al., 2020). It has also been observed that the preferences can interfere in the recruitment process. In order to avoid this inconvenience, the TECEPOC study was decided to partially randomise patients regarding their preferences, meaning the group allocation already considers the patient's choice during the recruitment process.

Another aspect to be taken into account with regard to preferences concerns the possibility of modification of the results especially in small sample studies, but no consistency has been observed with regard to the direction of this modification (Floyd and Moyer, 2010; Mills et al., 2011; Lehmann et al., 2020). The present preference study, TECEPOC, has shown that preferences were not related with the efficacy of the designed educational interventions. One possible explanation could be the larger sample size in our case, which means that the preference effect may have disappeared.

These studies have some strengths and limitations. The main strengths are the combination of two studies, with different epidemiological designs, with a big sample size and long follow-up (up to 1 year), which has allowed us to assess the role of patient's preferences and to know better how often to remind patients of the inhalation technique.

This study also had several limitations. First, the loss of estimation accuracy resulting from the missing data. To diminish this bias, we applied an increase of 40% in the sample size (expected losses) and several phone calls on different days and at different times for unreachable patients and additional appointments for the patients who did not attend the clinic visits. Second, a selection bias could play a role in the results. We got a dropout percentage that was lower than expected but when the similarities between the initial sample and the final sample were analysed, several differences were found. The dropout was more relevant for women, older people and participants with more cognitive impairment. Third, COPD is a chronic progressive illness and the 1 year of follow up could partly explain a higher deterioration in the health outcomes. Another bias, that was taken into account in the analysis of the results, was the rescue mechanism for participants in the control group where the interviewer only corrected the critical mistakes previously agreed by the research team and all interviewers who participated in the study followed the guidelines.

The present study demonstrates the effectiveness of direct training on inhalation technique by a trained professional (e.g. doctor, nurse, pharmacist) with adequate time (e.g. specific medication review consultation) to allow the patient to correct errors through teach-back and repetition. It is an easy intervention to perform, with potentially high effectiveness in real life Although an improvement was observed after the training, there was still a considerable group of patients who were unable to use their device correctly. This would require further analysis of patient characteristics in order to be able to modify some aspects of the training (more frequent reminders), or to assess the need to change inhalers or to use a spacer with some devices.

Further studies are needed to confirm the schedule of reminders and to demonstrate that the intervention can be effectively applied by professionals (doctors, nurses, pharmacists) providing direct clinical care to patients with inhaled medication.

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.

Ethics statement

The studies involving human participants were reviewed and approved by Ethical Committee of Distrito Sanitario Málaga; Ethical Committee Axarquia. The patients/participants provided their written informed consent to participate in this study.

Author contributions

All authors contributed to the conception and design of the study. PB-F, JL-F, and FL-F have participated in the design of the study intervention. FL-F as main researcher and PB-F and JL-F as senior researchers, are responsible for implementation of the study from the recruitment process until the end of experimental protocol. PB-F and VC-L are responsible for patients training in primary care centres. VA-L and VM-C have a substantial contribution in the implementation and database design. PB-F, VC-L, and FL-F perform the statistical analysis. PB-F, VM-C, and FL-F wrote the first draft of 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.

Publisher's note

References

Ahn, J. H., Chung, J. H., Shin, K. C., Choi, E. Y., Jin, H. J., Lee, M. S., et al. (2019). Critical inhaler handling error is an independent risk factor for frequent exacerbations of chronic obstructive pulmonary disease: Interim results of a single center prospective study. *Int. J. Chron. Obstruct. Pulmon. Dis.* 14, 2767–2775. doi:10.2147/COPD.S234774

Ahn, J. H., Chung, J. H., Shin, K. C., Jin, H. J., Jang, J. G., Lee, M. S., et al. (2020). The effects of repeated inhaler device handling education in COPD patients: A prospective cohort study. *Sci. Rep.* 10 (1), 19676–19679. Available from. doi:10.1038/s41598-020-76961-y

Aksu, F., Şahin, A. D., Şengezer, T., and Aksu, K. (2016). Effect of training by a physician on dynamics of the use of inhaler devices to improve technique in patients with obstructive lung diseases. *Allergy Asthma Proc.* 37 (5), e98–e102. doi:10.2500/aap.2016.37.3969

Al-Otaibi, H. (2020). Evaluation of health-care providers' knowledge in the science of aerosol drug delivery: Educational sessions are necessary. *J. Fam. Community Med.* 27, 62–66. [Internet]. doi:10.4103/jfcm.JFCM_138_19https://pubmed.ncbi.nlm.nih.gov/32030080/.[cited 2022 Jul 3];27(1):62–6. Available from:

Axtell, S., Haines, S., and Fairclough, J. (2017). Effectiveness of various methods of teaching proper inhaler technique: The importance of pharmacist counseling. *J. Pharm. Pract.* 30 (2), 195–201. doi:10.1177/0897190016628961

Barnestein-Fonseca, P., Leiva-Fernández, J., Acero-Guasch, N., García-Ruiz, A., Prados-Torres, D., and Leiva-Fernández, F. (2013). Técnicas de inhalación en pacientes con Enfermedad Pulmonar Obstructiva Crónica (EPOC). Eficacia de una instrucción periódica. *Med. Fam.* 14, 11–22.

Barnestein-Fonseca, P., Vázquez-González, N., Martín-Montañez, E., Leiva-Fernández, J., Cotta-Luque, V., and Leiva-Fernández, F. (2022). The clinical relevance of inhalation technique in chronic obstructive pulmonary disease patients. *Med. Clin.* 158 (10), 472–475. doi:10.1016/j.medcli.2021.04.034

Bhattarai, B., Walpola, R., Mey, A., Anoopkumar-Dukie, S., and Khan, S. (2020). Barriers and strategies for improving medication adherence among people living with copd: A systematic review. *Respir. Care* 65 (11), 1738–1750. doi:10.4187/respcare.07355

Bosnic-Anticevich, S. Z., Sinha, H., So, S., and Reddel, H. K. (2010). Metered-Dose inhaler technique: The effect of two educational interventions delivered in community pharmacy over time. *J. Asthma* 47 (3), 251–256. doi:10.3109/02770900903580843

Bouwmeester, C., Kraft, J., and Bungay, K. M. (2015). Optimizing inhaler use by pharmacist-provided education to community-dwelling elderly. Respir Med [Internet][cited 2022 Jul 6];109(10):1363–8. Available from: http://www.resmedjournal.com/article/S0954611115300287/fulltext.

Cabedo García, V. R., Garcés Asemany, C. R., Cortes Berti, A., Oteo Elso, J. T., and Ballester Salvador, F. J. (2010). [Effectiveness of the correct use of inhalation devices in patients with COPD: Randomized clinical trial]. *Med. Clin.* 135 (13), 586–591. doi:10.1016/j.medcli.2010.03.027

Choomuang, W., Pothirat, C., Chaiwong, W., Liwsrisakun, C., Theerakittikul, T., Phetsuk, N., et al. (2022). The effectiveness of large group demonstration training method on the use of pressurized metered-dose inhaler in elderly with chronic obstructive pulmonary disease. *J. Thorac. Dis.* 14 (4), 919–926. doi:10.21037/jtd-21-1612

Chronic obstructive pulmonary disease in over 16s: Diagnosis and management. *Pract. Nurse.* 2018;48(12).

Chrystyn, H., Van Der Palen, J., Sharma, R., Barnes, N., Delafont, B., Mahajan, A., et al. Device errors in asthma and COPD: Systematic literature review and meta-analysis.*npj Prim Care Respir Med* [Internet]. 2017 [cited 2017 Dec 19];27. Available from: https://www.nature.com/articles/s41533-017-0016-z.pdf.

Crane, M. A., Jenkins, C. R., Goeman, D. P., and Douglass, J. A. (2014). Inhaler device technique can be improved in older adults through tailored education: Findings from a randomised controlled trial. *NPJ Prim. Care Respir. Med.* 241, 14034. [Internet]. 2014 Sep 4 [cited 2022 Jul 6];24(1):1–5. Available from:. doi:10.1038/npjpcrm.2014.34https://www.nature.com/articles/npjpcrm201434.

Cvetkovski, B., Hespe, C., Tan, R., Kritikos, V., Azzi, E., and Bosnic-Anticevich, S. (2020). General practitioner use of generically substitutable inhaler devices and the impact of training on device mastery and maintenance of correct inhaler technique. *Pulm Ther* [Internet][cited 2022 Jul 3];6(2):315–31Available from: https://pubmed.ncbi.nlm.nih.gov/33038005/.

Devon, W. J., and Holman (1966). Instructions for use of questionnaire on respiratory symptoms. *Med. Res. Counc. Comm. Res. into chronic bronchitis*.

Dhand, R., Mahler, D. A., Carlin, B. W., Hanania, N. A., Ohar, J. A., Pinto-Plata, V., et al. (2018). Results of a patient survey regarding COPD knowledge, treatment experiences, and practices with inhalation devices. *Respir. Care* 63 (7), 833–839. doi:10.4187/respcare.05715

Duarte-De-Araújo, A., Teixeira, P., Hespanhol, V., Correia-De-Sousa, J., and DuArte-de-ArAujo, A. (2019). Copd: Misuse of inhaler devices in clinical practice. *Int. J. Chron. Obstruct. Pulmon. Dis.* 14, 1209–1217. doi:10.2147/COPD.S178040

Dundon, A., Cipolla, D., Mitchell, J., and Lyapustina, S. (2020). Reflections on digital health tools for respiratory applications. *J. Aerosol Med. Pulm. Drug Deliv.* 33, 127–132. [Internet]. doi:10.1089/jamp.2020.1597https://pubmed.ncbi.nlm.nih.gov/32176547/.[cited 2022 Jul 4];33(3):127–32. Available from:

Efil, S., Enç, N., and Ece, T. (2020). Effect of training provided to patients with chronic obstructive pulmonary disease on drug management. *Jpn. J. Nurs. Sci.* 17 (3), 123333. doi:10.1111/jjns.12333

Ferrer, M., Alonso, J., Prieto, L., Plaza, V., Monsó, E., Marrades, R., et al. (1996). Validity and reliability of the St george's respiratory questionnaire after adaptation to a different language and culture: The Spanish example. *Eur. Respir. J.* 9 (6), 1160–1166. doi:10.1183/09031936.96.09061160

Floyd, A. H. L., and Moyer, A. (2010). Effects of participant preferences in unblinded randomized controlled trials. *J. Empir. Res. Hum. Res. Ethics.* 5 (2), 81–93. doi:10.1525/jer.2010.5.2.81

Giner, J., Macián, V., and Hernández, C. (2002). Grupo EDEN[Multicenter prospective study of respiratory patient education and instruction in the use of inhalers (EDEN study)]. *Arch. Bronconeumol.* 38 (7), 300–305. doi:10.1016/s0300-2896(02)75222-8

Global Iniciative for Copd (2022). *Global strategy for the diagnosis, treatment, management and prevention of chronic obstructive pulmonary disease 2022*. Report [Internet]. GOLD ReportAvailable from: https://goldcopd.org/2022-gold-reports-2/.

Harb, H. S., Laz, N. I., Rabea, H., and Abdelrahim, M. E. A. First-time handling of different inhalers by chronic obstructive lung disease patients./ 0190214820201789903 [Internet]. 2020 Aug 8 [cited 2022 Jul 4];46(7):258–69. Available from: https://www.tandfonline.com/doi/abs/10.1080/01902148.2020.1789903 101080

Herdman, M., Gudex, C., Lloyd, A., Janssen, M., Kind, P., Parkin, D., et al. (2011). Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res* [Internet][cited 2015 Oct 15];20(10):1727–36. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3220807&tool=pmcentrez&rendertype=abstract.

Janevic, M. R., Janz, N. K., Dodge, J. A., Lin, X., Pan, W., Sinco, B. R., et al. (2003). The role of choice in health education intervention trials: A review and case study. *Soc. Sci. Med.* 56 (7), 1581–1594. doi:10.1016/s0277-9536(02)00158-2

Jia, X., Zhou, S., Luo, D., Zhao, X., Zhou, Y., and Cui, Y-M. (2020). Effect of pharmacist-led interventions on medication adherence and inhalation technique in adult patients with asthma or COPD: A systematic review and meta-analysis. *J. Clin. Pharm. Ther.* 45, 904–917. doi:10.1111/jcpt.13126

Kaplan, A., and Price, D. (2018). Matching inhaler devices with patients: The role of the primary care physician. *Can Respir J* [Internet][cited 2022 Jul 3];2018. Available from: https://pubmed.ncbi.nlm.nih.gov/29951160/.

Kim, J. S., Hashweh, N., Li, H., Choudhary, S., Santosh, S., and Charbek, E. (2021). Effectiveness of one-on-one coaching in improving pressurized metered dose inhaler (pMDI) technique among COPD patients: A prospective clinical study. *BMC Pulm. Med.* 21 (1), 266–267. Available from. doi:10.1186/s12890-021-01627-y

Klijn, S. L., Hiligsmann, M., Evers, S. M. A. A., Román-Rodríguez, M., van der Molen, T., and van Boven, J. F. M. (2017). Effectiveness and success factors of educational inhaler technique interventions in asthma & COPD patients: A systematic review. *NPJ Prim. Care Respir. Med.* 27, 24. [Internet][cited 2019 Mar 25];27(1Available from:. doi:10.1038/s41533-017-0022-1

Kocks, J. W. H., Chrystyn, H., van der Palen, J., Thomas, M., Yates, L., Landis, S. H., et al. (2018). Systematic review of association between critical errors in inhalation and health outcomes in asthma and COPD. *NPJ Prim. Care Respir. Med.* 28 (1), 43–46. Available from. doi:10.1038/s41533-018-0110-x

Lareau, S. C., and Hodder, R. (2012). Teaching inhaler use in chronic obstructive pulmonary disease patients. *J. Am. Acad. Nurse Pract.* 24 (2), 113–120. doi:10.1111/j.1745-7599.2011.00681.x

Lavorini, F., Janson, C., and Braido, F., Stratelis, G., and Lokke, A. (2019). What to consider before prescribing inhaled medications: A pragmatic approach for evaluating the current inhaler landscape. *Ther. Adv. Respir. Dis.* 13, 1753466619884532–28. doi:10.1177/1753466619884532

Lee, J. Y., Yoo, K. H., Kim, D. K., Kim, S-H., Kim, T-E., Kim, T-H., et al. (2016). Effects of educational interventions for chronic airway disease on primary care. *J. Korean Med. Sci.* 31 (7), 1069–1074. doi:10.3346/jkms.2016.31.7.1069

Lehmann, B. A., Lindert, L., Ohlmeier, S., Schlomann, L., Pfaff, H., and Choi, K. E. (2020). And then He got into the wrong group": A qualitative study exploring the effects of randomization in recruitment to a randomized controlled trial. *Int. J. Environ. Res. Public Health* 17, 1886. [Internet]Mar 2 [cited 2022 Jul 6];17(6). Available from:. doi:10.3390/ijerph17061886

Leiva-Fernández, F., Leiva-Fernández, J., Zubeldia-Santoyo, F., García-Ruiz, A., Prados-Torres, D., and Barnestein-Fonseca, P. (2012)., .Efficacy of two educational interventions about inhalation techniques in patients with chronic obstructive pulmonary disease (COPD), *TECEPOC study Protoc. a Partial. randomized Control. trial (preference trial)* 13. Trials, 64

Leiva-Fernández, J., Leiva-Fernández, F., Vázquez-Alarcón, R. L., García-Ruiz, A., Prados-Torres, D., and Barnestein-Fonseca, P. (2014). *Study protocol for a randomized, controlled trial comparing the efficacy of two educational interventions to improve inhalation techniques in patients with chronic obstructive pulmonary disease (COPD): TIEPOC study*. London: Drugs Context.

Lindh, A., Theander, K., Arne, M., Lisspers, K., Lundh, L., Sandelowsky, H., et al. (2019). Errors in inhaler use related to devices and to inhalation technique among patients with chronic obstructive pulmonary disease in primary health care. *Nurs. Open* 6 (4), 1519–27. doi:10.1002/nop2.357

Lindh, A., Theander, K., Arne, M., Lisspers, K., Lundh, L., Sandelowsky, H., et al. (2022). One additional educational session in inhaler use to patients with COPD in primary health care – a controlled clinical trial. *Patient Educ. Couns.* 105, 2969–2975. doi:10.1016/j.pec.2022.05.013

Lobo, A., Saz, P., and Marcos, G. G. de T. Z. (2002). *Mmse: Examen cognoscitivo mini-mental*. Madrid: TEA Ediciones.

Mahler, D. A., Weinberg, D. H., Wells, C. K., and Feinstein, A. R. (1984). The measurement of dyspnea. Contents, interobserver agreement, and physiologic correlates of two new clinical indexes. *Chest* 85 (6), 751–8. doi:10.1378/chest.85.6.751

Melani, A. S. (2007). Inhalatory therapy training: A priority challenge for the physician. *Acta Biomed.* 78 (3), 233–45.

Melani, A. S. (2021). Inhaler technique in asthma and COPD: Challenges and unmet knowledge that can contribute to suboptimal use in real life. *Expert Rev. Clin. Pharmacol.* 14 (8), 991–1003. doi:10.1080/17512433.2021.1929922

Mills, N., Donovan, J. L., Wade, J., Hamdy, F. C., Neal, D. E., and Lane, J. A. (2011). *Exploring treatment preferences facilitated recruitment to randomized controlled trials.*J Clin Epidemiol, 64, (10),

Miravitlles, M., Calle, M., Molina, J., Almagro, P., Gómez, J-T., Trigueros, J. A., et al. (2022). Spanish COPD guidelines (GesEPOC) 2021: Updated pharmacological treatment of stable COPD. *Arch. Bronconeumol.* 58 (1), 69–81. doi:10.1016/j.arbres.2021.03.005

O'Dwyer, S., Greene, G., MacHale, E., Cushen, B., Sulaiman, I., Boland, F., et al. . Personalized Biofeedback on Inhaler Adherence and Technique by Community Pharmacists: A Cluster Randomized Clinical Trial. *J allergy Clin Immunol Pract* [Internet]. 2020 Feb 1 [cited 2022 Jul 6];8(2):635–44. Available from: https://pubmed.ncbi.nlm.nih.gov/31568927/.

Ozoglu Aytac, S., Kilic, S. P., and Ovayolu, N. (2020). Effect of inhaler drug education on fatigue, dyspnea severity, and respiratory function tests in patients with COPD. *Patient Educ. Couns.* 103 (4), 709–16. Available from:. doi:10.1016/j.pec.2019.11.003

Padmanabhan, M., Tamilarasu, K., Rajaram, M. B. G., and Batmanabane, G. (2019). Inadequate inhaler technique, an everlasting problem, is associated with poor disease control - a cross sectional study. *Adv. Respir. Med.* 87 (4), 217–25. doi:10.5603/ARM.a2019.0021

Plaza Moral, V., Giner Donaire, J., Bustamante Madariaga, V., Máiz Carro, L., Viejo Casas, A., Nieto Royo, R., et al. (2018). Guía GEMA. Inhaladores. Terapia inhalada: Fundamentos, dispositivos y aplicaciones prácticas. *J. Chem. Inf. Model.* 78, 233–245.

Plaza, V., Giner, J., Rodrigo, G. J., Dolovich, M. B., and Sanchis, J. (2018). Errors in the use of inhalers by health care professionals: A systematic review. J allergy Clin

Immunol Pract [Internet][cited 2022 Jul 3];6(3):987–95. Available from: https://pubmed.ncbi.nlm.nih.gov/29355645/.

Preference Collaborative Review Group (2008). Patients' preferences within randomised trials: Systematic review and patient level meta-analysis. *BMJ* 337, a1864. doi:10.1136/bmj.a1864

Price, D., Keininger, D. L., Viswanad, B., Gasser, M., Walda, S., and Gutzwiller, F. S. (2018). Factors associated with appropriate inhaler use in patients with COPD – lessons from the REAL survey. *Int. J. Chron. Obstruct. Pulmon. Dis.* 13, 695–702. doi:10.2147/COPD.S149404

Rincon-Montaña, M. R. D. (2019). Inhalation devices for asthma and COPD: A review of the literature. *Rev. Colomb. Neumol.* 31 (1), 32–42.

Sanchis, J., Corrigan, C., Levy, M. L., and Viejo, J. L. (2013). Inhaler devices – from theory to practice. *Respir Med* 107, (4),[Internet][cited 2019 Mar 25];107(4): 495–502. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23290591. ADMIT group

Sanchis, J., Gich, I., Pedersen, S., and Sci, M. (2016). Systematic review of errors in inhaler use has patient technique improved over time? 150(2) 394-406[Internet] [cited 2017 Dec 19];150(2):394–406. Available from: http://journal.chestnet.org/article/S0012-3692(16)47571-9/pdf.

Schrijver, J., Lenferink, A., Brusse-Keizer, M., Zwerink, M., van der Valk, P. D. L. P. M., and van der Palen, J. E, T. W. (2020). Self-management interventions for people with chronic obstructive pulmonary disease (Review). *Cochrane Database Syst. Rev.* (1), CD002990.

Schulte, M., Osseiran, K., Betz, R., Wencker, M., Brand, P., Meyer, T., et al. (2008). Handling of and preferences for available dry powder inhaler systems by patients with asthma and COPD. *J. Aerosol Med. Pulm. Drug Deliv.* 21 (4), 321–8. doi:10.1089/jamp.2007.0634

Takaku, Y., Kurashima, K., Ohta, C., Ishiguro, T., Kagiyama, N., Yanagisawa, T., et al. (2017). How many instructions are required to correct inhalation errors in patients with asthma and chronic obstructive pulmonary disease? *Respir. Med.* 123, 110–115. doi:10.1016/j.rmed.2016.12.012

Takemura, M., Mitsui, K., Ido, M., Matsumoto, M., Koyama, M., Inoue, D., et al. (2013). Effect of a network system for providing proper inhalation technique by community pharmacists on clinical outcomes in COPD patients. *Int. J. Chron. Obstruct. Pulmon. Dis.* 8, 239–244. doi:10.2147/COPD.S44022

Takemura, M., Mitsui, K., Itotani, R., Ishitoko, M., Suzuki, S., Matsumoto, M., et al. (2011). Relationships between repeated instruction on inhalation therapy, medication adherence, and health status in chronic obstructive pulmonary disease. *Int. J. Chron. Obstruct. Pulmon. Dis.* 6, 97–104. doi:10.2147/COPD.S16173

Toumas, M., Basheti, I. A., and Bosnic-Anticevich, S. Z. (2009). Comparison of small-group training with self-directed internet-based training in inhaler techniques. *Am. J. Pharm. Educ.* 73 (5), 85. doi:10.5688/aj730585

Usmani, O. S., Bosnic-Anticevich, S., Dekhuijzen, R., Lavorini, F., Bell, J., Stjepanovic, N., et al. (2022). Real-world impact of nonclinical inhaler regimen switches on asthma or COPD: A systematic review. *J. Allergy Clin. Immunol. Pract.* 10, 2624–2637. [cited 2022 Jul 3]; Available from. doi:10.1016/j.jaip.2022.05.039

World Health Organization (2015). *Report on the 2Nd who global forum on innovation for ageing populations*.

Yoo, K. H., Chung, W. Y., Park, J. H., Hwang, S. C., Kim, T. E., Oh, M. J., et al. (2017). Short-term evaluation of a comprehensive education program including inhaler training and disease management on chronic obstructive pulmonary disease. *Tuberc. Respir. Dis.* 80 (4), 377–84. doi:10.4046/trd.2017.0041

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