Measurement of Health-Related Quality of Life in Children and Adolescents with Chronic Conditions

Karina Mayoral Ortiz

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Doctoral Thesis - 2023

Department of Paediatrics,
Obstetrics and Gynaecology, and
Preventive Medicine and Public Health

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Universitat Autònoma de Barcelona

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Under the direction of doctors

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Barcelona, May 2023

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CERTIFY:

That **Karina Mayoral Ortiz** has carried out under our supervision the thesis entitled **"Measurement of Health-Related Quality of Life in Children and Adolescents with Chronic Conditions",** which meets the necessary conditions for its presentation as a doctoral thesis.

Montserrat Ferrer, PhD, MD
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Barcelona, 17 of May 2023.

A mi madre,

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Abstract

The general aim of this doctoral thesis was to evaluate the measurement properties of the EQ-5D-Y for monitoring the Health-Related Quality of Life (HRQL) and the impact of the disease in children and adolescents with chronic conditions, as well as to explore its administration through different electronic versions. Three specific objectives were considered: two focused on evaluating the validity, reliability, and responsiveness of the generic instrument EQ-5D-Y among paediatric patients with diabetes and asthma; and a third objective that aimed at designing and pilot-testing a smartphone mobile application to monitor children and adolescents with persistent asthma.

The data used to perform this thesis come from two projects. The first one, "Digital EQ-5D-Y & KIDSCREEN", was a clinical trial in children and adolescents (8-19 years old) with type 1 diabetes mellitus (T1DM) (n=205), designed to evaluate the impact of routine use of HRQL assessment in clinical practice using the electronic version of KIDSCREEN-27 and of the EQ-5D-Y. The analysis of the 136 patients who completed the EQ-5D-Y at baseline and follow-up demonstrated the acceptability, construct validity, reliability, and responsiveness of the instrument for evaluating HRQL in paediatric patients with T1DM.

The second project, "Asthma Research in Children and Adolescents (ARCA)", was a longitudinal prospective multicentre observational study aimed to assess the evolution of disease control, the HRQL, and the risk of severe asthma exacerbations in children and adolescents aged between 6 and 16 years with persistent asthma, through regular follow-up. The study involved 189 patients recruited between January 2018 and July 2020. An electronic health tool consisting of a smart-phone application (ARCA app) that collects Patient-Reported Outcome Measures, and of an online platform to provide paediatricians with access to their patients' information. The follow-up is also carried out through telephone interviews and variables obtained from the clinical records.

The development process of the ARCA app followed seven phases, which included defining and designing the tool, testing its functionality, and evaluating its usability. Three versions of the app were created for different age groups, including parents/proxy (of 6–7 years old children), children (8–11 years old), and adolescents (12–16 years old). Results from the app usability survey were excellent for parents, children, and adolescents.

The ARCA app automatically administers questionnaires to monitor HRQL, including the EQ-5D and PROMIS Pediatric Asthma Impact Scale. We evaluated the psychometric properties of the EQ-5D-Y descriptive system and utility index, both in its self-completed and its proxy version, for children with asthma. The analysis of 119 patients that downloaded the app and completed the telephone interview showed the feasibility, construct validity, and reliability of the EQ-5D-Y for evaluating HRQL when administered through a smartphone application and self-responded by children and adolescents with mild-to-moderate persistent asthma, or through proxy response by parents. This study was the first to evaluate the psychometric properties of the EQ-5D-Y utility index, which will allow the calculation of Quality-Adjusted Life Years for economic evaluations in future studies.

Resumen

El objetivo general de esta tesis doctoral fue evaluar las propiedades métricas del EQ-5D-Y para la monitorización de la Calidad de Vida Relacionada con la Salud (CVRS) y el impacto de la enfermedad en niños y adolescentes con patologías crónicas, así como explorar su administración a través de diferentes versiones electrónicas. Se consideraron tres objetivos específicos: dos enfocados en evaluar la validez, fiabilidad y capacidad de respuesta del instrumento genérico EQ-5D-Y en pacientes pediátricos con diabetes y asma; y un tercer objetivo destinado a diseñar y realizar la prueba piloto de una aplicación móvil para 'smartphones' para la monitorización de niños, niñas y adolescentes con asma persistente.

Los datos utilizados para realizar esta tesis proceden de dos proyectos. El primero, "EQ-5D-Y y KIDSCREEN digitales", era un ensayo clínico en niños, niñas y adolescentes (8-19 años) con diabetes mellitus tipo 1 (DM1) (n=205), diseñado para evaluar el impacto del uso rutinario de la evaluación de la CVRS en la práctica clínica mediante la versión electrónica del KIDSCREEN-27 y del EQ-5D-Y. El análisis de los 136 pacientes que completaron el EQ-5D-Y al inicio y en el seguimiento demostró la aceptabilidad, validez de constructo, fiabilidad y sensibilidad al cambio del instrumento para evaluar la CVRS en pacientes pediátricos con DM1.

El segundo proyecto, "Asthma Research in Children and Adolescents (ARCA)", era un estudio multicéntrico observacional longitudinal prospectivo destinado a evaluar la evolución del control de la enfermedad, la CVRS y el riesgo de exacerbaciones asmáticas graves en niños, niñas y adolescentes de entre 6 y 16 años con asma persistente, a través de un seguimiento regular. Se reclutaron 189 pacientes entre enero de 2018 y julio de 2020. Se desarrolló y probó una herramienta de salud electrónica que consta de una aplicación para 'smartphones' (aplicación ARCA) que recoge resultados reportados por los pacientes y de una plataforma online para proporcionar a los pediatras acceso a la información recogida. Además, se realiza seguimiento con entrevistas telefónicas y se obtienen variables de la historia clínica.

El proceso de desarrollo de la aplicación ARCA siguió siete fases, incluyendo la definición y el diseño de la herramienta, la prueba de su funcionalidad y la evaluación de su usabilidad. Se crearon tres versiones de la aplicación para los diferentes grupos de edad, incluidos padres/representantes (de niños/as con 6-7 años), niños/as (8 a 11 años) y adolescentes (12 a 16 años). Los resultados de la encuesta de usabilidad de la aplicación fueron excelentes para padres, niños, niñas y adolescentes.

La aplicación ARCA administra automáticamente cuestionarios para monitorizar la CVRS, incluidos el EQ-5D y la escala de impacto del asma pediátrica PROMIS. Evaluamos las propiedades psicométricas del sistema descriptivo e índice de utilidad del EQ-5D-Y, tanto en la versión autoadministrada como en su versión proxy, para niños/as con asma. El análisis de 119 pacientes que descargaron la aplicación y completaron la entrevista telefónica mostró la factibilidad, validez de constructo y fiabilidad del EQ-5D-Y para evaluar la CVRS cuando se administró a través de una aplicación para 'smartphones' y es autocompletado por niños, niñas y adolescentes con asma persistente de leve a moderado, o mediante la respuesta reportada por los padres. Este estudio fue el primero en evaluar las propiedades psicométricas del índice de utilidad del EQ-5D-Y, que permitirá calcular los Años de Vida Ajustados por Calidad para evaluaciones económicas en futuros estudios.

Resum

L'objectiu general d'aquesta tesi doctoral va ser avaluar les propietats mètriques de l'EQ-5D-Y per al seguiment de la Qualitat de Vida Relacionada amb la Salut (QVRS) i l'impacte de la malaltia en nens, nenes i adolescents amb malalties cròniques, així com explorar la seva administració mitjançant diferents versions electròniques. Es van considerar tres objectius específics: dos centrats en avaluar la validesa, la fiabilitat i la capacitat de resposta de l'instrument genèric EQ-5D-Y en pacients pediàtrics amb diabetis i asma; i un tercer objectiu destinat a dissenyar i realitzar la prova pilot d'una aplicació mòbil per a 'smartphones' per la monitorització de nens, nenes i adolescents amb asma persistent.

Les dades utilitzades per realitzar aquesta tesi provenen de dos projectes. El primer, "EQ-5D-Y i KIDSCREEN digitals", va ser un assaig clínic en nens, nenes i adolescents (8-19 anys) amb Diabetis Mellitus tipus 1 (DM1) (n=205), dissenyat per avaluar l'impacte de l'ús rutinari de l'avaluació de la QVRS en la pràctica clínica mitjançant la versió electrònica de KIDSCREEN-27 i de l'EQ-5D-Y. L'anàlisi dels 136 pacients que van completar l'EQ-5D-Y a l'inici i al seguiment van demostrar l'acceptabilitat, la validesa del constructe, la fiabilitat i la sensibilitat al canvi de l'instrument per avaluar la QVRS en nens i adolescents amb DM1.

El segon projecte, "Asthma Research in Children and Adolescents (ARCA)", era un estudi multicèntric observacional longitudinal prospectiu destinat a avaluar l'evolució del control de la malaltia, la QVRS i el risc d'exacerbacions asmàtiques greus en nens, nenes i adolescents entre 6 i 16 anys amb asma persistent, mitjançant un seguiment regular. Es van reclutar 189 pacients entre el gener del 2018 i el juliol del 2020. Es va desenvolupar i provar una eina de salut electrònica que consta d'una aplicació per a 'smartphones' (aplicació ARCA) que recull resultats reportats pels pacients i d'una plataforma online per proporcionar als pediatres accés a la informació recollida. A més, es realitza un seguiment mitjançant entrevistes telefòniques i s'obtenen variables de la història clínica.

El procés de desenvolupament de l'aplicació ARCA va seguir set fases, incloent-hi la definició i el disseny de l'eina, la prova de la seva funcionalitat i l'avaluació de la seva usabilitat. Es van crear tres versions de l'aplicació pels diferents grups d'edat, incloent-hi pares/representants (de nens/es de 6-7 anys), nens/es (8 a 11 anys) i adolescents (12 a 16 anys). Els resultats de l'enquesta d'usabilitat de l'aplicació van ser excel·lents per a pares, nens, nenes i adolescents.

L'aplicació ARCA administra automàticament qüestionaris per monitoritzar la QVRS, inclosos l'EQ-5D i l'escala d'impacte de l'asma pediàtrica PROMIS. Vam avaluar les propietats psicomètriques del sistema descriptiu i índex d'utilitat de l'EQ-5D-Y, tant en la versió auto administrada com en la seva versió proxy, per a nens i nenes amb asma. L'anàlisi de 119 pacients que van descarregar l'aplicació i van completar l'entrevista telefònica va mostrar la factibilitat, la validesa de constructe i la fiabilitat de l'EQ-5D-Y per avaluar la QVRS quan es va administrar mitjançant una aplicació per a 'smartphones' i va ser auto completat per nens, nenes i adolescents amb asma persistent de lleu a moderada, o mitjançant la resposta reportada pels pares. Aquest estudi va ser el primer en avaluar les propietats psicomètriques de l'índex d'utilitat de l'EQ-5D-Y, que permetrà calcular els Anys de Vida Ajustats per Qualitat en avaluacions econòmiques de futurs estudis.

Preface

The thesis titled "Measurement of Health-Related Quality of Life Assessment in Children and Adolescents with Chronic Conditions" is a compendium of publications derived from two projects. The first project, "EQ-5D-Y & KIDSCREEN digital, a clinical trial in children and adolescents (8-19 years) with type 1 diabetes," aims to evaluate the routine use of quality-of-life evaluations in clinical practice. The second project, called "The Asthma Research in Children and Adolescents (ARCA)", is a longitudinal prospective multicentre observational study designed to provide evidence about the evolution of health in children and adolescents (6-16 years) with persistent asthma. The study was funded by the Instituto de Salud Carlos III FEDER: Fondo Europeo de Desarrollo Regional (grant PI15/00449).

The thesis includes three published articles, with an additional sent to the journal and included as an annex:

1) **Mayoral K,** Rajmil L, Murillo M, Garin O, Pont A, Alonso J, Bel J, Perez J, Corripio R, Carreras G, Herrero J, Mengibar JM, Rodriguez-Arjona D, Ravens-Sieberer U, Raat H, Serra-Sutton V, Ferrer M. Measurement Properties of the Online EuroQol-5D-Youth Instrument in Children and Adolescents With Type 1 Diabetes Mellitus: Questionnaire Study. J Med Internet Res. 2019 Nov 12;21(11):e14947. doi: 10.2196/14947. PMID: 31714252; PMCID: PMC6880238.

2) **Mayoral K**, Garin O, Caballero-Rabasco MA, Praena-Crespo M, Bercedo A, Hernandez G, Castillo J, Lizano Barrantes C, Pardo Y, Ferrer M; ARCA group. Smartphone App for monitoring Asthma in children and adolescents. Qual Life Res. 2021 Nov;30(11):3127-3144. doi: 10.1007/s11136-020-02706-z. Epub 2021 Jan 2. PMID: 33387290.

3) **Mayoral K**, Garin O, Lizano-Barrantes C, Pont A, Caballero-Rabasco AM, Praena-Crespo M, Valdesoiro-Navarrete L, Guerra MT, Castillo JA, Mir I, Tato E, Alonso J, Serra-Sutton V, Pardo Y, Ferrer M; ARCA Group. Measurement properties of the EQ-5D-Y administered through a smartphone app in children with asthma: a longitudinal questionnaire study. Health Qual Life Outcomes. 2022 Mar 28;20(1):51. doi: 10.1186/s12955-022-01955-5. PMID: 35346225; PMCID: PMC8959271.

The first article, published in the Journal of Medical Internet Research, discusses the metric properties of the online EQ-5D-Y instrument in children and adolescents with type 1 diabetes mellitus. The second article, published in Quality of Life Research, describes the design and pilot test of a smartphone app “ARCA App" for monitoring children and adolescents with asthma. The third article, published in Health and Quality of Life Outcomes, focuses on the metric properties of the EQ-5D-Y proxy and self-respond versions in patients with asthma administered through a smartphone app. Articles number one and three provide relevant information on one of the most robust generic instruments to measure HRQL in children with chronic conditions. The administration mode for the

EQ-5D-Y instrument was electronic in the trial of diabetes and via a smartphone app for the longitudinal study of patients with asthma.

Finally, taking into account that the Food and Drug Administration published in March/2020 a warning about serious neuropsychiatric side effects in patients with asthma treated with montelukast, a fourth article was included as an ANNEX to this thesis for synthesizing the impact of montelukast in paediatric patients with asthma and/or allergic rhinitis, measured with Patient-Reported Outcome Measures (PROMs):

- Mayoral K, Lizano-Barrantes C, Zamora V, Pont A, Miret C, Barrufet C, Caballero-Rabasco M.A, Praena-Crespo M, Bercedo A, Valdesoiro-Navarrete L, Guerra MT, Pardo Y, Martínez Zapata MJ, Garin O, Ferrer M, ARCA Group. ***Impact of montelukast in paediatric asthma and allergic rhinitis from the patients' perspective: a systematic review and meta-analysis.***

TABLE OF CONTENTS

Abbreviations

ADA - American Diabetes Association
AHCL - Advanced hybrid closed loop
AIR - Anti-inflammatory reliever
ARCA - Asthma Research in Children and Adolescents
COMSA Core Outcome Measures sets for paediatric and adult Severe Asthma
COSMIN - COnsensus-based Standards for the selection of health status Measurement INstruments checklist
EEA - European Economic Area
eHealth - Electronic health
EMA - European Medicines Agency
EMDs - Electronic monitoring devices
EU - European Union
EU MDR - European Union Medical Device Regulation
FDA - Food and Drug Administration [United States]
GAN - Global Asthma Network
GBD - Global burden of disease
GINA - Global Initiative for Asthma
HR-PRO - Health related patient-reported outcomes
HRQL - Health-Related Quality of Life
ICF - International Classification of Functioning, Disability and Health
IDF - International Diabetes Federation
ISAAC, 1992–2012 - Study of Asthma and Allergies in Childhood
ISOQOL - Society for Quality of Life Research
ICHOM International Consortium for Health Outcomes Measurement
LABA - Long-Acting Beta-Agonists
MART - Maintenance-and-reliever therapy
mHealth - Mobile health
MHRA - Medicines and Healthcare products Regulatory Agency
MY-Q - Monitoring Individual Needs in Diabetes Youth Questionnaire
NAEPP - National Asthma Education and Prevention Program [United States]
OCS - Oral Corticosteroids
QALYs - Quality-Adjusted Life-Years
RPM - Remote patient monitoring
SABA - Short-acting beta-agonists
SMART - Single maintenance and reliever therapy
SPIRIT - Standard Protocol Items: Recommendations for Interventional Trials
T1DM - Type 1 diabetes mellitus
VAS - Visual analogue scale
WHO - World Health Organization

Questionnaires' abbreviations

ACQ - Asthma Control Questionnaire
ADDQoL-Teen - Dependent Quality of Life-Teen version
AQoL-6D - Quality of Life Assessment
c-ACT - Childhood Asthma Control Test
CAQ - Childhood Asthma Questionnaire
CHIP - Child Health and Illness Profile
CHQ - Child Health Questionnaire
CHQ-CF87 - Child Health Questionnaire-Child Form
CHU-9D - Child Health Utility
DISABKIDS - DISABKIDS condition- specific modules
DISABKIDS- DCGM - DISABKIDS chronic generic module
DISABKIDS-DM - DISABKIDS-Diabetes Module
DQOLY - Diabetes Quality of Life for Youth scale - Short Form
DQOL-Youth - Diabetes Quality of Life-Youth questionnaire
EQ-5D-Y-5L - EQ-5D version with 5 levels
KINDL-R - Revised KINDer Lebensqualitätfragebogen
KINDL-R-DM - KINDL-R-Diabetes Module
PACQLQ - Paediatric Asthma Caregiver's Quality of Life Questionnaire
PAQLQ - Paediatric Asthma Quality of Life Questionnaire
PedsQL ™ - PedsQL Diabetes Module
PedsQL4.0 - Pediatric Quality of Life Inventory 4.0
PedsQL-AM - Pediatric Quality of Life Inventory-asthma module
PedsQL-DM - PedsQL-Diabetes Module
P-PAID-C - Problem Areas In Diabetes Scale - Child Version

1. INTRODUCTION

1.1. EPIDEMIOLOGY OF CHRONIC CONDITIONS IN CHILDREN AND ADOLESCENTS

Non-communicable diseases (NCDs) are defined as a set of diseases resulting from the interaction of a combination of genetic, physiological, environmental, and behavioural factors (1). They are not transmitted from person to person, have a long duration, a slow progression, and are rarely completely curable, presenting a significant burden on individuals of all ages, communities, and economic resources (2,3). According to the results of the global burden of disease (GBD) study 2019 (4,5), NCDs account for more than 60% of disease burden measured as Disability-Adjusted Life Years (DALYs) globally and 80% in high-income nations, including adults, adolescents and children. At a global level, cardiovascular disease accounts for 393.11 million DALYs lost, followed by 251.39 million DALYs lost from cancer, 103.53 million DALYs lost due to respiratory diseases, and 1.5 million 112.73 million DALYs lost from diabetes (5). These four groups of diseases alone cause 80% of premature NCD-related deaths (6).

Young people under the age of twenty represent more than a third of the global population. According to the Global Burden of Disease Report 2019, over 2.1 billion children were affected by NCDs in 2017 (1). NCDs caused 24.8% of DALYs and 14.6% of deaths among children and adolescents that year (4). In 2019, in all European Union Member States, NCDs accounted for 38.8% of total deaths and 77.1% of DALYs among people aged 10–24 years (7). The Table 1, which is organized according to the NCDs global mortality ranking, shows that cancer was the leading cause of death, with close to 6 million children and adolescents affected by it in 2017. Moreover, chronic respiratory disorders affected over 108 million children, followed by cardiovascular disease, which affected 13.9 million children, and diabetes, with over 8.8 million children and adolescents affected globally. Additionally, as many as 231 million children and adolescents were affected by mental health disorders.

Table 1. Burden of major NCDs globally and in young people (<20 years) (1,6).

Measure	Deaths globally	Death (<20 years)	Prevalence (<20 years)	Incidence (<20 years)
Cardiovascular disease	17.9 million	71 thousand	13.9 million	1.7 million
Cancer	9.3 million	147 thousand	5.9 million	392 thousand
Chronic respiratory disorders	4.1 million	23 thousand	108.9 million	28 million
Diabetes	2.0 million*	6.3 thousand	8.8 million	1.7 million

* Including kidney disease deaths caused by diabetes

Within the main types of NCD, type 1 diabetes (T1DM) is placed under the category of diabetes. T1DM is a chronic disease that commonly affects children and adolescents. Although T1DM can occur at any age, it is most commonly diagnosed in childhood (8,9). According to the 10th edition of the International Diabetes Federation (IDF) Atlas, an estimated 1,211,900 children and adolescents under 20 years of age are living with T1D

globally. Approximately 108,200 children and adolescents under the age of 15 are diagnosed each year, with this number rising to 149,500 when the age range extends to under 20 years (10) (Table 2).

The European Region has the highest number of children and adolescents with type 1 diabetes (295,000) as well as the highest incidence annually, with 31,000 new cases per year. The European Region also has the second highest average cost per person with diabetes (USD 3,086). In 2021, 189.3 billion USD was spent on diabetes, representing 19.6% of the total spent worldwide. The IDF estimates that the total diabetes-related health expenditure will reach USD 1.03 trillion by 2030 and USD 1.05 trillion by 2045 (10).

Finland and Sweden are the countries with the highest incidence of T1DM in Europe, with 52.2 and 44.1 per 100,000 inhabitants/year respectively. The incidence in Spain in children under 14 years of age is between 10 and 20 cases per 100,000 inhabitants/year (10). However, a review of Spanish children with T1DM under 15 years of age published in 2014 calculated an incidence rate of 17.69 cases per 100,000 inhabitants/year, highlighting the higher incidence in the southern communities than in the north (11).

Table 2. Global estimates for type 1 diabetes in children and adolescents (0–14 years and 0–19 years) in 2021 (10).

Global population (0-14 years)	1.99 billion
Global population (0-19 years)	2.61 billion
Type 1 diabetes in children and adolescents (0-14 years)	
Number of prevalent (existing) cases of type 1 diabetes	651,700
Number of incident (new) cases of type 1 diabetes per year	108,300
Type 1 diabetes in children and adolescents (0-19 years)	
Number of prevalent (existing) cases of type 1 diabetes	1,211,900
Number of incident (new) cases of type 1 diabetes per year	149,500

Under the category of chronic respiratory disorders, asthma is one of the most common in children (12,13). It is considered a major global health problem, causing an estimated 495,100 deaths in 2017 (14) and 22.8 million disability-adjusted life-years in the same year (15). The International Study of Asthma and Allergies in Childhood (ISAAC, 1992–2012) has provided a vast collection of global epidemiological data about asthma and allergic disease by establishing a standardized methodology and facilitating international collaboration. Its methodology has been followed by the Global Asthma Network (GAN) Phase I study, which has provided information on the prevalence and severity of asthma symptoms in school-aged children since 2003 (16).

The findings of the GAN study (16) indicate that there is a rising prevalence of current wheeze and severe asthma symptoms in Africa and the Eastern Mediterranean regions, while there is a decreasing prevalence in South-East Asia and the Western Pacific regions. Furthermore, changes in the prevalence of asthma symptoms appear to be associated with country income. Over a period of 27 years (1993-2020), there was a decrease in the

prevalence of current wheezing in low-income countries among both children (-1.37, CI 95% -2.47 to -0.27) and adolescents (-1.67, CI 95% -2.70 to -0.64). Conversely, there was an increase in the prevalence of current wheezing in lower-middle-income countries among children (1.99, CI 95% 0.33 to 3.66) and adolescents (1.69, CI 95% 0.13 to 3.25), while the prevalence remained stable in upper-middle-income and high-income countries.

In Spain, the first available data on the prevalence of asthma, obtained in 1998, indicated a prevalence of asthma in the previous year of 6.2% in children aged 6-7 years and 9.3% in adolescents aged 13-14 years (17). Subsequently, higher prevalences were found in the ISAAC 2002-2003 study, with rates of 9.9% in schoolchildren and 10.6% in adolescents. According to the Spanish GAN study (18), conducted on a large population of schoolchildren aged 6-7 years and adolescents aged 13-14 years, the prevalence of recent wheezing (previous 12 months) was higher than in the ISAAC 2002-2003 study, with rates of 10.4% in schoolchildren and 15.3% in adolescents in 2003. The prevalence of recent wheezing varied geographically, with rates ranging from 10.2% in Cartagena to 19% in Bilbao among adolescents, and from 7% in Pamplona to 11.7% in Cartagena among schoolchildren. In addition, the prevalence of people reporting having asthma at some time was high, with rates of 12.4% in schoolchildren and 21.3% in adolescents (18).

1.2. TREATMENT OF CHRONIC CONDITIONS IN CHILDREN AND ADOLESCENTS

Chronic health conditions in children and adolescents are multifaceted and involve ongoing care from their families, schools, and communities (19). Treatment of chronic illness comes in many forms, involving a combination of pharmacological and non-pharmacological interventions, including lifestyle modifications, education, and psychological support.

General principles for managing chronic disease in adolescents have been published by the WHO (20). When working with adolescents with any medical condition, the treatment of disease, prevention of ill health, and promotion of healthy behaviours are influenced by the rapid physical, psychological, cognitive and social developmental changes that children undergo during their transition to adolescence (21,22).

Effective treatment of chronic conditions in children and adolescents is essential to manage symptoms, prevent complications, and improve overall quality of life (23). Qualitative research shows that adolescents with chronic illness experience extra effort, restriction, pain, and additional worries because of chronic illness (24,22). It is important to involve children in decisions about their care, and communication must be appropriate for their stage of development and level of understanding (25,22).

1.2.1. TYPE 1 DIABETES MELLITUS TREATMENT

Type 1 diabetes mellitus (T1DM) is a chronic autoimmune disease characterized by T-cell-mediated destruction of pancreatic β cells, resulting in a deficiency of insulin synthesis and secretion (26). The classic trio of symptoms associated with disease onset are polydipsia, polyphagia, and polyuria, along with overt hyperglycaemia remain diagnostic hallmarks in children and adolescents. An immediate need for exogenous insulin replacement is also a hallmark of type 1 diabetes, for which lifetime treatment is needed (27).

As stated by the American Diabetes Association (ADA), the principal goal in the management of T1DM is to maintain blood glucose levels as close to normal as possible with the aim of avoiding or delaying disease-related micro and macrovascular complications, including retinopathy, neuropathy, diabetic kidney disease, and atherosclerotic cardiovascular disease (28), which represent the major cause of morbidity and mortality in developed societies (27,29,30). Additional goals of therapy are to alleviate symptoms of hyperglycaemia, minimize hypoglycaemia and other adverse effects, minimize treatment burden, and maintain quality of life (30).

Glycaemic control has well documented benefits in terms of reducing both short-term and long-term complications associated with T1DM, but overly intensive control has also led to poor outcomes. Thus, glycaemic targets should be individualized for each patient and should be based on balanced considerations of clinical trial evidence and patient-specific factors (31).

The management of DM requires a continuous cycle of care, as outlined in the 12th edition of the DiPiro's Pharmacotherapy book. This cycle consists of five steps: information collection, assessment, planification, implementation, and follow-up monitoring and evaluation. These steps are important for personalized management of DM and for ensuring that the patient receives the best possible care (Figure 1) (30).

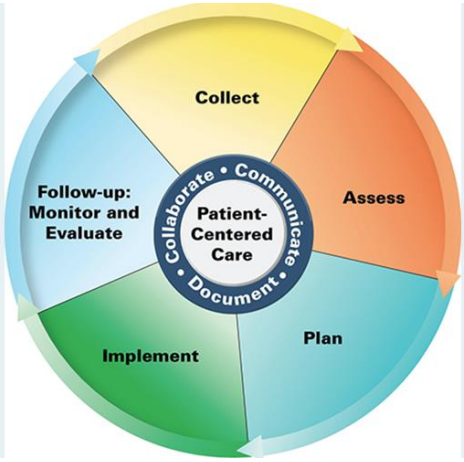


Figure 1. Patient Care Process for the Management of Diabetes Mellitus (30).

Table 3 explains the types of intensive insulin therapy by injection proposed by the ADA (32), which involves the use of bolus or prandial insulins (rapid-acting and short-acting insulins) and basal insulins (intermediate-acting and long-acting insulin).

Table 3. Types of insulin (32).

- **Rapid-acting insulin** begins to work about 15 minutes after injection, peaks in about one or two hours after injection, and lasts between two to four hours. *Types: insulin aspart (Fiasp, NovoLog), Insulin glulisine (Apidra), and insulin lispro (Admelog, Humalog, Lyumjev).*
- **Regular or short-acting insulin** usually reaches the bloodstream within 30 minutes after injection, peaks anywhere from two to three hours after injection, and is effective for approximately three to six hours. *Types: Human Regular (Humulin R, Novolin R, Velosulin R).*
- **Intermediate-acting insulin** generally reaches the bloodstream about two to four hours after injection, peaks four to 12 hours later, and is effective for about 12 to 18 hours. *Types: NPH (Humulin N, Novolin N, ReliOn).*
- **Long-acting insulin** reaches the bloodstream several hours after injection and tends to lower glucose levels up to 24 hours. *Types: degludec (Tresiba), detemir (Levemir), and glargine (Basaglar, Lantus).*
- **Ultra-long acting insulin** reaches the blood stream in six hours, does not peak, and lasts about 36 hours or longer. *Types: glargine U-300 (Toujeo).*

Insulin can be administered subcutaneously via various methods such as vial and syringe, insulin pen, and continuous subcutaneous insulin infusion, commonly called insulin pump therapy (33). The management of T1DM is increasingly reliant on technology, with continuous glucose monitors and insulin pumps often used as an essential component of care. While most insulin pumps use an infusion set with tubing, patch pumps are an alternative that deliver insulin directly from a pod attached to the skin, with an integrated or very short infusion set (34-36). Insulin pump technology has undergone several advancements, including the ability to program multiple basal rates of insulin infusion (during the day and the night) and deliver boluses at meals in various patterns. Bolus calculators or advisers integrated into the pump or handset can provide advice on insulin dosing, often using a nutrition database (37). Advanced hybrid closed loop (AHCL) systems that combine the glucose monitor and insulin pump in an automated closed-loop insulin delivery system (38,39) have been shown to improve glycaemic control, particularly overnight, which is crucial for parents of children with T1DM who fear undetected hypoglycaemia and hyperglycaemia during sleep (40-43). Most insulin products for the chronic management of diabetes are applied subcutaneously except for inhaled human insulin, which is a dry powder of human recombinant DNA regular insulin that is inhaled and absorbed through pulmonary tissue (30).

Lastly, there have been some novel approaches to deliver insulin through inhalation instead of subcutaneous injection also allows for a faster onset of action. Exubera® was the first inhaled product approved by the US FDA in 2006 for the treatment of diabetes (44). It was a dry powder formulation that required an inhaler device and had pharmacokinetic and pharmacodynamic properties similar to insulin (45). However, due to the requirement for

pulmonary function tests (before treatment initiation, after 6 months and annually) (46), the bulky delivery device, higher cost, and lower preference by patients and physicians, the product was withdrawn from the market by Pfizer in 2007. Afrezza® (Sanofi and MannKind), approved in 2014 (39), is currently the only inhaled insulin on the market in the United States. Unlike other rapid-acting and ultra-rapid insulins, which are analogues of human insulin, Afrezza® is a recombinant human regular insulin that has been formulated as a dry powder to be inhaled into the lungs via its dedicated device (47,48). Afrezza® has a rapid onset of action and a quick time to peak action (15 minutes), but a shorter duration of action (2-3 hours) compared with both human regular insulin or rapid-acting analogue insulins (47,49). Common side effects include transient non-productive cough and a modest reduction in lung function initially (49). Currently, inhaled insulin prescription remains limited by technical problems associated with its inhaler devices, cost, and long-term safety concerns, especially with regard to lung function.

1.2.1.1. ADVERSE DRUGS EVENTS

Adverse effects of insulin could be classified according to those caused by the drug itself and those caused by the specific route of administration (50). The most common adverse effect of insulin therapy is hypoglycaemia. The key contributors to severe hypoglycaemia are asymptomatic hypoglycaemia and nocturnal hypoglycaemia; both conditions inhibit the patients' ability to recognize hypoglycaemia when it is occurring and take appropriate action. As a result, many patients with T1DM are reluctant to follow and/or adjust their insulin regimens as needed because of fear of hypoglycaemia, resulting in exposure to chronic hyperglycaemia, oxidative stress, and long-term complications (51). Severe hypoglycaemia can be prevented through vigilance in identifying patients at risk, utilizing appropriate medications and medication regimens, and effective glucose monitoring strategies and technologies.

The other known adverse effects of insulin therapy include the Somogyi and the dawn phenomena. The Somogyi effect is presented in some patients who take insulin before bed and wake up with high blood sugar levels (52). This effect occurs when the insulin causes a hypoglycaemic condition in the body, which activates the antihyperglycemic hormones such as cortisol and adrenaline, growth hormone, and glucagon, leading to activation of gluconeogenesis and resultant hyperglycaemia in the early morning (53). It is corrected by reducing the dose of bedtime insulin or changing the time of insulin dosing. However, more recent studies involving continuous glucose monitoring have disputed this theory (52). It has been observed that patients with early morning hyperglycaemia tend to have high blood glucose measurements at night, rather than low (54).

The dawn phenomenon, on the other hand, is the presence of high blood glucose levels in the body in the early hours of the day due to inadequate insulin in the body (50). This phenomenon is corrected by increasing the dose of bedtime insulin needed to be able to keep the blood glucose levels under control throughout the night and the early hours of the morning. To diagnose both the Somogyi effect and the dawn phenomenon, it is useful to

measure plasma glucose levels for several nights and use a continuous glucose monitoring system. Although their treatment differs, the best way of preventing these two phenomena is an optimal diabetes control with insulin therapy (54).

The other adverse effects of insulin therapy include weight gain and, rarely, electrolyte disturbances like hypokalaemia, especially when used along with other drugs causing hypokalaemia (50). The subcutaneous route of administration also has adverse effects. Pain at the injection site and lipodystrophy at the injection site are the most common adverse effects of daily subcutaneous injections (55).

1.2.2. ASTHMA TREATMENT

Asthma is defined by 'the history of respiratory symptoms that include wheeze, shortness of breath, chest tightness, and cough that vary over time and in intensity, together with variable expiratory airflow limitation' (56). Evidence suggests that appropriate treatment can control the clinical manifestations of asthma, including symptoms, sleep disturbances, limitations of daily activity, lung function impairment, and the use of rescue medications (56).

Asthma control is defined as the extent to which the various manifestations of asthma are reduced or removed by treatment. According to the Global Initiative for Asthma (GINA) guidelines (56), achieving and maintaining asthma control should be the major goal of asthma care. Hence, this concept includes not only the patient's recent clinical manifestations but also considers their "future risk" - that is to say, their potential for experiencing adverse outcomes such as loss of control in the near of distant future, exacerbations, accelerated decline in lung function, or treatment-related side effects (57).

Two organizations drive classification and treatment recommendations for asthma: the Global Initiative for Asthma (GINA) (56) and the United States National Asthma Education and Prevention Program (NAEPP) (58). The GINA guidelines are updated annually, whereas the NAEPP published a focused update in 2020, but the previous full guideline update was in 2007. The recommendations from each organization vary slightly when classifying asthma, but both guidelines focus on raising awareness and ensuring appropriate diagnosis and management to reduce asthma-related morbidity and mortality (59).

In the emerging era of personalized medicine, tailored interventions and treatments customized to particular individuals with specific characteristics are needed (58). In personalized control-based asthma management, pharmacological and non-pharmacological treatment is defined by a continuous cycle involving assessment, adjustment, and review of the patient's symptom control and modifiable risk factors for exacerbations, other adverse outcomes, and comorbidities, and considering the patient's preferences and objectives (Figure 2) (56). This approach has shown to improve asthma outcomes and is essential for asthma management (60).

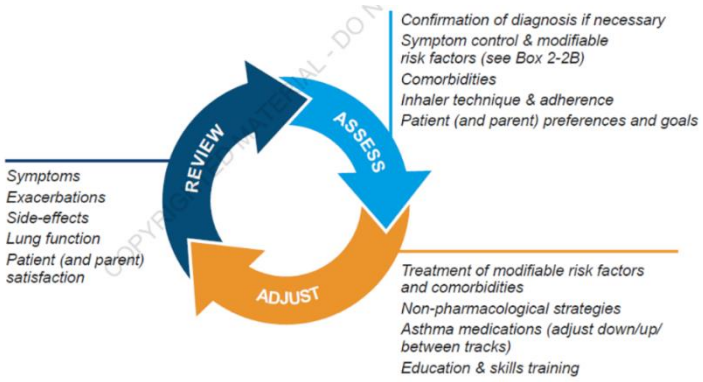


Figure 2. The asthma management cycle for personalized asthma care (56).

Asthma medication therapy in the GINA 2023 is divided into three main categories (56): controller medications, reliever medications, and add-on therapy for patients with severe asthma.

- Controller medications: in the past, this term mostly referred to medications contain ICs that were used to reduce airway inflammation, control symptoms, and reduce risk such as exacerbations and related decline in lung function. For patients who are prescribed short-acting beta-agonists (SABA) reliever, controller treatment is delivered through an anti-inflammatory reliever (AIR), low-lose ICs-formoterol, taken when symptoms occur and before exercise or allergen exposure; in steps 3-5, the patient also takes maintenance controller treatment (daily or twice-daily ICs-formoterol). This is called maintenance-and-reliever therapy (MART). The dose and regimen of controller medications should be optimized to minimize the risk of medication side-effects, including risk of needing Oral Corticosteroids (OCS).

- Reliever medications: these are provided to all patients for as-needed relief of breakthrough symptoms, including during worsening asthma or exacerbations. They are also recommended for short-term prevention of exercise-induced bronchoconstriction. Relievers include the anti-inflammatory relievers ICs-formoterol and ICs-SABA, and SABA alone.

- Add-on therapy for patients with severe asthma: difficult-to-treat asthma is asthma that is uncontrolled despite prescribing medium- or high-dose ICs with a second controller, usually Long-Acting Beta-Agonists (LABA), or with maintenance OCS treatment. Add-on treatments for severe asthma include Long-Acting Muscarinic Antagonist (LAMA), Leukotriene Receptor Antagonist LTRA, low-dose azithromycin (adults), and biologic agents for severe asthma.

Pharmacotherapy is based on a stepwise approach to treatment, where each patient is assigned from one to five treatment steps according to their individual grade of asthma control. For each treatment step, a preferred controller and reliever medication is recommended, the one that provides the best benefit for symptom control and risk reduction.

The stepwise treatment approach to control symptoms and minimize future risks proposed by GINA 2023 (56) is illustrated in Figure 3. The treatment figure for adults and adolescents (age>12 years) shows two "tracks" based on the choice of reliever (56). Treatment may be stepped up or down within track using the same reliever at each step, or treatment may be switched between tracks, according to the individual patient's needs. Other treatment options with less evidence for efficacy and/or safety than Track 1 or 2 options are specified in each figure.

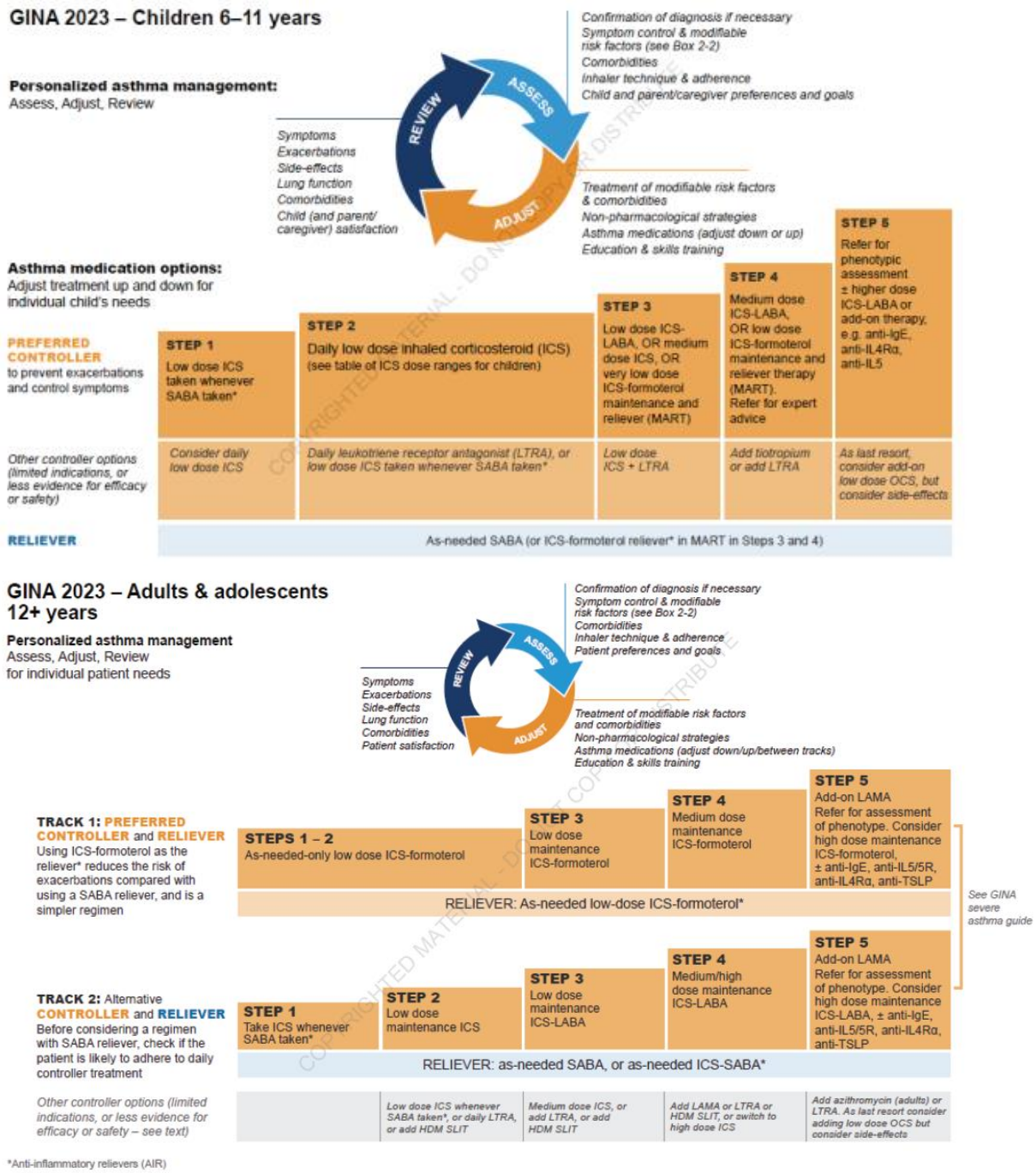


Figure 3. Stepwise approach proposed by GINA in 2023 to control symptoms and minimize future risks in children aged 6-11 years and adolescents/adults >12 years (56).

- **Track 1**, in which the reliever is low-dose ICs-formoterol, is the preferred approach recommended by GINA. When a patient at any step has asthma symptoms, they use low-dose ICs-formoterol as needed for symptoms relief. In steps 3-5, they also take ICs-formoterol as regular daily treatment. This approach is recommended because it reduces the risk of severe exacerbations compared with using a Short-Acting Beta Agonist (SABA) reliever, with similar symptom control.

- **Track 2** is an alternative if track 1 is not possible, or if a patient is stable, with good adherence and no exacerbations in the past year on their current therapy. In step 1, the patient takes a SABA and a low-dose ICs together for symptoms relief (in combination if available, or with the ICs taken immediately after the SABA). In steps 2-5, the reliever is a SABA or ICs-SABA combination, and the patient takes maintenance ICs-containing medication regularly every day.

The NAEPP, in its latest 2020 update, also provided a strong recommendation for ICs/formoterol in a single inhaler as both daily single maintenance and reliever therapy (SMART), compared with either higher-dose ICs as a daily controller therapy and a SABA for quick-relief therapy or same-dose ICs/LABA as a daily controller therapy and a SABA for quick-relief therapy in individuals aged 4 years and older with moderate to severe persistent asthma. Additionally, the panel made a conditional recommendation for ICs/formoterol in a single inhaler used as both a daily controller and reliever therapy instead of a higher-dose ICs/LABA as a daily controller therapy and a SABA for quick-relief therapy in individuals aged 12 years and older with moderate to severe persistent asthma (58).

1.2.2.1. ADVERSE DRUGS EVENTS

Since last century there have been important changes in asthma treatment that have been largely marked by the evidence of adverse drug events. For LABAs, in 2003 the United States' Food and Drug Administration (FDA) required boxed warning for all LABAs, on the basis of findings that suggested they were associated with serious adverse outcomes. The main investigations that raised these concerns had been conducted at a time when patients taking LABAs were not necessarily using concomitant ICs. In 2010, the FDA required label changes to indicate the contraindication of LABAs use without concomitant ICs in all asthma patients, and to recommend that only fixed-dose LABAs plus ICs combination formulations be used in paediatric patients (61). In 2011, the FDA required manufacturers to conduct clinical trials evaluating the safety of a regimen of LABAs plus ICs, compared to ICs alone (62). Five clinical trials were required, four were completed (63-65), whereas one of the adult and adolescent trials was terminated early (Novartis discontinued marketing of formoterol fumarate in the United States). Results of a combined analysis of these trials (66), published in 2018, indicated that LABAs plus ICs therapy did not result in a significantly higher risk of serious asthma-related events compared to ICs alone, but resulted in significantly fewer asthma exacerbations (RR 0.83; 95% CI: 0.78-0.89).

For montelukast, in 2009 the FDA requested a review of the clinical trials with montelukast performed by Merck KGaA, which found that suicidality and behaviour-related adverse experiences were infrequent events and similar to those seen in control subjects (67,68). However, between 2014 and 2018, several cases were notified as suspected adverse neuropsychiatric events (69). In 2019, a European Medicines Agency (EMA) review (70) identified some cases in which there had been a delay in recognizing neuropsychiatric reactions as a possible adverse drug reaction, and the United Kingdom's Medicines and Healthcare products Regulatory Agency (MHRA) activated a warning including nightmares, depression, insomnia, aggression, anxiety, and abnormal behaviour or changes in behaviour. In 2020, the FDA required a boxed warning (71-73) advising healthcare providers to avoid prescribing montelukast for patients with mild symptoms (72), and this ban has been also joined by asthma guidelines (74-76).

More recently, in 2019 GINA conducted a comprehensive review of evidence on the adverse outcomes of SABA-only treatment and the impact on asthma exacerbations and deaths of any form of ICs in mild asthma, and found that the risk of severe exacerbations and mortality increase incrementally with higher SABA use, independent of treatment step. Prescribing of three or more 200-dose SABA inhalers in a year, corresponding to more than once-daily use, is associated with an increased risk of severe exacerbations (77,78) and, in one study, increased mortality (77). GINA resolved that there was sufficient evidence to recommend that adults and adolescents with asthma should not be treated with SABA alone (79). Therefore, using SABAs in monotherapy is no longer recommend by the GINA (56).

1.3. PATIENT-REPORTED OUTCOME MEASURES

The patient's perception plays an increasing part in clinical research, with the recognition that a patient-centred approach is necessary for comprehensive management of the impact of diseases, treatment and care. Traditional survival, disease, and physiological outcomes may demonstrate the physiological benefits of treatment; however, the patient's perspective provides a more holistic interpretation and a comprehensive assessment of the benefits of the treatment under investigation (80,81). Moreover, taking into account the patients' views has other advantages, further than avoiding observer bias (inevitable if asking clinicians about them): patients welcome being involved (and this may have health benefits in itself), and patients' response rates are invariable better than the clinicians' (a patient only has to complete one questionnaire, whereas a clinician has to do it for every patient) (80).

Patient-Reported Outcomes (PRO) and Patient-Reported Outcomes Measures (PROMs) are umbrella terms that cover any outcome based on data provided by the patient or patient proxy (82). According to the FDA's definition, "a PRO is any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else" (83). PROMs are designed to measure a specific concept (that is a construct) in a standardized way, and evaluate any treatment or outcome through interviews, self-completed questionnaires, diaries or other data collection tools such as hand-held devices and online systems (84).

There are different types of outcomes (Figure 4) (84) covered by PROMs, from symptoms to Health-Related Quality of Life (HRQL); and they are usually measured either by different instruments or by those that combine several concepts. Even PROMs that only assess symptoms or functional limitations are of primary interest to the physician as indicative of disease severity. Most PROMs administered nowadays assess Health-Related Quality of Life (Figure 4) (85). 'PROMs' is used as an umbrella term covering concepts like disease symptoms, satisfaction with life in general or with the delivery of care, limitations in daily life performance, general health perceptions, or those expressions often interchangeably used in the medical literature such as Health-Related Quality of Life (HRQL), health status, functional status and wellbeing (86).

Figure 5 shows a comprehensive model that can be understood as a common framework for classifying PRO measures regarding their content (84). It is based on the model of Wilson and Cleary (87), integrating it with the theoretical model underpinning the International Classification of Functioning, Disability and Health (ICF) developed by the World Health Organization, which is based on a sociological perspective of health that considers disability along the whole functioning continuum (88).

The two models have been conceived independently (87,88), but share significant characteristics. They both differentiate health-related variables and contextual factors, further splitting the latter into environmental and individual characteristics. Biological and physiological variables in the model by Wilson and Cleary correspond to the structure component of the ICF, and functional variables in the first model equally correspond to the activities and participation components of the latter. Current and previous successful mapping of responses to PROM measures onto the ICF support the validity of this integration (84). Based on the model by Wilson and Cleary, this comprehensive model differentiates and defines the following concepts: symptom status, functional status, health perceptions, and HRQL.

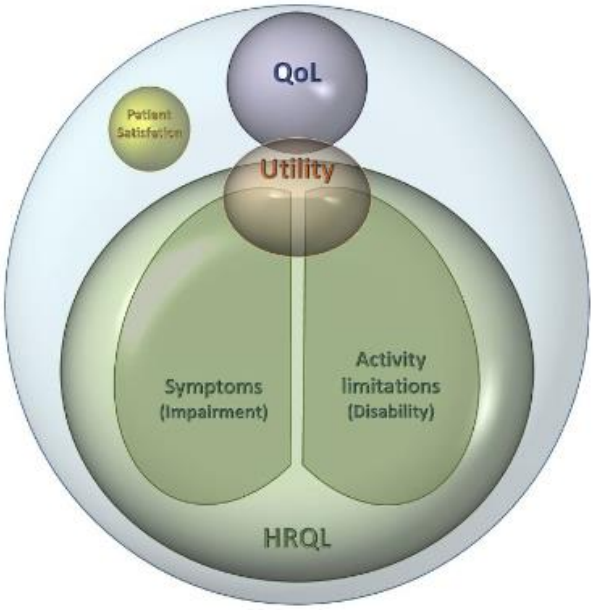


Figure 4. Types of PROs currently used in medical research (85).

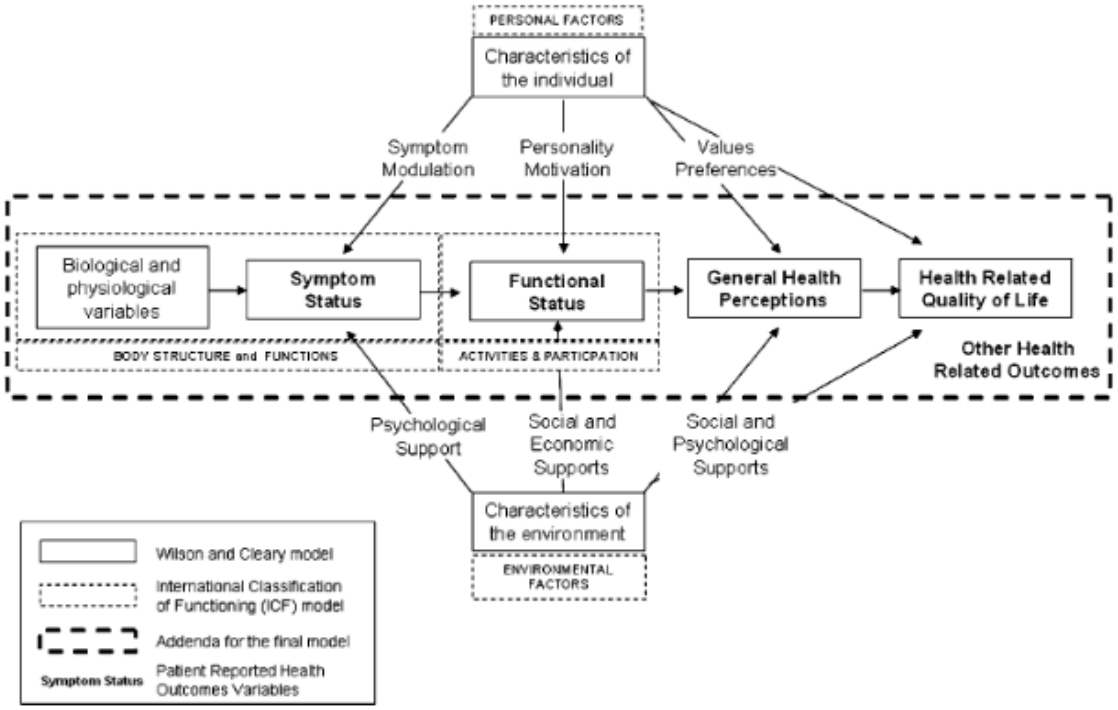


Figure 5. An integrated model for health outcomes (84).

1.3.1. DEFINITIONS OF HRQL

In 1948, the World Health Organization (WHO) defined health as not only the absence of disease and infirmity, but also the presence of physical, mental and social well-being (89). Since then, the definition of HRQL and related concepts such as quality of life (for many researchers—limited to what is of primary concern to the patient's (86) health status and perceived health—has been disputed, without reaching a consensus (82,90). In 1993 Patrick and Erickson (91) defined HRQL as "the value assigned by individuals, groups, or society to the duration of survival as modified by impairments, functional states, perceptions, and social opportunities influenced by disease, injury, treatment, or policy". However, as shown in Taillefer's systematic review (92), the definitions for HRQL in published articles are often not clearly provided or differ in their content.

1.3.2. ENHANCING TRANSPARENCY AND STANDARDIZATION IN PROMs: CURRENT CHALLENGES AND GUIDELINES

HRQL measures assess a person's physical, psychological, and social health domains, which are influenced by their experience, beliefs, expectations, and perceptions. These instruments have been developed since the early 1970s to evaluate a person's health status in comparison to their desired state (93,94).

Despite the frequent use of HRQL measures (89,95) and the relevance of PROMs following FDA recommendations (83), physicians may be hesitant to use PROMs routinely due to the

time required for administration and their perceived value (96). This reluctance is partially due to the lack of formal training available for physicians and researchers on PROM evaluation and interpretation (97,98). Gaps of knowledge on which PROMs to use and how to use them in clinical practice pose major obstacles to their systematic integration into routine clinical care (99).

Efforts have been made to standardize and enhance transparency in PROs evaluation and reporting in randomized clinical trials. The SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) and CONSORT (Consolidated Standards of Reporting Trials) guidelines provide checklists for the essential items to be included in trial protocols and primary reports of completed randomized trials, respectively. These guidelines aim to ensure transparency and provide sufficient information for replication and critical appraisal of the study.

In 2009, the FDA and the EMA released guidance to improve efficiency and transparency of discussions between sponsors and the FDA, streamline review of PRO measures, and consider patients' perspectives in the medical product review process (83). In 2013, the International Society for Quality of Life Research (ISOQOL) published comprehensive reporting standards (100), which led to the development of the CONSORT-PRO Extension in 2015 (101), including 14 items and considered the minimum reporting items for PRO endpoints in RCTs. The CONSORT-PRO extension (101) includes five newly developed PRO-specific reporting recommendations, such as providing evidence of validity of PRO measures, and reporting statistical approaches for dealing with missing PRO data. The remaining nine CONSORT-PRO items are elaborated from the CONSORT-2010 statement to specifically address PROs (102).

In 2018, the SPIRIT-PRO guidance was released (103), to be used with the SPIRIT 2013 (104) statement when developing trials protocols with PRO as primary or secondary endpoints. It consists of 16 items, including 11 new PRO-specific extensions and five elaborations on existing SPIRIT 2013 items. The SPIRIT-PRO extension items address the PRO study rationale, objectives, eligibility criteria, domains used to evaluate the intervention, assessment time points, selection of PRO measures, measurement properties of the PRO measures, the PRO data collection plan, translation of PRO measures into other languages, proxy completion, strategies to minimize missing PRO data, and whether PRO data will be monitored during the active trial phase to inform the clinical care of participants (103).

1.3.3. TYPE OF PROMs ACCORDING TO TARGET POPULATION

PROMs have traditionally been differentiated as generic or specific, each group presenting its own characteristics. Generic measures can be used for patients with any type of disorder or for general population (105). Their broad applicability is in general derived from their coverage of the complete spectrum of function, disability and distress that is relevant (symptoms, emotional function, or social relations). Generic instruments allow to determinate the effects of the intervention on different aspects without the use of multiple

instruments. Also, by using them one can compare the effects on similar interventions in different diseases. However, they may not focus on aspects of specific interest to the investigator. Inadequate focus on specific issues is likely to result in an unresponsive instrument that may miss small, but still clinically important, changes.

On the other hand, specific measures focus on aspects that are specific to the area of primary interest. The instruments may be specific to the disease (such as asthma), specific to a population (such as children), specific to a certain function or symptom (such as dyspnoea), or specific to a given condition or problem (such as pain). The disadvantages of specific measures are that they are not comprehensive and cannot be used to compare across subpopulations or conditions. Nevertheless, as disease-specific instruments are designed to focus on elements of a specific condition, they may be more responsive to the effects of health care, and relate more closely to clinical symptoms (106).

1.3.4. PROMs ACCORDING TO DEVELOPMENT PROCESS

The growing interest in PROMs resulted in the development of many instruments to assess a person's interpretation of their health status in comparison to how they might hope to be (93,94). PROMs were developed from two fundamentally different approaches: health status or psychometric profiles and value or preference-based utility index (Figure 6). In general, health status measures provide information on several concepts describing a person's functioning by a profile of interrelated scores or domains (e.g., physical functioning or mental wellbeing). In contrast, preference-based utility indexes assess the desirability of a state of health against an external metric that summarizes a single global score (index). They incorporate societal preferences for health states (utilities) that can be used to calculate Quality-Adjusted Life-Years (QALYs) for use in economic evaluations (107,108).

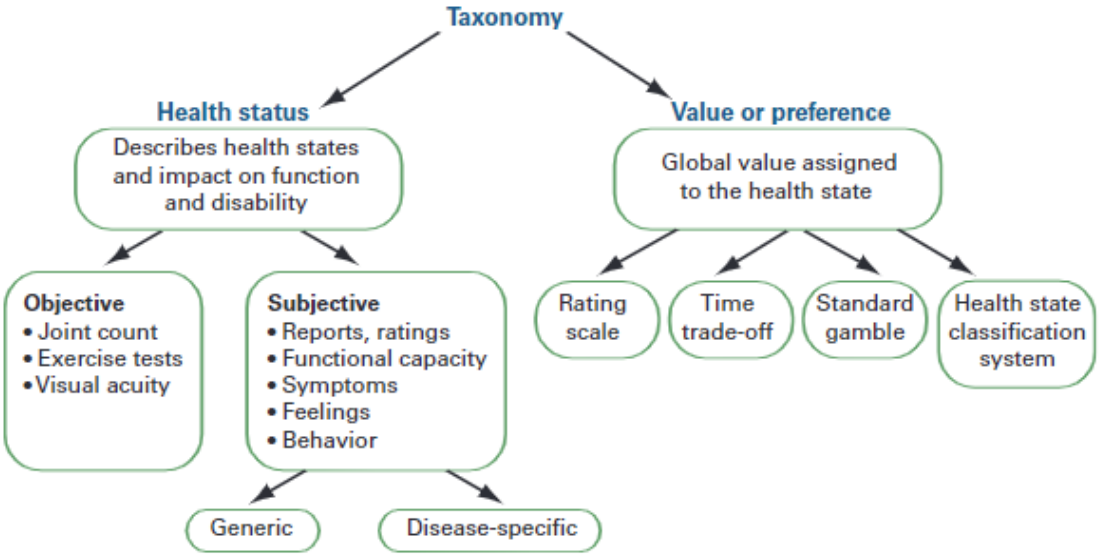


Figure 6. Health-Related Quality of Life Taxonomy (108).

Health status profiles are instruments that attempt to measure all the important aspects of HRQL, share a common scoring system, and can be aggregated into a small number of scores and sometimes into a single score (109). One of the most popular generic HRQL profile instruments is the KIDSCREEN-27 (110), which was developed by the European Commission within the project "Screening and Promotion for Health-related Quality of Life in Children and Adolescents - A European Public Health Perspective". This instrument evaluates five dimensions: physical well-being, psychological well-being, autonomy and relationships with parents, social support and relationships with friends, and school environment. Responses are recorded on a five-option Likert scale, with a recall period of one week for most questions. Scores are calculated following the developers' recommendations and are standardized to a mean of 50 and a standard deviation of 10, based on a reference sample of 22,000 European children and adolescents (111).

Preference-based utility indexes are derived from economic and decision theory; they reflect the preferences of patients or the general population for treatment process and outcome (86). The key elements of these indexes are that they incorporate preference and relate health states to death. Hence, they can combine life duration and quality of life estimating QALYs allowing cost-utility analyses. Preference-based utility indexes provide a summary as a single number along a continuum that usually extends from death (0.0) to full health (1.0), although scores lower than zero are possible, representing states considered worse than death (112).

There are two fundamental approaches to preference-based utility indexes. One, based on multi-attribute utility theory, is to ask patients some questions about their functioning, classify them on the basis of their responses, and give each category a utility (previously established using, for example, a random sample of the general population) (86,113). The second approach is to ask patients to make a rating that takes into account all aspects of their HRQL.

Preference-based utility indexes have the major advantage of allowing cost-utility analysis in economic evaluation, where the cost of an intervention is related to the number of QALYs gained through applying the intervention. The cost-utility of different interventions can then be compared. Potentially, this information can help policymakers choose the optimal allocation of scarce resources.

1.3.5. METRIC PROPERTIES

HRQL instruments must have adequate measurement properties to be useful in their extensive potential applications, in order to confirm that results are free from random error (reliability), corroborate that they measure what they claim to be measuring (validity), and to assess the ability of the instrument to detect change over time (responsiveness).

In 1994, the Medical Outcomes Trust (MOT) created an independently functioning Scientific Advisory Committee (SAC), which designed a set of attributes and review criteria for HRQL-assessing instruments (114). In 2002, those experts updated and revised the materials to take

account of the expanding theories and technologies upon which instruments should be validated. Table 3 shows a modified version of the eight attributes and the main criteria for each of them proposed by the Scientific Advisory Committee of the MOT (114).

Table 3. Attributes and criteria for evaluating PROMs (114).

1. **Conceptual and measurement model:** The rationale for, and description of, the concept and populations that a measure is intended to assess and the relationship between these concepts.
2. **Reliability:** The degree in which an instrument is free from random error.
    a) *Internal consistency*: The precision of a scale, based on the homogeneity (inter-correlations) of the scale's items at one point in time.
    b) *Reproducibility:* Stability of an instrument over time (test–retest) and inter-rater agreement at one point in time.
3. **Validity:** The degree to which the instrument measures what it tries to measure.
    a) *Content-related*: Evidence that the domain of an instrument is appropriate regarding its intended use.
    b) *Construct-related*: Evidence that supports a proposed interpretation of scores based on theoretical implications associated with the constructs being measured.
    c) *Criterion-related*: Evidence that shows the extent to which scores of the instrument are related to a criterion measure.
4. **Responsiveness:** An instrument's ability to detect change over time.
5. **Interpretability:** The degree to which one can assign easily understood meaning to an instrument's quantitative scores.
6. **Respondent and administrative burden:** The time, effort, and other demands placed on those to whom the instrument is administered (respondent burden) or on those who administer the instrument (administrative burden).
7. **Alternative forms:** These include self-reporting, interviewer-administered, trained observer rating, computer-assisted interviewer-administered, evidence on reliability, validity, responsiveness, interpretability, and burden for each mode of administration performance-based measures.
8. **Cultural and language adaptations**: This refers to the assessment of conceptual and linguistic equivalence, as well as to the evaluation of measurement properties

In 2010, the COSMIN group developed the COnsensus-based Standards for the selection of health status Measurement INstruments checklist (COSMIN) by performing an international Delphi study to evaluate the methodological quality of studies on measurement properties of health-related patient-reported outcomes (HR-PROs) (115). Consensus-based definitions of all included measurement properties in the COSMIN checklist are presented in Table 4 (115). In 2017, the COSMIN checklist was adapted into a version exclusively for use in systematic reviews of PROMs, with the aim of assessing the risk of bias of studies on measurement properties (116).

Table 4. Consensus-based definitions of measurement properties included in the COSMIN checklist (115).

Domain	Measurement property	Aspect of a measurement property	Definition
Reliability			The degree to which the measurement is free from measurement error.
Reliability (extended)			The extent to which scores for patients who have not changed are the same for repeated measurement under several conditions (e.g., using different sets of items from the same health related patient-reported outcomes (HR-PRO) (internal consistency), over time (test-retest), by different persons on the same occasion (inter-rater), or by the same persons (i.e. raters or responders) on different occasions (intra-rater).
	Internal consistency		The degree of the interrelatedness among the items.
	Reliability		The proportion of the total variance in the measurements which is due to 'true' differences between patients.
	Measurement error		The systematic and random error of a patient's score that is not attributed to true changes in the construct to be measured.
Validity			The degree to which an HR-PRO instrument measures the construct(s) it purports to measure.
	Content validity		The degree to which the content of an HR-PRO instrument is an adequate reflection of the construct to be measured.
		Face validity	The degree to which (the items of) an HR-PRO instrument indeed looks as though they are an adequate reflection of the construct to be measured.
	Construct validity		The degree to which the scores of an HR-PRO instrument are consistent with hypotheses (for instance with regard to internal relationships, relationships to scores of other instruments, or differences between relevant groups) based on the assumption that the HR-PRO instrument validly measures the construct to be measured.
		Structural validity	The degree to which the scores of an HR-PRO instrument are an adequate reflection of the dimensionality of the construct to be measured.
		Hypotheses testing	Idem construct validity.
		Cross-cultural validity	The degree to which the performance of the items on a translated or culturally adapted HR-PRO instrument are an adequate reflection of the performance of the items of the original version of the HR-PRO instrument.
	Criterion validity		The degree to which the scores of an HR-PRO instrument are an adequate reflection of a 'gold standard'.
Responsiveness			The ability of an HR-PRO instrument to detect change over time in the construct to be measured.
	Responsiveness		Idem responsiveness.
Interpretability*			Interpretability is the degree to which one can assign qualitative meaning – that is, clinical or commonly understood connotations – to an instrument's quantitative scores or change in scores.

* It is not considered a measurement property, but an important characteristic of a measurement instrument

1.3.6. PROMs FOR CHILDREN AND ADOLESCENTS IN CLINICAL PRACTICE

The National Quality Forum and the International Society for Quality of Life Research have advocated for the inclusion of PROMs in clinical practice, and provided guidance for clinicians who want to incorporate the patient's perspective into their practice (117). Despite its increasing use, PROM assessment is still not widely used in paediatric care (118,119). Many PROMs exist in paediatrics and across its various subdisciplines, capturing a range of health outcomes including HRQL and symptom severity in paediatrics and child health (120). Paediatric PROMs include both generic and disease-specific instruments, as previously mentioned.

PROMs have the potential to improve healthcare quality and serve as performance indicators for overall child health and paediatric care (121,122). PROMs also have the potential to enable early detection of symptoms and, as a result, prevent disease complications (123). Their evaluation can also provide valuable information for patient-centred care by identifying child and family health concerns and treatment preferences, which may differ from those of clinicians (117,124). This information can be used to involve patients and their families in medical decision-making and treatment planning (117,125). Additionally, PROMs can be used to monitor changes in child health over time and evaluate treatment effectiveness. The routine use of PROMs in clinical care can facilitate disease monitoring and treatment adherence and management, enable patients to become more involved in managing their disease, enhance satisfaction with care, and improve patient-physician communication (117,126-129), which is especially important during adolescence when compliance with treatment recommendations often declines.

The Mental Health Division of the World Health Organization (WHO) has published guidelines for the development of child-specific HRQL instruments (130). These guidelines require the instruments to be child centred, age-appropriate, cross-culturally comparable, and essentially generic, with the possibility of including disease-specific modules. Instrument development should incorporate the views of the target group. The FDA and EMA guidelines for the assessment of PROMs in paediatric populations have also recommended age-appropriate wording and a short recall period or time frame to avoid comprehension and memory problems (83,131,132). Prior to implementation, age ranges must be evaluated within the intended target population. To ensure that the target group can understand the contents, paediatric PROMs should be validated by involving children in early qualitative research stages through interviews, electronic or paper formats, or mHealth applications with children and their parents (119). The child should complete the PROM as much as possible to avoid bias, and proxy reports should only be used when necessary and analysed separately (120). It is important to consider that patients and their caregivers may have different views about the content assessed in PROMs, and thus their reported outcomes should not be weighed equally. Furthermore, paediatric PROMs may need to be reviewed and calibrated accordingly for different cultures and languages (133,134). In order to make sure that instruments are related to the developmental stage, children and adolescents' perspectives should be integrated in the developmental process, e.g. by conducting focus groups and comprehensive cognitive debriefings in the pilot stage of the development process (135).

Reviews from 2008 (135) identified a variety of generic and disease-specific instruments to measure the HRQL of children and adolescents, either as a single index or profile measures. However, there are few preference-based HRQL measures specifically designed for children and adolescents (135). A 2012 systematic review (136) analysed the characteristics of instruments developed or adapted to assess HRQL in children from 2000 to 2010, identifying several instruments, 14 of which were disease-specific. Approximately ten were generic instruments, such as the Child Health and Illness Profile (CHIP), the EQ-5D-Y, the Child Health Questionnaire (CHQ), and the KIDSCREEN. Another systematic review (137), which sought to identify studies that measured health utilities directly from patients or their proxies, indicated that three of the most commonly used generic instruments for measuring health utilities in children and adolescents are: Quality of Life Assessment (AQoL-6D), Child Health Utility (CHU-9D), and EQ-5D-Y.

1.3.6.1 PROM INSTRUMENTS FOR TYPE 1 DIABETES MELLITUS

A systematic review conducted in 2007 (138) on HRQL in adolescents with diabetes (including both type 1 and type 2) identified five disease-specific and four generic questionnaires. The authors suggested that the PedsQL-DM and KINDL-R questionnaires were the most suitable instruments at that time, and emphasized the need to evaluate their responsiveness. A more recent systematic review published in 2022 (139), aiming to identify relevant PROMs in paediatric endocrinology (specifically T1DM) for patients under 18 years old, identified six PROMs, measuring either HRQL alone (140-143), or both disease-related symptoms and HRQL (144,145). Some of the studies developed new PROMs, while others modified existing adult PROMs (140,145). Of the PROMs identified in 2022, four questionnaires measured both patient- and proxy-reported outcomes (140-142,144), while two studies used only patients' self-reported information (143,145). Instruments identified in both systematic reviews are listed in Table 5.

The authors of the 2022 systematic review (139) applied COSMIN to assess the methodological quality of the identified PROMs. They found that the short form of the Diabetes Quality of Life for Youth scale (145) and Problem Areas In Diabetes Scale for children (140) had the best methodological quality, receiving a score of "very good" in the domains of structural validity, internal consistency, cross-cultural validity, and hypothesis testing for construct validity. However, despite the high quality of these papers, all studies received an overall COSMIN score of "inadequate" due to poorly detailed PROM development. As a result, the review suggests that further research and development of PROM tools are needed in paediatric endocrinology to improve patient care. The authors recognize that, due to the limited scope and quality of existing PROMs, it is challenging to recommend their use. The newest questionnaires available were published in 2012 (143) and 2019 (140), indicating the need for updated PROMs to align with the most recent guidelines for PROM development (139).

Table 5. Disease-specific PROM instruments for children and adolescents with diabetes (138,139).

PROMs administered in Diabetes	Acronym	Author (Year of publication)
Diabetes-specific		
Audit of Diabetes Dependent Quality of Life-Teen version (146)	(ADDQoL-Teen)	McMillan et al. (2004)
Diabetes Quality of Life for Youth scale - Short Form (145)* ⁑	DQOLY	Skinner et al. (2006)
Diabetes Quality of Life-Youth questionnaire (147)	DQOL-Youth	Ingersoll et al. (1991)
DISABKIDS condition- specific modules (141)⁑	DISABKIDS	Baars et al. (2005)
KINDL-R-Diabetes Module (148)	KINDL-R-DM	Ulrike R. et al. (2001)
Monitoring Individual Needs in Diabetes Youth Questionnaire (143) ⁑	MY-Q	Wit et al. (2012)
PedsQL Diabetes Module (144)⁑	PedsQL ™	Varni et al. (2003)
Problem Areas In Diabetes Scale - Child Version (140)* ⁑	P-PAID-C	Evans et al. (2019)
Generic		
Child Health Questionnaire-Child Form (149)	CHQ-CF87	Landgraf et al. (1996)
DISABKIDS chronic generic module (142)⁑	DISABKIDS-DCGM	Simeoni et al. (2007)
Pediatric Quality of Life Inventory 4.0 (150)	PedsQL4.0	Varni et al. (2001)

**Adapted from an adult population instrument;* ⁑ *instruments identified only in the 2022 review* (139)

1.3.6.2 PROMs FOR PAEDIATRIC ASTHMA

The significant interest in measuring PROMs in patients with asthma is evident from the development of numerous specific questionnaires for this disease. In the 1990s, the focus was on HRQL, and during that decade was when the majority of asthma-specific instruments measuring this construct were developed, primarily for adults. In the 21st century there has been a shift of interest towards other constructs such as asthma control, starting with the Asthma Control Questionnaire (ACQ) in 1999, followed by the Asthma Control Test (ACT) in 2004. The children's version of the latter instrument was published in 2007.

A systematic review published in 2014 (151) identified 68 disease-specific and 28 generic PROMs instruments that had been evaluated for use in people with asthma, though the majority of PROMS identified were designed for adult populations. Table 6, adapted from this systematic review (151), lists the paediatric asthma-specific PROMs that were found to

be well-validated and warrant a full-quality appraisal, ordered by year of publication. There were 4 for children and 1 for children's caregivers. The evaluation of PROMs published before 2014 suggested that they required further validation (151), especially those specific for children. The psychometric properties were found to need more robust validation work.

The Paediatric Asthma Quality of Life Questionnaire (PAQLQ) (152) for children is a derivative of the AQLQ, and it was the only PROM for children with asthma that addressed asthma-related HRQL comprehensively. The PedsQL (153) is a generic tool with disease-specific modules, including one for asthma. The GINA asthma guidelines 2023 (56) recommend the use of the ACQ and the ACT for the assessment of symptom control in adolescents and adults. For children aged 6-11 years, the recommendation is to use the Childhood Asthma Control Test (c-ACT), with separate sections for the parent/caregiver and the child to complete, as well as the ACQ.

Table 6. Disease-specific PROM instruments for children with asthma identified in a systematic review published in 2014 (151).

PROMs administered in Asthma	Acronym	Author (Year of publication)
Asthma-specific for children		
Childhood Asthma Questionnaire (154)	CAQ	Christie et al. (1993)
Paediatric Asthma Quality of Life Questionnaire (152)	PAQLQ	Varni et al. (1999)
Pediatric Quality of Life Inventory-asthma module (153)	PedsQL-AM	Varni et al. (2004)
Childhood Asthma Control Test (155)	C-ACT	Liu et al. (2007)
Asthma-specific for child´s caregiver		
Paediatric Asthma Caregiver's Quality of Life Questionnaire (156)	PACQLQ	Juniper et al. (1996)

1.4. EQ-5D-Y

The EuroQol Group perceived a growing interest in measuring HRQL in younger age groups and acknowledged the need for a child health measure, as the EQ-5D was not necessarily suitable for use with children and adolescents. The group established a research program with researchers from 7 countries (157,158), aimed at developing a child health measure by adapting the original EQ-5D and making it appropriate for children. They also aimed to test the adaptations and generate value sets for this new measure. This process ultimately resulted in the development of the EQ-5D-Y (157) in 2009/2010 to enable young individuals from 8 years onwards to self-report their health (157). The EQ-5D-Y contributed to fill the lack of correspondence and continuity between HRQL instruments designed for children and those designed for adults, which can hinder the analysis of HRQL changes using a life course approach. An EQ-5D-Y proxy version was also developed (159) for children under eight years old; it asks proxies to rate the child's HRQL in their own opinion, and has the same characteristics as the self-reported version. Moreover, in 2019, a new version with 5 levels (EQ-5D-Y-5L) was developed to reduce ceiling effects and improve sensitivity by expanding the number of severity levels (160).

1.4.1. DESCRIPTIVE SYSTEM

The resulting descriptive system of the EQ-5D-Y comprises the original five dimensions of the EQ-5D (mobility, self-care, usual activities, pain or discomfort, and anxiety or depression) (see Figure 7), since their developmental process supported their applicability for children and adolescents. However, changes were made to clarify the meaning of the dimensions to younger respondents. The dimension "self-care" was renamed "looking after myself," and examples such as "washing and dressing" were included. The dimension "anxiety or depression" was replaced by "feeling worried, sad or unhappy" (157). Each dimension presents three levels of problems using a different wording than the one for adults: "no problems," "some problems," and "a lot of problems" (161). The descriptive system of EQ-5D-Y generates 243 different health states, which can be described by a 5-digit code comprising one level for each of the five dimensions (e.g., 12132) (157).

1.4.2. EQ-VAS

The EQ-5D-Y includes a visual analogue scale (VAS) in which the respondent rates their overall health on a vertical scale from 0 "worst health you can imagine" to 100 "best health you can imagine" (see Figure 7) (157). The wording of the VAS rating was adapted to be more child-friendly in the development of the EQ-5D-Y. In addition to the VAS rating, the 5 dimensions, questionnaire layout, and wording were also adapted to be more child-friendly, to ensure better comprehension (157).

1.4.3. PILOT TESTING OF EQ-5D-Y AND COMPARISON TO EQ-5D-3L

The questionnaire, developed in English, was translated and adapted according to a standardized protocol into four languages (German, Italian, Spanish, and Swedish) and given to respondents aged 8 to 18. After self-completing the EQ-5D-Y, the respondents participated in cognitive interviews designed to obtain information about comprehensibility, acceptability, and any misunderstandings related to the new instrument. Almost all children and adolescents answered the questions without any help, and comprehension was good. Only minor modifications to the translated versions were required, based on a number of specific cultural factors. For the English source version, however, no further adaptations were needed (157).

Both questionnaires, EQ-5D and EQ-5D-Y were administered to a sample of school-aged children in Germany, Spain, and South Africa. Results obtained from the 2 versions were compared, and respondents indicated more problems on EQ-5D-Y for the dimensions “mobility,” “having pain or discomfort,” and “feeling worried, sad or unhappy”. The EQ-5D-Y had fewer missing values and, overall, participants indicated that EQ-5D-Y was easier to understand than EQ-5D (157).

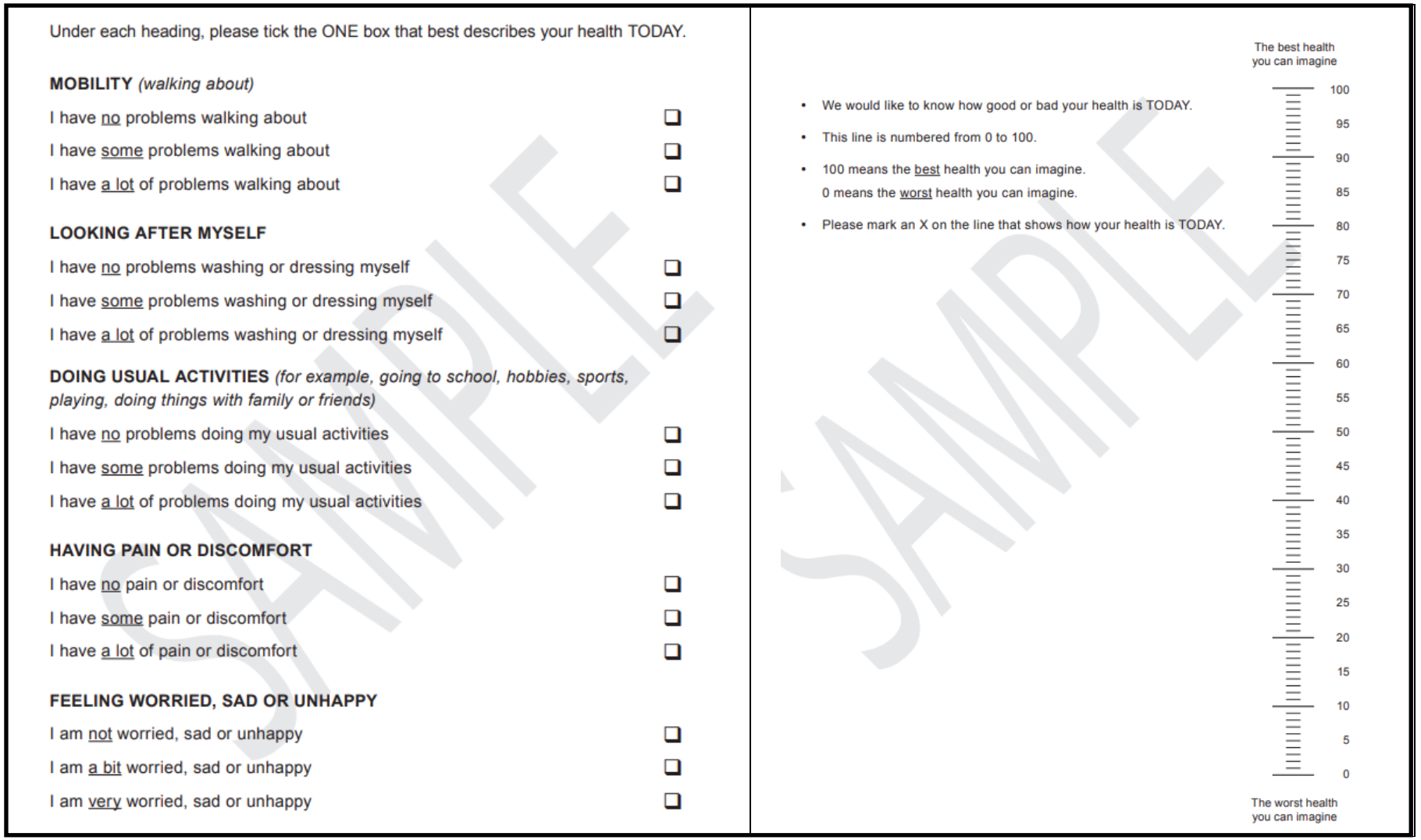


Figure 7. Descriptive system and the visual analogue scale (VAS) of the EQ-5D-Y

1.4.4. EQ-5D-Y USE

The EQ-5D-Y is becoming an increasingly popular instrument, with 586 studies using it, as registered with the EuroQol Group, between November 2010 and March 2018. Its use has been steadily increasing, with an average of 2.5 studies registered per month in 2010-2011 and 32.7 studies registered per month in 2018. The instrument has been utilized in various study designs, including interventional studies, observational research, routine data collection, and randomized controlled trials. The majority of studies were conducted in the United Kingdom, followed by the United States, the Netherlands, and Sweden. The EQ-5D-Y has been applied in a range of therapeutic areas, such as orthopaedic conditions, diabetes, and other chronic conditions (162).

1.4.5. EQ-5D-Y ADMINISTRATION MODE

EQ-5D-Y was designed for self-completion by children and adolescents aged 8-15 years. and is available in both paper and digital versions. The EQ-5D is ideally suited for use in online or postal surveys, clinics, and interviews (face-to-face or telephone) due to its availability in these formats. Proxy versions are also available for populations in which self-completion is not possible (see Table 7).

Table 7. EQ-5D-Y modes of administration and language versions (161).

Modes of administration	Total number of languages versions available
Self Complete Versions	
Paper	>90
PDA/Smartphone	>30
Tablet	>70
Laptop/Desktop	>10
Proxy versions	
Proxy version 1 (Paper)[a]	>70
Proxy version 2 (Paper)[b]	>15

a Proxy version 1: The proxy (parent, other caregiver or informant) is asked to respond to the questionnaire by providing their own impression of the child or adolescent's health status on the day of administration.
b Proxy version 2: The proxy is asked to rate how they think the child or adolescent would rate their own health on the day if they were able to complete the questionnaire

1.4.6. CHALLENGES FACED FOR THE GENERATION OF THE VALUE SET

The main challenges faced in calculating value sets in children were determining the appropriate group to elicit preference values for their health states. The normative argument was that the general population, who paid for healthcare interventions, should be used (163-

165). However, the main argument against this approach was that the population may not have had enough information about the health states being valued (165-167).

Patients had been suggested as an alternative, because they had experienced health impairments, but this approach had been criticized as patients may have overestimated the burden caused by their health impairments, leading to their disease receiving greater consideration with respect to resource allocation (165,166). On the other hand, patients might have become accustomed to their health problems, leading to undervaluation. Hence, they might have rated health problems less severely than the general population (166). Relatives, especially parents, had also been suggested as appropriate respondents because they knew their children and could estimate the influence of health impairments (168).

In 2020, an international valuation protocol for the EQ-5D-Y-3L was designed with the aim of resolving doubts and providing a framework to enable the implementation of cost-utility analyses for evaluating healthcare interventions for younger populations. The international protocol was a two-step approach based on an online discrete choice experiment (Step 1) plus a face-to-face composite time-trade-off exercise (Step 2) (169). The preference value set to generate the EQ-5D-Y utility index for Spain (170) was obtained from adults thinking as a hypothetical 10-year-old child.

1.5. DIGITAL HEALTH TECHNOLOGY

Digital health technologies have emerged as a crucial asset for improving healthcare services, offering an enormous potential to accurately diagnose and treat diseases (171). Digital health is frequently employed as a comprehensive term that encompasses electronic health (**eHealth**) (172), which refers to health care services delivered with the support of information and communication technology (173). eHealth includes mobile health (mHealth), wearable devices, telehealth, telemedicine, and personalized medicine (172). The WHO defines **mHealth** as a medical and public health practice that is supported by mobile devices, such as mobile phones, patient monitoring tools, and other wireless equipment (174).

Digital health interventions have increasingly been permeating into patient care, enabling the development of novel healthcare concepts, including the field of remote patient monitoring (175,176). Most remote patient monitoring via mHealth technologies involves the use of smartphones and specialized mobile apps, but it can also be carried out through wearable devices, which are especially important for improving the health and control of chronically ill patients with conditions such as asthma, diabetes, and cardiovascular disease (177).

There are numerous potential advantages of using eHealth solutions for children and young people, including the ability to conduct multidomain and multi-informant assessments (ie, through the child or adolescent, parent or caregiver, and health care professional), undertake continuous monitoring, and assist with timely connection to personalized clinical care (178,179). A recent systematic review summarizing evidence about eHealth tools designed

to assess and track health in children or adolescents (180) concluded that they have the potential to facilitate collaborative decision-making, improve communication, transmit remote health data and real-time assessment, and tracking.

According to the International Telecommunication Union, in 2021 there were 8.3 billion mobile phone/device subscriptions for 7.9 billion inhabitants in the world. Penetration rates for mobile subscriptions in developed nations today are above 100 percent, and in developing nations it's between 75% and 79%. Overall, 80% of the world's population owns a mobile phone, young people being the driving force of connectivity with 75% of the 15–24-year-olds actively online, compared with 65% among the rest of the population (181,182). Mobile phones are small devices which people tend to carry on them at all times (183), giving more leeway for easy access. Therefore, the administration of PROMs via mHealth applications may bring more privacy and autonomy to children and adolescents when answering, reducing unprompted adult participation that may interfere with their answers (184). Children and adolescents appear to be particularly willing to use eHealth programs, because they often have a greater facility and comfort with technologies such mobile phones, and they spend more time using them (185).

Due to safety concerns in the field of medical devices, including mobile apps, there are specific regulations currently in place (186). The US Food & Drug Administration (FDA) has its own set of regulations for medical devices (187). The Medical Device Regulation (EU MDR) 2017/745 (188) has been implemented to cover these functions in the European Union (EU) and the European Economic Area (EEA), and its legal application started in 2021 (186). The MDR's requirements for software qualification are more stringent than the FDA's regulations, particularly in terms of the classification of health apps and software (186). If a mobile app or software performs an action on data beyond storage, archiving, communication, or simple search, and the performed action is for medical purposes and the benefit of an individual patient, it is likely to qualify as a medical device and is subject to the MDR (186).

The ARCA (Asthma Research in Children and Adolescents) App was developed before the MDR came into effect, therefore no such classification was applied at the time. But this eHealth tool, which comprises a mobile health application for patients and an associated online platform for paediatricians to monitor them, was carefully developed according to the Spanish Organic Law 3/2018 of December 5 on the Protection of Personal Data and the Guarantee of Digital Rights, and keeping further security protocols and legal aspects in mind.

2. THESIS RATIONALE

Health-related quality of life (HRQL) and other Patient-Reported Outcome Measures (PROMs) are crucial for evaluating the effectiveness of interventions and for serving as performance indicators for child health and paediatric care. In recent years, a variety of generic and disease-specific paediatric PROMs have been developed, but few of them are econometric instruments that generate a preference-based utility index, thus limiting the calculation of quality-adjusted life-years for the economic evaluations of health programs involving these age groups.

Systematic reviews of PROMs for type 1 diabetes and asthma (139,151) indicated that there was scarce evidence available on the development and psychometric properties of the identified paediatric instruments. The more recent systematic review suggests the need for updated instruments to align with the most recent guidelines for PROM development to improve patient care.

The EuroQol Group developed the EQ-5D-Y in 2010 to solve the acknowledged need for generic preference-based utility measures that would be suitable for young individuals from 8 years onwards to self-report their HRQL (157). The development process involved children and adolescents to ensure that the instrument was age-appropriate and easy for young people to understand, meting the World Health Organization (WHO) criteria for the development of paediatric questionnaires. The EQ-5D-Y has a low administration burden and uses a short recall period to avoid memory gaps. Unlike other questionnaires, it addresses the lack of continuity and correspondence between HRQL instruments designed for children and for adults, enabling comparisons to be made over time and between conditions.

The EQ-5D-Y metric properties have been evaluated in various pathologies, including chronic kidney disease, cystic fibrosis, juvenile idiopathic arthritis, and idiopathic scoliosis, among others. However, there has been a lack of metric properties evaluation in children and adolescents with type 1 diabetes and asthma. To fill this gap, we planned to provide evidence on the metric properties of the EQ-5D-Y questionnaire in patients with these two important chronic paediatric conditions. Furthermore, beyond the suitability of the instrument and the robustness of its metric properties, the mode of administration has become a key factor for its applicability in different contexts, especially now with the incursion of new digital technologies. Therefore, we planned to evaluate the electronic administration mode, both for the laptop/desktop version of the EQ-5D-Y in patients with T1DM, and for the personal digital assistant (PDA)/smartphone version in patients with asthma.

Currently, 80% of the world's population is estimated to own a mobile phone (181,182), with young people being the driving force of connectivity. Mobile technologies are particularly relevant due to their ease of use, broad reach, and wide acceptance. The growing evidence on the benefits of monitoring PROMs in clinical practice, along with the asthma stepwise treatment approach based on monitoring symptoms, underscores the importance of real-time data in monitoring patients. Electronic administration of PROMs provides easy access,

objective monitoring, and increased privacy and autonomy for children and adolescents. However, designing electronic tools for monitoring the health of children and adolescents with chronic conditions remains a challenge, considering the novelty of this topic. Therefore, we developed and pilot tested an editable electronic tool, including a smartphone mobile application (ARCA app) for paediatric asthma patients, and an associated platform for paediatricians to monitor them.

Finally, taking into account a warning published by the United States Food and Drug Administration in March 2020 about serious neuropsychiatric side effects in patients with asthma treated with Montelukast, we planned a systematic review to synthesize the evidence on the impact of montelukast on paediatric patients with asthma and/or allergic rhinitis, measured with PROMs, when compared with other treatments or with placebo.

3. OBJECTIVES OF THE DOCTORAL THESIS

3.1. GENERAL OBJECTIVE

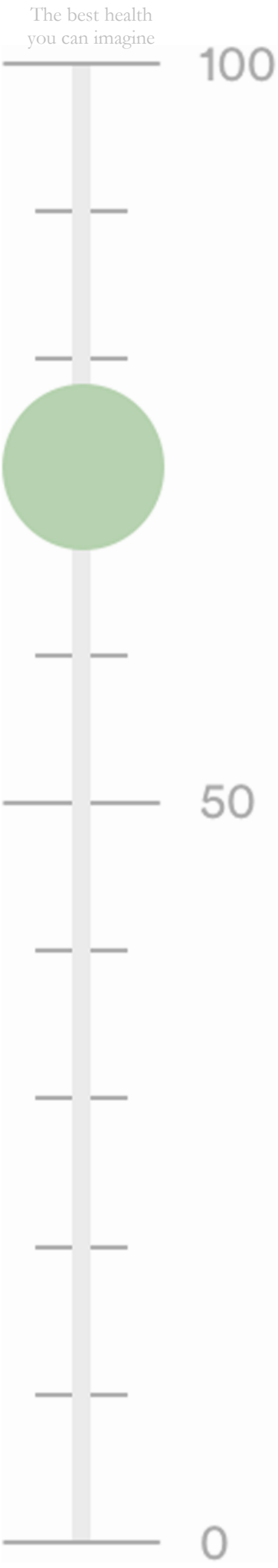
To evaluate the measurement properties of the EQ-5D-Y for monitoring the Health-Related Quality of Life and the impact of the disease in children and adolescents with chronic conditions, as well as to explore its administration through different electronic versions.

3.2. SPECIFIC OBJECTIVES

1. To evaluate the metric properties (acceptability, validity, reliability and responsiveness) of the EQ-5D-Y administered online in children and adolescents with type 1 diabetes mellitus.

2. To design a smartphone mobile application (ARCA App) to monitor asthma in children and adolescents, developed as an editable tool which will allow modifications according to future needs and provide paediatricians with patient information.

3. To evaluate the measurement properties (feasibility, validity, reliability and responsiveness) of the EQ-5D-Y descriptive system and utility index to allow the assessment of Health-Related Quality of Life through a smartphone mobile application (ARCA app) in children with asthma aged 8–11 years old (self-response version) or under 8 years old (proxy-response version).



4.1 ARTICLE 1

Mayoral K, Rajmil L, Murillo M, Garin O, Pont A, Alonso J, Bel J, Perez J, Corripio R, Carreras G, Herrero J, Mengibar JM, Rodriguez-Arjona D, Ravens-Sieberer U, Raat H, Serra-Sutton V, Ferrer M. ***Measurement Properties of the Online EuroQol-5D-Youth Instrument in Children and Adolescents With Type 1 Diabetes Mellitus: Questionnaire Study.*** J Med Internet Res. 2019 Nov 12;21(11):e14947. doi: 10.2196/14947. PMID: 31714252.

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Original Paper

Measurement Properties of the Online EuroQol-5D-Youth Instrument in Children and Adolescents With Type 1 Diabetes Mellitus: Questionnaire Study

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Abstract

Background: The lack of continuity between health-related quality of life (HRQoL) instruments designed for children and adults hinders change analysis with a life course approach. To resolve this gap, EuroQol (EQ) developed the EQ-5D-Youth (EQ-5D-Y), derived from the EQ-5D for adults. Few studies have assessed the metric properties of EQ-5D-Y in children with specific chronic conditions, and none have done so for children with type I diabetes mellitus (T1DM).

Objective: This study aimed to evaluate the acceptability, validity, reliability, and responsiveness of the EQ-5D-Y in children and adolescents with T1DM, when administered online.

Methods: Participants with T1DM were consecutively recruited from July to December 2014, from a list of potential candidates aged 8-19 years, who attended outpatient pediatric endocrinology units. Before every quarterly routine visit, participants received an email/telephone reminder to complete the online version of two generic HRQoL questionnaires: EQ-5D-Y and KIDSCREEN-27. The EQ-5D-Y measures five dimensions, from which an equally weighted summary score was constructed (range: 0-100).

Completion rate and distribution statistics were calculated. Construct validity was evaluated through known group comparisons based on general health, acute diabetic decompensations, mental health, family function, and a multitrait, multimethod matrix between EQ-5D-Y and KIDSCREEN by using Spearman correlations. Construct validity hypotheses were stated a priori. Reliability was assessed with the intraclass correlation coefficient and responsiveness by testing changes over time and calculating the effect size. Reliability and responsiveness were tested among the stable and improved subsamples defined by a KIDSCREEN-10 index change of <4.5 points or ≥4.5 points, respectively, from the first to the fourth visit.

Results: Of the 136 participants, 119 (87.5%) responded to the EQ-5D-Y at the last visit. The dimensions that showed higher percentages of participants with problems were "having pain/discomfort" (34.6%) and "worried/sad/unhappy" (28.7%). The mean (SD) of the EQ-5D-Y summary score was 8.5 (10.9), with ceiling and floor effects of 50.7% and 0%, respectively. Statistically significant HRQoL differences between groups defined by their general health (excellent/very good and good/regular/bad) and mental health (Strengths and Difficulties Questionnaire score ≤15 and >16, respectively) were found in three EQ-5D-Y dimensions ("doing usual activities," "having pain/discomfort," and "feeling worried/sad/unhappy"), summary score (effect size for general health and mental health groups=0.7 and 1.5, respectively), and KIDSCREEN-10 index (effect size for general health and mental health groups=0.6 and 0.9, respectively). Significant differences in the EQ-5D-Y dimensions were also found according to acute diabetic decompensations in "looking after myself" (P=.005) and according to family function in "having pain/discomfort" (P=.03). Results of the multitrait, multimethod matrix confirmed three of the four relationships hypothesized as substantial (0.21, 0.58, 0.50, and 0.46). The EQ-5D-Y summary score presented an intraclass correlation coefficient of 0.83. Statistically significant change between visits was observed in the improved subsample, with an effect size of 0.7 (P<.001).

Conclusions: These results support the use of the EQ-5D-Y administered online as an acceptable, valid, reliable, and responsive instrument for evaluating HRQoL in children and adolescents with T1DM.

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KEYWORDS

health-related quality of life; type 1 diabetes; EQ-5D-Y; EuroQol; validity

Introduction

Type 1 diabetes mellitus (T1DM) is one of the most common chronic childhood illnesses, affecting approximately 1 in every 400-600 children and adolescents [1]. Treatment includes a multifaceted regimen with daily subcutaneous insulin injections (or insulin infusion), blood glucose monitoring, carbohydrate counting, dietary plan, and physical activity [2]. Due to its complexity, T1DM management can be overwhelming even for the most competent patient [3]. Children might feel different from their peers because of their need for disruptive self-care activities [4] and the impact of T1DM on psychological aspects [5]. Health-related quality of life (HRQoL) captures the individual's health perception, adding the patients' perspective into T1DM clinical monitoring and research.

The lack of correspondence and continuity between HRQoL instruments designed for children and those designed for adults hinders the analysis of HRQoL changes using a life course approach. To solve this gap, in 2006, the EuroQol Group developed the EQ-5D-Youth (EQ-5D-Y) as a version of the EQ-5D for adults. The EQ-5D-Y was designed by adapting the EQ-5D dimensions to the requirements of HRQoL measurement in children and adolescents aged 8 years or older [6,7]. The main rationale of the new version was to enable young individuals to self-report their health [6,8]. A EQ-5D-Y proxy version was also developed [9] for children below 8 years of age. Given its generic and econometric nature, it allows comparison between different populations and conditions, and cost-utility analysis for economic evaluation. Another econometric instrument, the Health Utility Index [10], has a self-administered version for adults and adolescents and a proxy version for children (5-12 years of age), but its administration burden is substantially greater.

The EQ-5D-Y is a very short (2-3 minutes) and simple instrument to fill out. There are several studies assessing the metric properties of the EQ-5D-Y in the general population [11,12] or in school environments [13-16]. A Swedish study [12] suggested that the EQ-5D-Y was comprehensible, acceptable, and feasible for self-completion. A multicountry study supported its feasibility, reliability, and validity [11]. Furthermore, a Spanish study [16] compared the paper and Web-based versions of EQ-5D-Y, showing acceptable levels of agreement.

Only a few studies have assessed the metric properties of EQ-5D-Y in children with specific chronic conditions. A multicenter study among patients with cystic fibrosis [17] concluded that the EQ-5D-Y can be considered a valid instrument, which reflects the differences in health according to the progression of this life-long chronic disease. A comparison between the EQ-5D-Y and the Pediatric Asthma Quality of Life Questionnaire [18] supported EQ-5D-Y's convergent validity for asthmatic children and adolescents. In addition, a study in youth with chronic kidney disease provided evidence of the EQ-5D-Y validity, as it discriminated among groups that differed with regard to the disease-related clinical burden [19]. Finally, we have only identified one descriptive study of HRQoL in children with T1DM [20] measured with the EQ-5D-Y, but without assessing its metric properties. Our aim was to evaluate acceptability, validity, reliability and responsiveness of the EQ-5D-Y administered online in children and adolescents with T1DM.

Data was obtained from a clinical trial on children and adolescents with T1DM, designed to evaluate the impact of routine use of HRQoL assessment in clinical practice by using the KIDSCREEN-27 as the primary outcome. Previous publications of this trial reported that the baseline HRQoL of children and adolescents with T1DM [21] was similar to that of the European population of the same age, but with slightly worse physical well-being, and that routine assessment and face-to-face patient-physician discussion of HRQoL results improved after a year of follow-up, especially psychological well-being and school environment [22].

Methods

Participants and Study Design

Subjects were consecutively recruited from July to December 2014, from a list of 205 potential candidates with T1DM, aged between 8 and 19 years, attending outpatient pediatric endocrinology units of 5 hospitals. Exclusion criteria were as follows: T1DM diagnosed within the last 6 months and presence of cognitive problems that prevented comprehension of the questionnaires. Seven pediatricians were randomly assigned to either the intervention or control group (four and three pediatricians, respectively).

Families of children that fulfilled the inclusion criteria were informed about the project, and those who agreed to participate received a reminder by email and then by telephone, if necessary, before every quarterly routine visit to complete the online questionnaires within the 48 hours prior to the visit (for children with limited access to internet, a laptop was available at the doctor's office).

The intervention involved a discussion of the HRQoL scores between the doctor and the participant at each routine visit. The KIDSCREEN-27 and EQ-5D-Y results were displayed with different colors, similar to a traffic light, marking green for good, yellow for medium, and red for poor outcomes. Evolutionary results were displayed in the second, third, and fourth visits, to show a comparison with the previous results. At each visit, pediatricians invited the patients to comment and discuss the results, identifying dimensions with low value scores, exploring possible solutions and actions, and coming back to these actions over time with advice. Before starting the study, the pediatricians in this group had received standardized training in the use and interpretation of HRQoL questionnaires.

The control group also completed the questionnaires online. However, the questionnaires completed by the control group 48 h before each visit were about physical activity and diet, and the HRQoL questionnaires were completed only before the first and fourth visits. During the consultation, the patients received usual care without commenting on the results of the questionnaires (physicians did not receive any instruction on clinical management).

Study Variables

Information collected from clinical records included age, gender, weight, height, and glycated hemoglobin (HbA_{1c}) levels. Acute diabetic decompensations during the previous 3 months were registered: hypoglycemia (<60 mg/dL) with decreased level of consciousness, requiring glucagon or the help of others to recover, and hyperglycemia (>400-450 mg/dL), which required intervention of professionals or presented with diabetic ketoacidosis.

HRQoL evaluation consisted of the administration of the Spanish online version of the KIDSCREEN-27 and the EQ-5D-Youth (EQ-5D-Y). The descriptive system of the EQ-5D-Y [6] consists of five dimensions ("mobility," "looking after myself," "doing usual activities," "having pain/discomfort," and "feeling worried/sad/unhappy") with three-level Likert scale responses (no problems, moderate problems, and serious problems). It includes also a visual analogue scale (EQ-VAS) on the general health status rated from 0 (worst health status) to 100 (best health status possible). The time frame for both dimensions and EQ-VAS is "today." As no preference weights were available for the EQ-5D-Y to estimate utilities [23], an equally weighted summary score of the five dimensions was calculated [24-26], ranging from 0 (no problem in any dimension) to 100 (serious problems in all dimensions).

The KIDSCREEN-27 [27] contains 5 dimensions: physical well-being (5 items), psychological well-being (7 items), autonomy and relationships with parents (7 items), social support and relationship with friends (4 items), and school environment (4 items). Responses were categorized into five-option Likert scales that assess the frequency or intensity of the attribute, with a recall period of 1 week in most questions. Scores were calculated following developers' recommendations [27] for the KIDSCREEN-27 dimensions and for the KIDSCREEN-10 index, constructed with 10 items that sufficiently represent the longer KIDSCREEN profiles. The KIDSCREEN scores are standardized to a mean of 50 and a SD of 10, from a reference sample of 22,000 European children and adolescents [28].

In addition to HRQoL, children's mental health status and family function were assessed. The Strengths and Difficulties Questionnaire (SDQ) [29] consists of 25 items measuring a range of mental health symptoms including conduct problems, hyperactivity-inattention, emotional symptoms and peer problems, and prosocial behaviors. All items are scored on a 3-point scale (0=not true, 1=somewhat true, and 2=certainly true). Items are summed to give a total difficulties score ranging from 0 (no problems) to 40 (maximum problems). The Spanish version of the SDQ has shown to be reliable and valid [30]. The family function questionnaire [31,32] was designed to measure the patient's satisfaction with the support from the family through five items: Adaptation, Partnership, Growth, Affection, and Resolve (APGAR). These items have three response options (from almost always to hardly ever), and the total score ranges from 0 to 10 (low to high satisfaction).

Ethics Considerations

The study was approved by the ethics committee of participant hospitals in accordance with national and international guidelines (code of ethics, Helsinki Declaration) as well as legislation on data confidentiality (Organic Law 15/1999 of December 13 Data Protection character staff). Signed consent to participate was requested from parents and children over 12

years. The collection and transfer of data were carried out according to strict security and data encryption.

Analytical Strategy

Considering the 136 patients included in the T1DM clinical trial, this sample size gave a statistical power of 0.80 to detect a moderate-to-large difference of 0.65 SDs in the EQ-5D-Y summary score between unequally distributed known groups (80% and 20% of participants in each category) using a two-sided test with type I error of 5%. Statistical power was calculated using published formulas [33].

Characteristics of the sample were described by calculating percentages, or means and SDs, according to the type of variable. To evaluate the acceptability of the EQ-5D-Y, we calculated the completion rate and the distribution of the response options in each dimension. Distribution of the EQ-5D-Y summary score, EQ-VAS, and the KIDSCREEN-10 index was described by calculating the observed range, floor, and ceiling effects (proportion of participants with the worst and best possible score, respectively) and statistics of central tendency and dispersion.

Construct validity was assessed by applying two different approaches: (1) comparison of known groups and (2) the multitrait, multimethod matrix with data from the first visit. Known groups were defined according to the general health (through a question from KIDSCREEN-27), dichotomized as excellent/very good and good/regular/bad; acute diabetic decompensations during the previous 3 months; mental health, dichotomized by the total SDQ score cutoff of 15; and family, classified as dysfunctional (total APGAR score≤6) or functional (total APGAR score=7-10) [32]. To assess differences between known groups, a Chi-square test was used for proportions of participants with problems, Wilcoxon nonparametric test was used for the EQ-5D-Y summary score and EQ-VAS, and unpaired *t*-test was used for KIDSCREEN scores. The magnitude of the differences between groups was assessed by the Cohen effect size (difference of mean/pooled SD) [34]. General guidelines define an effect size of 0.2 as small, 0.5 as moderate, and 0.8 as large [35]. The hypotheses raised a priori, based on available evidence, were higher EQ-5D-Y summary score (worse HRQoL) in children reporting worse general health [11], with previous acute diabetic decompensations [36,37], worse mental health [11,38], and with a dysfunctional family [39,40].

The multitrait, multimethod matrix between the EQ-5D-Y and the KIDSCREEN was constructed using Spearman correlations. The logical relationship between two instruments can be categorized as convergent and discriminant. For the convergent validity [7] (different instruments measuring a similar concept), we hypothesized substantial correlations between “mobility” (EQ-5D-Y) and “physical well-being” (KIDSCREEN-27), “feeling worried/sad/unhappy” (EQ-5D-Y) and “psychological wellbeing” (KIDSCREEN-27), and the KIDSCREEN-10 index with the EQ-5D-Y summary score and EQ-VAS. In contrast, for the discriminant validity [7] (different instruments measuring different traits or constructs), we hypothesized low correlations between the EQ-5D-Y dimension of “looking after myself” and the following three KIDSCREEN-27 dimensions: “autonomy and relationships with parents,” “social support and relationship with friends,” and “school environment.” The strength of Spearman correlations was defined [41] as insignificant (≤0.30), moderate (0.31-0.44), or substantial (0.45-0.60).

The reliability was assessed in terms of reproducibility (stability of an instrument over time) in a subsample of stable participants—those in the control group with an absolute change <4.5 points in the KIDSCREEN-10 index from the first to the fourth visit, which corresponds to a small magnitude of change (effect size<0.45). To measure the agreement in EQ-5D-Y summary score and EQ-VAS between both administrations, the intraclass correlation coefficient (ICC) was calculated. To assess responsiveness, we classified participants experiencing “improvement” as those with a change in KIDSCREEN-10 index ≥4.5 points (moderate effect size) between the first and the fourth visits. Differences for the EQ-5D-Y dimensions were compared using the McNemar paired test, while differences between the EQ-5D-Y summary score and EQ-VAS were tested with the Wilcoxon paired test. The magnitude of change was also measured by the effect size coefficient (mean of change/SD of change). Program STATA.14 software (StateCorp LP, College Station, Texas) was used in the analysis.

Results

Sample Characteristics

Of 205 potential candidates with T1DM, 61 were not included due to change of address, transfer to the adult unit, or no attendance at the follow-up visits; in addition, 8 subjects rejected participation. Finally, 136 participants were included in the study. Table 1 shows the characteristics of the sample. Mean age was 14 years, around half of the participants were girls, 71 (52.2%) had HbA_{1c} levels ≤7.5% (58 mmol/mL), 123 (90.4%) did not present acute diabetic decompensations during the previous 3 months, and the majority (n=95) rated their health as good or very good.

Table 1. Demographic and clinical characteristics of the participants (N=136).

Characteristic	Value
Age (years)[a], mean (SD)	13.99 (0.2)
8-12, n (%)	45 (33.3)
13-15, n (%)	54 (40.0)
16-18, n (%)	35 (25.9)
>18, n (%)	1 (0.7)
Sex, n (%)	
Girls	72 (52.9)
Boys	64 (47.1)
Metabolic control, HbA_{1c}[b], mean (SD)	7.7 (1.3)
>7.5, n (%)	65 (47.8)
≤7.5, n (%)	71 (52.2)
Acute diabetic decompensations (previous 3 months), n (%)	
Yes	13 (9.6)
No	123 (90.4)
General Health Question (KIDSCREEN-27), n (%)	
Excellent	19 (13.9)
Very good	44 (32.4)
Good	54 (39.7)
Regular	17 (12.5)
Bad	2 (1.5)
Mental health (total SDQ[c] score), mean (SD)	10.64 (5.3)
0-15, n (%)	113 (83.1)
16-40, n (%)	23 (16.9)
Family function (APGAR[d]), n (%)	
Dysfunctional	52 (38.2)
Functional	84 (61.8)

[a]The age of one participant is missing (N=135).

[b]HbA_{1c}: glycated hemoglobin.

[c]SDQ: Strengths and Difficulties Questionnaire.

[d]APGAR: Adaptation, Partnership, Growth, Affection, and Resolve.

Distribution of Dimensions and Indices of Health-Related Quality of Life

Children and adolescents with T1DM reported relatively fewer health problems in the EQ-5D-Y dimensions (Table 2), especially for "mobility" (n=3, 2.2%) and "looking after myself" (n=4, 2.9%). Dimensions showing higher percentages of participants with problems were "having pain or discomfort" (n=47, 34.6%) and "feeling worried/sad/unhappy" (n=39, 28.6%). Means and 95% CI of KIDSCREEN-27 dimensions (Table 3) were below 50 (European sample mean [28]) for "physical well-being" (46.2, 95% CI 44.7-47.7) and over 50 for "school environment" (52.0, 95% CI 50.4-53.6) and "social support/relationship with friends" (53.6, 95% CI 52.1-55.1). As shown in Table 4, the mean (SD) of the EQ-5D-Y summary score was 8.5 (10.9), with ceiling and floor effects of 50.7% and 0%, respectively. The EQ-VAS ranged in our sample from 31 to 100, with a mean (SD) of 80.4 (14.7). The KIDSCREEN index ranged from 40.0 to 83.8, and the mean (SD) was 49.7 (8.3).

Table 2. Distribution of the EuroQol-5D-Youth (EQ-5D-Y) dimensions.

EQ-5D-Y dimensions	No problems, n (%)	Some problems, n (%)	A lot of problems, n (%)
Mobility	133 (97.8)	3 (2.2)	0 (0.0)
Looking after myself	132 (97.1)	4 (2.9)	0 (0.0)
Doing usual activities	119 (87.5)	17 (12.5)	0 (0.0)
Having pain/discomfort	89 (65.4)	45 (33.1)	2 (1.5)
Feeling worried/sad/unhappy	97 (71.3)	35 (25.7)	4 (2.9)

Table 3. Distribution of KIDSCREEN-27 dimensions.

KIDSCREEN-27 dimensions	Mean (SD), 95% CI	Median
Physical well-being	46.2 (9.0), 44.7-47.7	44.7
Autonomy/relationships with parents	50.5 (8.2), 49.1-51.9	49.5
School environment	52.0 (9.3), 50.4-53.6	51.1
Social support and relationship with friends	53.6 (9.1), 52.1-55.1	53.3
Psychological well-being	49.7 (9.7), 48.1-51.3	48.5

Table 4. Distribution of the EuroQol-5D-Youth (EQ-5D-Y) summary score, EuroQol-Visual Analog Scale (EQ-VAS), and KIDSCREEN-10 index.

Distribution of scores	EQ-5D-Y summary score	EQ-VAS	KIDSCREEN-10 index
Theoretical range	0-100	0-100	–3.54 to 83,81
Observed range	0-40	31-100	40.0-83.81
Proportion of participants with the best health (%)	50.7	8.1	0.7
Proportion of participants with the worst health (%)	0	0	0
Mean (SD)	8.5 (10.9)	80.4 (14.7)	49.7 (8.3)

Construct Validity of the EuroQol-5D-Youth Online

Table 5 shows statistically significant HRQoL differences between groups defined by their general health in three of five EQ-5D-Y dimensions as well as EQ-5D-Y summary score, EQ-VAS, and KIDSCREEN-10 index (P<.001, P<.001, and P=.02, respectively) with moderate-large effect sizes (0.7, 1.0, and 0.6, respectively). Similar significant HRQoL differences were found according to mental health with large effect sizes, except for the EQ-VAS. The only significant difference between those with and without acute diabetic decompensations was found in the "looking after myself" dimension (P=.005). Finally, HRQoL differences between functional and dysfunctional families were statistically significant for the "having pain and discomfort" EQ-5D-Y dimension (P=.03) and KIDSCREEN-10 index (P<.001).

Table 5. Comparison of health-related quality of life between known groups measured at baseline.

Variables	EQ-5D-Y[a] dimensions					EQ-5D-Y summary score, mean (SD), median	EQ-VAS[b], mean (SD), median	KIDSCREEN-10 index, mean (SD), median
	M[c]	LAM[d]	DUA[e]	HP/D[f]	W/S/U[g]			
General health question								
Excellent/very good	0.0%	3.2%	4.8%	22.2%	19.1%	5.08 (8.4), 0	87.6 (10.5), 90	52.24 (6.9), 53.1
Good/regular/bad	4.1%	2.7%	19.2%	45.2%	37.0%	11.51 (12.1), 10	74.1 (15.0), 75	47.47 (8.9), 45.7
P value	.25	1.00	.02[h]	<.01[h]	.02[h]	<.001[h]	<.001[h]	.02[h]
Effect size (95% CI)	N/A[i]	N/A	N/A	N/A	N/A	0.7 (0.39-1.09)	1.0 (0.66-1.38)	0.6 (0.25-0.94)
Acute diabetic decompensations								
Yes	7.7%	15.4%	23.1%	38.5%	46.2%	13.85 (13.2), 10.0	74.9 (18.0), 75	50.21 (9.8), 46.9
No	1.6%	1.6%	11.4%	34.2%	26.8%	7.97 (10.6), 0	80.9 (14.3), 81	49.63 (8.2), 48.3
P value	.26	.005[h]	.23	.76	.14	.08	.21	.81
Effect size (95% CI)	N/A	N/A	N/A	N/A	N/A	0.5 (–0.04 to 1.12)	0.4 (–0.17 to 0.99)	0.07 (–0.5 to 0.65)
Mental health (SDQ[j])								
Score 0-15	0.9%	2.7%	8.9%	28.3%	20.4%	6.11 (8.4), 0	81.3 (14.8), 81	50.84 (8.3), 49.8
Score 16-40	8.7%	4.4%	30.4%	65.2%	69.6%	20.43 (14.3), 20	75.7 (13.5), 75	44.01 (5.6), 43.4
P value	.07	.53	.004[h]	.001[h]	<.001[h]	<.001[h]	.06	<.001[h]
Effect size (95% CI)	N/A	N/A	N/A	N/A	N/A	1.5 (1.01-1.98)	0.4 (–0.07 to 0.83)	0.9 (0.40-1.32)
Family function (APGAR [k])								
Score≤6	1.2%	4.8%	10.7%	27.4%	25.0%	7.02 (9.9), 0	81.6 (15.1), 85	51.46 (8.6), 50.6
Score 7-10	3.9%	0.0%	15.4%	46.2%	34.6%	10.96 (12.3), 10	78.3 (13.9), 80	46.81 (6.9), 46.9
P value	.56	.30	.42	.03[h]	.23	.06	.12	<.001[h]
Effect size (95% CI)	N/A	N/A	N/A	N/A	N/A	0.4 (0.01-0.71)	0.2 (–0.12 to 0.58)	0.6 (0.22-0.93)

[a]EQ-5D-Y: EuroQol-5D-Youth.

[b]EQ-VAS: EuroQol-Visual Analog Scale.

[c]M: mobility.

[d]LAM: looking after myself.

[e]DUA: doing usual activities.

[f]HP/D: having pain/discomfort.

[g]W/S/U: feeling worried/sad/unhappy.

[h]Statistically significant difference.

[i]N/A: not applicable.

[j]SDQ: Strengths and Difficulties Questionnaire.

[k]APGAR: Adaptation, Partnership, Growth, Affection, and Resolve.

Table 6 presents the multitrait, multimethod matrix between EQ-5D-Y and KIDSCREEN. Regarding convergent validity, of the four correlations previously hypothesized as substantial, subscript a), three obtained coefficient values of 0.45 or greater: 0.58 between EQ-5D-Y "feeling worried/sad/unhappy" and KIDSCREEN "psychological wellbeing," 0.50 between the EQ-5D-Y summary score and KIDSCREEN-10 index, and 0.46 between the EQ-VAS and KIDSCREEN-10 index. In contrast, the correlation between the mobility dimension of the EQ-5D-Y and the physical well-being dimension of the KIDSCREEN-27 was 0.21. For discriminant validity, the three relationships hypothesized as insignificant (subscript b) ranged from 0.02 to 0.06, as expected.

Table 6. Multitrait, multimethod matrix between the EuroQol-5D-Youth (EQ-5D-Y) and the KIDSCREEN in children and adolescents with type 1 diabetes mellitus at baseline evaluation.

EQ-5D-Y	KIDSCREEN-27					KIDSCREEN-10 index
	Physical well-being	Psychological well-being	Autonomy and relationships with parents	Social support and relationship with friends	School environment	
Mobility	0.21[a]	0.19	0.02	0.06	0.12	0.16
Looking after myself	0.02	0.07	0.06[b]	0.02[b]	0.06[b]	0.03
Doing usual activities	0.17	0.29	0.08	0.14	0.25	0.25
Having pain/discomfort	0.27	0.31	0.23	0.13	0.17	0.32
Feeling worried/sad/unhappy	0.30	0.58[a]	0.22	0.36	0.40	0.56
EQ-5D-Y summary score	0.23	0.10	0.01	0.18	0.00	0.50[a]
EuroQol-Visual Analog Scale	0.38	0.31	0.21	0.14	0.35	0.46[a]

[a]Correlations hypothesized as substantial (0.45-0.60).

[b]Correlations hypothesized as insignificant (≤0.30).

Reproducibility and Responsiveness

Table 7 shows EQ-5D-Y test-retest results in the "stable" subsample between the first and the fourth visit. The ICC was 0.83 and 0.74 for the EQ-5D-Y summary score and EQ-VAS, demonstrating stability over time for this subsample. Regarding responsiveness, this "improvement" subsample presented significant changes in three dimensions, in the EQ-5D-Y summary score, and EQ-VAS between the first visit and the fourth visit. The effect sizes were 0.70 and 0.74, indicating an improvement of moderate-to-large magnitude.

Table 7. Reproducibility and responsiveness of EuroQol-5D-Youth (EQ-5D-Y): problems reported by each dimension, summary score, and EuroQol-Visual Analog Scale (EQ-VAS) at the first and fourth visits.

EQ-5D-Y	Test-retest reproducibility among stable participants (n=18)			Responsiveness among participants with improvement (n=58)		
	First visit	Fourth visit	*P* value	First visit	Fourth visit	*P* value
EQ-5D-Y dimensions						
Mobility, n (%)	0 (0.0)	1 (5.6)	—[a]	3 (5.2)	1 (1.7)	.63
Looking after myself, n (%)	1 (5.6)	0 (0.0)	—	2 (3.5)	1 (1.7)	>.99
Doing usual activities, n (%)	1 (5.6)	1 (5.6)	.06	9 (15.5)	2 (3.5)	.02[b]
Having pain/discomfort, n (%)	4 (22.2)	4 (22.2)	.13	27 (46.6)	11 (18.9)	<.001[b]
Feeling worried/sad/unhappy, n (%)	6 (33.3)	5 (27.8)	.14	23 (39.7)	10 (17.2)	<.001[b]
EQ-5D-Y summary score			.71			<.001[b]
Mean (SD)	6.67 (9.1)	6.11 (7.8)		11.90 (12.6)	4.31(7.0)	
Effect size (95% CI)	N/A[c]	0.07 (–0.61 to 0.74)		N/A	0.70 (0.31 to 1.02)	
ICC[d] (95% CI)	N/A	0.83 (0.55 to 0.94)		N/A	N/A	
EQ-VAS			.15			<.001[b]
Mean (SD)	82 (13.5)	86 (9.1)		76.0 (16.6)	86.9 (13.0)	
Effect size (95% CI)	N/A	0.35 (–0.34 to 1.03)		N/A	0.74 (0.36 to 1.12)	
ICC (95% CI)	N/A	0.74 (0.31 to 0.90)		N/A	N/A	

[a]Not available.

[b]Statistically significant difference.

[c]N/A: not applicable.

[d]ICC: intraclass correlation coefficient.

Discussion

To the best of our knowledge, this is the first study evaluating metric properties of the new EQ-5D-Y in T1DM children and adolescents. We found this generic preference-based instrument to be acceptable for children and adolescents with T1DM and easy to administer online, but with a high ceiling effect (50.7% of participants reported no problem in any dimension). The EQ-5D-Y showed good validity, considering the results obtained in the known groups' analysis based on general health, acute diabetic decompensations, mental health, and family function, and those obtained from the multitrait, multimethod matrix with KIDSCREEN. Test-retest reproducibility was high, indicating good reliability, and the moderate-large change observed between the first and fourth visits among the selected subsample of "improvement" supports its responsiveness.

Of the 136 participants in the T1DM study, all responded to the EQ-5D-Y at the first visit and 119 (87.5%) responded at the fourth visit, which is similar to the response rates reported by studies carried out in the clinical (96% [18]) and school (77% [16]) settings. It is important to remark that the participants answering the EQ-5D-Y entirely completed the instrument, including the five dimensions, and the EQ-VAS. These rates of completion support the acceptability of the EQ-5D-Y among children and adolescents with T1DM when administered online. Taking into account the quick expansion of online recreational habits among the new generations born in the digital era, acceptability could be even higher with the incorporation of other devices such as apps for smartphones or tablets. However, completion rates in routine clinical practice could be lower than under clinical trial conditions, which indicates the need for closer monitorization.

Ceiling effect in the sample of children and adolescents with T1DM was high for the EQ-5D-Y summary score (50.7%) and for the three out of its five dimensions, which exceeded 85% of participants reporting no problem ("mobility," "looking after myself," and "doing usual activities"). A European multicountry study of EQ-5D-Y metric properties [11] reported a similar ceiling effect for these dimensions, which was up to 80% in children with chronic conditions. Half of the children and adolescents with no problem in any dimension (value=0 in EQ-5D-Y summary score) could be considered to show a really high ceiling effect, taking into account the established recommendations of 15% for HRQoL scores [42]. However, this is a general standard, as there are none specific for children. This high ceiling effect could be considered coherent with the relative low impact of diabetes on HRQoL for most children and adolescents, partially explained by their capacity of adaptation to the demanding tasks related to care [43]. The main disadvantage of this high ceiling effect is that it avoids the detection of improvement in children and adolescents who reported the highest level of health, which could affect the instrument's responsiveness.

On the other hand, our study showed a substantial proportion of children and adolescents with T1DM reporting problems in the dimensions of "having pain or discomfort" (n=47, 34.6%) and "feeling worried/sad/unhappy" (n=43, 28.7%). These results are consistent with a previous study [44] showing this latter EQ-5D-Y dimension as the most affected in children and adolescents with T1DM. They are also consistent with studies using the 21-item Beck Depression Inventory and the Child Health Questionnaire PF-50 [45,46], which highlighted the impact of T1DM on the psychological dimension, especially due to the lack of autonomy, worrying for future chronic complications and the self-care routines that these children and adolescents have to experience.

As hypothesized, the EQ-5D-Y presented a good discrimination capacity between groups defined by the general health question and SDQ score in the summary score and in three dimensions: "doing usual activities," "having pain/discomfort," and "feeling worried/sad/unhappy." These dimensions presented the highest correlations with general and mental health in previous studies of children and adolescents with T1DM [41] or chronic conditions [10]. The magnitude of the difference between groups defined by these constructs was larger when HRQoL was measured with the EQ-5D-Y summary score (effect size for general health and mental health groups=0.7 and 1.5, respectively) than with the KIDSCREEN-10 index (effect size for general health and mental health groups=0.6 and 0.9, respectively).

It is important to highlight the problems reported in the "looking after myself" dimension among those participants who had previously experienced acute diabetic decompensations, which is consistent with previous studies comparing good and bad metabolic control [37,47]. These participants showed differences in the physical well-being and health perception dimensions, measured with KINDL-R [37] and the Diabetes Quality of Life questionnaire [42]. A priori hypotheses on the relationship between family function and HRQoL were based on studies that reported an increased risk for depressive symptoms in families with a disadvantaged socioeconomic status [39,48]. Our results, showing problems of "having pain and discomfort" more frequently and poorer HRQoL with KIDSCREEN-10 index in children and adolescents with dysfunctional families, are in line with the social component of health [39,48].

Correlations between EQ-5D-Y and KIDSCREEN showed the expected pattern for convergent and divergent validity, which were very similar to those obtained in the abovementioned European multicountry study [11]. The dimensions reflecting the emotional aspects of EQ-5D-Y ("feeling worried/sad/unhappy") and KIDSCREEN-27 ("psychological well-being"), in addition to the EQ-5D-Y summary score and EQ-VAS, presented a substantial correlation with the KIDSCREEN-10 index, which provides a summary of the HRQoL. The EQ-5D-Y "mobility" dimension failed to display convergent validity with the KIDSCREEN dimension "physical wellbeing," similar to a previous study [11] (r=0.10-0.25). Considering the content of the instruments, it can be argued that KIDSCREEN is more focused on the energy level and less focused on the physical functioning, which is the case of the EQ-5D-Y.

Our study shows good reproducibility of the questionnaire according to the established standards [7] for reliability coefficients: 0.7 and 0.9 for group and individual measurements,

respectively. The ICC of 0.83 and 0.74 obtained for the EQ-5D-Y summary score and EQ-VAS allows recommending its use. Nine months between the first and the fourth visit is too long a period to evaluate reproducibility, since HRQoL could change considerably during this time. This long period explains the low number of children and adolescents in the stable subsample (n=18). Previous EQ-5D-Y studies used the kappa coefficient to evaluate test-retest reporting from good to fair agreement, according to dimensions [11,15].

The EQ-5D-Y detected differences in the selected subsample of children and adolescents with T1DM classified as experiencing "improvement" between the first and the fourth visit, showing the capacity of this instrument to detect change. It is important to highlight that no other studies testing the responsiveness of the EQ-5D-Y have been found. A systematic review assessing metric properties of diabetes-specific HRQoL instruments also highlighted that the lack of testing for responsiveness is a major shortcoming [49]. The EQ-5D-Y summary score indicates a moderate-large improvement over time, a magnitude which can be considered reasonable when accounting for the length of the follow-up of participants (9 months), the nature of the intervention, and the course of the T1DM.

The T1DM clinical trial provides a comprehensive and complete database of EQ-5D-Y and disease-related variables to allow assessment of metric properties including validity, reliability, and responsiveness. However, some limitations need to be addressed. First, the assessment of the acceptability is not complete: Other indicators such as administration time needed to complete the questionnaire and patient views about the instrument should be included in further studies. Second, since the EuroQol group has not developed the value set for the EQ-5D-Y yet [23], the unweighted summary score was calculated as was done in previous studies [24-26]. However, this summary score did not allow cost-utility analysis. Third, the EQ-5D-Y does not cover social dimension, a key aspect of children's HRQoL, but it presents an acceptable capacity of discrimination between functional and dysfunctional families in our study. There are other generic pediatric instruments that cover social dimensions, such as KIDSCREEN [50] ("autonomy and relationships with parents," "social support," "relationship with friends," and "school environment"), PedsQol [51] ("social functioning" and "school functioning"), or the Child Health Questionnaire [52] ("role/social emotional and behavioral functioning"). Fourth, this is a secondary analysis of a study designed for purposes other than the evaluation of the metric properties of EQ-5D-Y. For example, as commented above, the 9-month period between test and retest is too long for measuring reproducibility, and no large change is expected with the intervention applied. Furthermore, results on stability should be interpreted with caution due to the small sample size. Finally, regarding external validity, the results of this study should not be generalized to other chronic conditions.

Despite the limitations discussed above, our results provide considerable evidence supporting the appropriate metric properties of the EQ-5D-Y in patients with T1DM. In conclusion, these findings suggest that the EQ-5D-Y administered online is an acceptable, valid, reliable, and responsive instrument for evaluating HRQoL in children and adolescents with this chronic condition. Since it is a preference-based health status measure, it will allow calculating quality-adjusted life-years (combining both the quantity and quality of life) for economic evaluations, once social preferences specifically for children become available. Given its short and easy administration, the EQ-5D-Y is a practical instrument to implement in primary care to routine monitoring. It is a promising instrument to compare the efficiency of different programs or treatment strategies, helping prioritize and invest at different levels.

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Authors' Contributions

KM contributed to the conception and design of the article, conceptualized and oversaw analyses, contributed to the interpretation of data, and wrote the article; LR conceived the study, participated in the design and coordination, and carried out the fieldwork; MM participated in the design and coordination of the study and carried out the fieldwork; OG contributed to the conception and design of the article, conceptualized and oversaw analyses, and contributed to the interpretation of data; AP contributed to the analysis and provided statistical support; JA contributed to the conception and design of the article, conceptualized and oversaw analyses, and contributed to the interpretation of data; JB participated in the design of the study and carried out the fieldwork; JP, RC, GC, XH, JMM, and DRA participated in the design of the study and carried out the fieldwork; URS conceived the study and participated in the design and coordination of the study; HR conceived the study and participated in the coordination of the study; VSS revised important intellectual content and the draft versions of the manuscript; MF oversaw all aspects, contributed to the conception and design of the article, contributed to the statistical analyses, carried out the interpretation of data, and contributed to the writing of the article. All the coauthors critically revised the manuscript and approved the final draft before submission, can attest to the validity and legitimacy of the data in the manuscript, and agree to be named as author of the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

APGAR: Adaptation, Partnership, Growth, Affection, and Resolve
DUA: doing usual activities
EQ-5D-Y: Youth EuroQoL version
EQ-VAS: EuroQol-Visual Analog Scale
EQ: EuroQol
ES: effect size
HbA_{1c}: glycated hemoglobin
HP/D: having pain/discomfort
HRQoL: health-related quality of life
ICC: intraclass correlation coefficient
LAM: looking after myself
SDQ: Strengths and Difficulties Questionnaire
T1DM: type I diabetes mellitus
W/S/U: feeling worried/sad/unhappy

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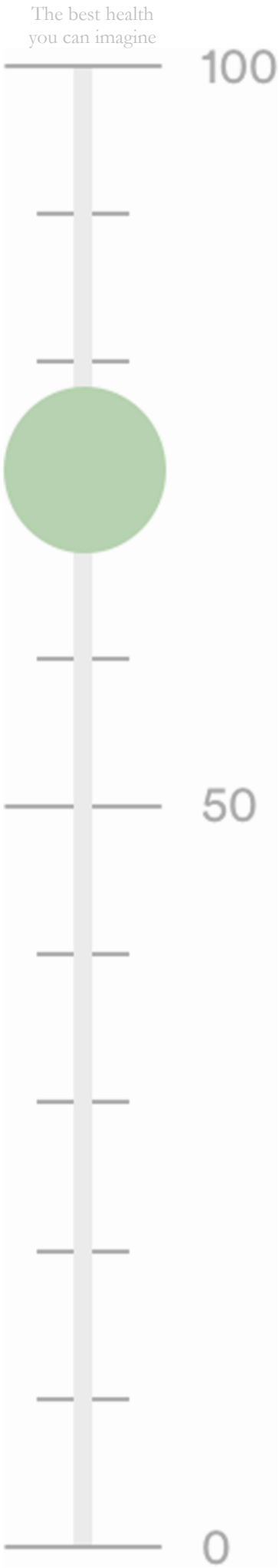

4.2. ARTICLE 2:

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SPECIAL SECTION: FEEDBACK TOOLS

Smartphone App for monitoring Asthma in children and adolescents

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Abstract

Purpose The asthma stepwise treatment approach recommended is based on monitoring patients' symptoms. The Asthma Research in Children and Adolescents (ARCA) cohort was created to provide evidence about the evolution of persistent asthma. This manuscript describes the development of an electronic health tool, comprising a mobile health application for patients with asthma and its associated online platform for pediatricians to monitor them.

Methods The development process followed 7 phases: the first 5 (Conceptualization, Preparation, Assessment scheduling, Image and user interface, and Technical development) defined and designed the tool, followed by a testing phase (functionality assessment and pilot test with ARCA patients), and a last phase which evaluated usability. Since the target population was aged 6–16 years, three versions were designed within the same smartphone application: parents/proxy, children, and adolescents. The online platform for pediatricians provides real-time information from the application: patients' responses over time with color-coded charts (red/amber/green, as in traffic lights).

Results The pilot test through semi-structured phone interviews of the first 50 participants included in the ARCA study ($n = 53$) detected their misunderstandings. Pediatricians were trained to emphasize that the application is free of charge and requires monthly answers. Median of the System Usability Scale scores ($n = 85$), ranging 0 (negative)–100 (positive), was > 93 in the three age versions of the application.

Conclusions Technology has the capability of transforming the use of patient-reported outcomes. Describing all the development phases of a mobile health application for monitoring children and adolescents with asthma may increase the knowledge on how to design applications for young patients.

Keywords e-health · m-health application · Asthma · Children · Patient-reported outcomes · Health-related quality of life · Monitoring

Introduction

Asthma is a chronic condition that affects more than 300 million people worldwide [1], and it is the most common chronic disease during childhood, affecting around 14% of children globally [2]. The stepwise treatment approach proposed by the Global Initiative for Asthma Management and Prevention (GINA) [3] requires treatment adjustments through frequent assessment of the patients' symptoms. However, in a real-life setting, it is challenging to monitor asthma patients. Barriers to monitoring patients are especially relevant in children and adolescents, which requires some degree of parent participation.

The Asthma Research in Children and Adolescents (ARCA) study (NCT04480242) was designed to provide evidence about the evolution of children and adolescents with persistent asthma through a regular follow-up. It was based on a previous project focused on the assessment of asthma patients (6–40 years old) in routine care by combining several sources of information [4–9] with an especially low response rate in the Web-based survey [10].

The members of ARCA group were included in acknowledgements section.

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Given the familiarity of children and adolescents born this century with smartphones, we decided to develop an electronic health (e-Health) tool consisting of a mobile health (m-Health) application for collecting patient-reported outcomes (PROs) regularly, and an online platform for the pediatricians to access the patients' information collected through this application.

There is growing evidence on the benefits of routine monitoring of PROs in clinical practice [11, 12]. Traditional administration forms of PROs at younger ages, such as paper or computer administration, involve proxy-reported measures or self-reported measures with the help of adults. On the one hand, this proxy report (when needed) could facilitate and improve the information collected, but on the other hand, when it is not needed, some parents may impose their own perspective or be tempted to answer questions, and some children and adolescents may feel inhibited or intend to please their parents when answering [13]. In fact, disagreement between parents' and their children's reported outcomes has been well documented [14–16]. Mobile phones are small devices which people tend to carry on them at all times [17], giving more leeway for easy access. Therefore, the administration of PROs via m-Health applications may bring more privacy and autonomy to children/adolescents when answering, reducing unprompted adult participation.

Since smartphones first came into the market a decade ago, the estimated number of m-Health applications has continually increased, reaching approximately 325,000 in 2017 [18]. Four systematic reviews [19–22] assessing the effects of applications for smartphones and tablets on individuals with asthma identified 14 studies, mostly in adults, and only five in adolescents [23–27]. All these applications were designed to provide the patients with information for their self-management, and only four applications for adults [28–31] allowed their clinicians to access the data records. Most of these reviews concluded that multifunctional m-Health applications have good potential in improving asthma control [19, 21, 22].

Beyond the currently available m-Health applications, we aim to design an editable tool which will allow modifications according to future needs and provide pediatricians with patient information. This manuscript describes the development and pilot testing of an e-Health tool, comprising an m-Health application for patients and its associated online platform for pediatricians to monitor children and adolescents with asthma.

Methods

ARCA is a longitudinal prospective multicenter observational study of patients that fulfilled the following inclusion criteria: children or adolescents aged 6–16 with a clinical diagnosis of asthma, undergoing treatment with inhaled corticosteroids (alone or combined with long-acting beta-agonists) for more than 6 months in the previous year, and with access to a smartphone (their own, or their parents'). Written informed consent was required from the parents or legally authorized representatives of all participants and additionally from adolescents ≥ 12 years old; oral consent was obtained from children < 12 years old. Patient-reported variables in this cohort are collected through a mobile application and computer-assisted telephone interviews (administered every 6 months). Due to our target population's age, telephone interviews were considered a complementary information source to reduce the administration burden of providing all the information through the application.

Developing an e-Health tool with a mobile application requires a multidisciplinary approach and the involvement of all stakeholders; we assembled a project team composed of pediatricians, PRO researchers, and a technical development group. Two members of the project team were parents of children with asthma. End users' involvement was high for pediatricians throughout the process; children and adolescents, however, were only involved in the last phases of development due to time and financial restrictions.

The development process is summarized in 7 phases (Fig. 1).

1. Conceptualization phase

The aim was to define the target population, end users, concept, and content of the e-Health ARCA tool through brainstorming and a critical review of available evidence.

The target population was defined as Spanish children and adolescents with persistent asthma, end users being them, their parents, and pediatricians. Due to our target population's characteristics, the team agreed on the need for the following concept aspects: (1) a friendly, intuitive, and low-burden application to achieve a long-term engagement through fluid interactions with users; and (2) a website where pediatricians can access real-time information on their patients' responses in the application. Therefore, they have an up-to-date overview of the patient's follow-up and can detect changes since the last visit, facilitating patient management in clinical practice.

A literature search of articles published since 2010 was performed in PubMed to review the constructs associated with asthma management in children and adolescents and then selected the most appropriate instrument reported directly by patients for measuring each construct. The terms used for the search were: asthma, child or adolescent, and disease management (full electronic search strategy in Online Resource Fig. 1). Two PRO researchers independently reviewed articles found in the literature search

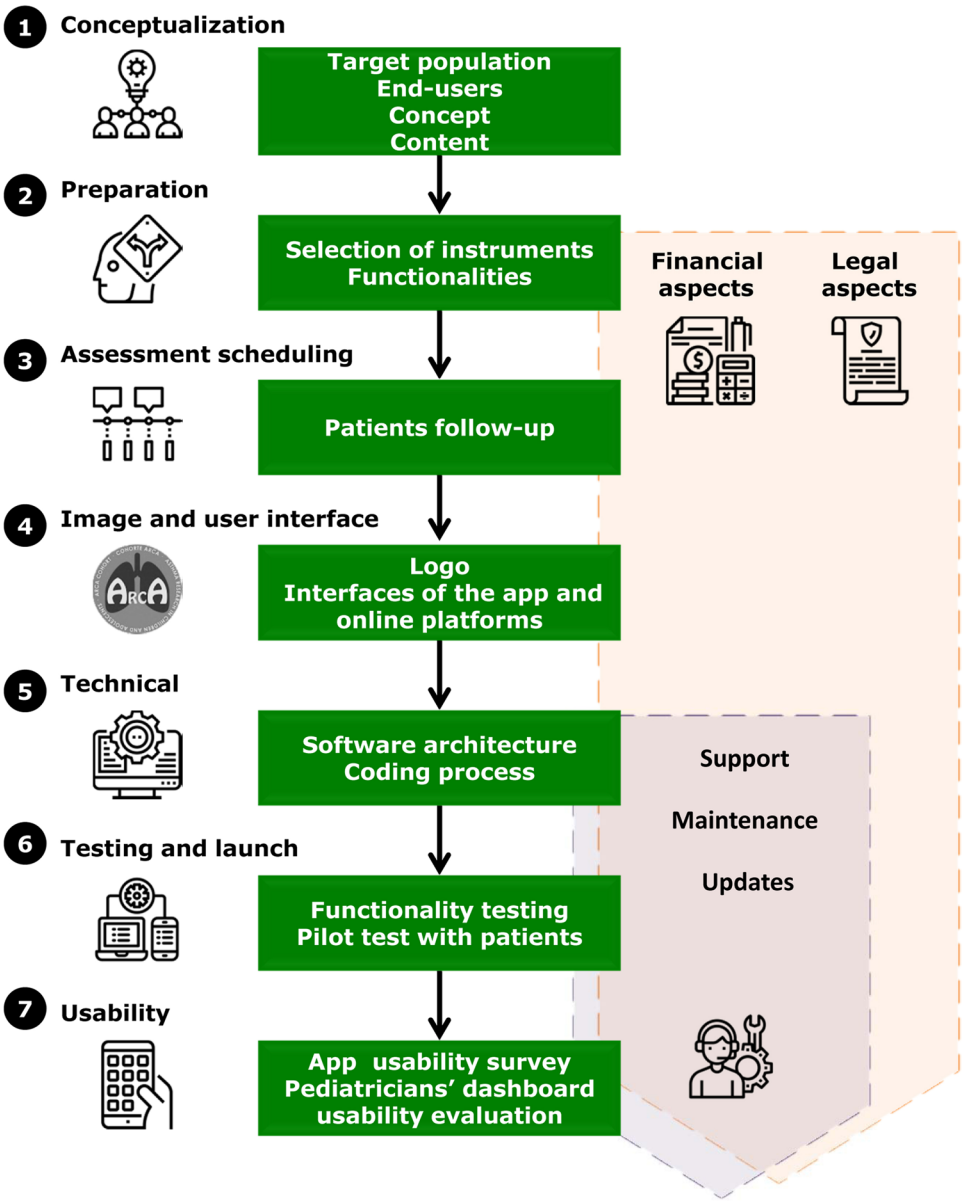

Fig. 1 e-Health tool development process

(Flow diagram in Online Resource Fig. 2). After reviewing the 1997 titles obtained, 109 articles were full-text reviewed also independently by two researchers, and 43 studies were finally identified for data extraction through consensus between reviewers: 32 primary studies, 3 clinical guidelines, and 8 systematic reviews. A total of 35 instruments (19 referencing development publication) were identified, measuring the following asthma-related constructs (Online Resource Table 1): adherence, triggers, illness perception, inhaler beliefs, symptom control, self-perceived health change, asthma exacerbations, generic and specific health-related quality of life (HRQoL), inhalation technique, severity, and illness knowledge and coping; a few other instruments focused on caregivers and health services. To evaluate instruments' characteristics, also 10 systemic reviews focused on PROs in children and adolescents were considered (Online Resource Table 2).

2. Preparation phase

In this phase, the instruments and functionalities of the ARCA e-Health tool were selected in accordance with the budget and legality.

Content aspects

The research team reviewed the identified constructs and the evidence on available instruments to measure them, in order to select the most appropriate ones and make informed decisions about their administration mode (application or telephone interview). Selection was based on metric properties, burden of administration, and availability of adequate versions for the application.

Table 1 shows the constructs and the 23 instruments that measure them (19 from the literature review and 4 from the previous project), with the development publication and references found in the literature review [4, 32–95], their characteristics and administration mode in the ARCA study. Only one or two instruments were found per construct, except for symptoms control and HRQoL. For example, of the two instruments measuring adherence, the reference on the development of the Inhaler Adherence Scale was only a congress abstract. The instruments not selected for the study are marked with a dash. The instruments chosen for measuring adherence [32, 33], triggers [36, 37], illness perceptions [38–40], and inhaler beliefs [33, 41, 42] were allocated to the telephone interviews, due to their high number of items. The selection of the Asthma Control Questionnaire (**ACQ**) [43, 44] was based on its extended use (it was included in 6 studies of the review [43, 44, 46–49]) and on a systematic review [45] which supports its use to distinguish between patients who are well controlled and those who are not. The ACQ age and administration versions fitted perfectly with the inclusion criteria of the ARCA study, where it is administered by telephone interview to all participants, as some age groups require trained interviewer administration. The Asthma Control Test (ACT) [50] was included in more articles of the review (13 studies [48, 49, 51–61]), but it was designed for patients older than 12 years.

For measuring HRQoL, the **EQ-5D** and the Patient-Reported Outcomes Measurement Information System (PROMIS) Pediatric Asthma Impact Scale were chosen for being the shortest generic and asthma-specific instruments and for their metric properties. The **PROMIS** Pediatric Asthma Impact Scale demonstrated a higher precision [78] than other asthma-specific instruments [79, 80], while using only 8 items due to its Item Response Theory-based development. The EQ-5D [76] was considered valid and reliable for its use in patients with asthma [77] and pediatric population [75], and practical to implement in routine monitoring [96, 97]. Moreover, the EQ-5D was the only generic instrument found in the primary studies of the literature search. Finally, even though there were several instruments measuring severity, illness knowledge, and coping, none was selected due to the low prioritization of these constructs for this initial project stage.

We decided to develop an application combining 3 age versions (6–7, 8–11, and 12–16 years) following the EQ-5D age cutoff points. The first one was designed for being answered by parents or guardians (proxy response) and the other two for self-response by the children or adolescents.

Functionality aspects

For our conceptual model, we identified the need for creating two online platforms (one for pediatricians and another one for the project manager) linked to the patients' application.

The pediatricians' online platform was designed to register the patient as an application user during recruitment and to display in real-time their patients' application responses. The project manager's platform was designed to allow the modification of contents, since we aimed to develop a mobile application that was editable independently from the technical company. To achieve this, the following specific requirements were established for the project manager's platform: managing the pediatricians' online dashboard, creating profiles with different access permissions, managing the mobile application's questionnaires and their scheduling, editing instructions and contents of the app, showing the patients' information, and exporting databases.

The application sends notifications to the users on a monthly basis. To avoid the sensation of burden while obtaining sufficient information, questionnaires were administered to each participant every 30 days. Also, to facilitate engagement, we incorporated the possibility of postponing the responses (during 1, 4, or 24 h) with flexible reminders when receiving notifications, giving patients more leeway to choose when they prefer to answer.

Financial aspects

The costs included the design and technical development of the application and platforms, including database characteristics (structure, variables, labels, and exportation), mobile operative system (Apple iOS and Google Android), device compatibility, and age versions. It was also necessary to consider the cost of licenses for questionnaires, publication in the Apple and Google application stores, storage of the database in secure computer servers fulfilling legal requirements, and an annual cost for the application's technical maintenance and updates.

Legal aspects

A statement on 'privacy policy' is compulsory, establishing how the patients' information will be used and the intellectual property of the application. Licenses were requested for the questionnaires included in the application to protect the intellectual property of their developers. To obtain

Table 1 Instruments identified to measure each construct and related references

Construct	Name (Acronym)	Age versions	e- version	Nº items	Author, year of publication References	Administration
Adherence	Medication Intake Survey-Asthma (MIS-A)	Proxy-administered (6–11 y) Self-administered (≥ 12 y)	No	15	Dima AL et al. 2017 [32] Ref. [33]	Telephone interview
	Inhaler adherence scale		–	– –	Abramson, M. 2014 [34] (Abstract published in congress) Ref. [35]	–
Triggers	Asthma Trigger Inventory	Self-administered (7–17 y)	No	32	Wood BL et al. 2007 [36] Ref. [37]	Telephone interview
Illness perception	Illness Perception Questionnaire (IPQ)	Self-administered (> 8 y)	No	34	Moss-Morris, R et al. 2002 [38] Ref. [39]: [40]	Telephonic interview
Inhaler beliefs	Beliefs About Medicines Questionnaire (BMQ)	Proxy-administered (6–11 y) Self-administered (≥ 12 y)	Web version	14	Horne, R et al. 1999 [41] Ref. [33, 42]	Telephone interview
Symptoms control	Asthma Control Questionnaire (ACQ) – Symptoms only	Interviewer-administered (6–10 y) Self-administered (11–17 y)	Web version	5	Juniper EF et al. 2010 [43] Ref. [44–49]:	Telephone interview
	Asthma Control Test (ACT)	Self-administered (> 12 y)	Web version	5	Nathan, R et al. 2004 [50] Ref. [48, 49, 51–61]	–
	Childhood Asthma Control Test (C-ACT)	Self-administered—child and caregiver (4–11 y)	No	7	Liu, A et al. 2007 [62] Ref. [42, 47, 48, 55, 60, 61, 63–67]	–
	Test for Respiratory and Asthma Control in Kids (TRACK)	Proxy-administered (< 5 y)	No	5	Murphy, K et al. 2009 [68] Ref. [47, 69]:	–
	Severity of Chronic Asthma scale (SCA)	Proxy-administered (> 8 y)	No	3	Horner, S et al. 2006 [70] Ref. [71]	–
Self-perceived health change	Global Rating of Change		–	– 2	Guyatt G et al. 2002 [72] Ref. [73]	ARCA application
Asthma exacerbations	Asthma Worsening Question	Proxy-administered (6–7 y) Self-administered (≥ 8 y)		– 1	Ad-hoc for the project using the definitions of the American Thoracic Society/ European Respiratory Society [74]	ARCA application
Health-related quality of life (HRQoL), generic instrument	EQ-5D-Y	Proxy-administered (6–7 y)	PDAs/ Smartphones and web version	5 and VAS	Rajmil L et al. 2012 [75] Ref. [42, 76, 77]	ARCA application
	EQ-5D-Y	Self-administered (8–18 y)				
	EQ-5D-5L	Self-administered (≥ 12 y)				

Table 1 (continued)

Construct	Name (Acronym)	Age versions	e- version	Nº items	Author, year of publication References	Administration
HRQoL, Asthma-specific instrument	PROMIS* Pediatric Asthma Impact Scale (PAIS)	Proxy-administered (5–17 y) Self-administered (8–17 y)	PDAs/ Smartphones and web version	8	Yeatts KB et al. 2010 [78] Ref. [35, 79, 80]	ARCA application
	Pediatric Asthma Quality of Life Questionnaire (PAQLQ)	Interviewer-administered (7–10 y) Self-administered (11–17 y)	No	23	Juniper EF et al. 1996 [81] Ref. [35, 46, 66, 67, 82–84]	–
	Mini Asthma Quality of Life Questionnaire (Mini AQLQ)	Self-administered (17–70 y)	Web version	15	Juniper EF et al. 1999 [85] Ref. [42]	–
Inhaler technique	Inhaler Technique Quality Scale	Proxy-administered (6–11 y) Self-administered (≥ 12 y)		– 5	Van Ganse E et al. 2015 [4] Ref. [86, 87]	ARCA application
Illness severity	Asthma Treatment Assessment Questionnaire (ATAQ)	Proxy-administered (5–17 y)	No	20	Skinner, E et al. 2004 [88] Ref. [47]	–
	Childhood asthma severity (CHAS)		–	– 14	Ortega, A et al. 2001 [89] Ref. [90]	–
Illness knowledge and copping	Asthma Knowledge Questionnaire (AKQ14)	Parents completed	No	17	Rodríguez C et al. 2005 [91] Ref. [83, 92]:	–
	Coping Scale for Children and youth (CSCY)	Self-administered (10–15 y)	No	29	Brodzinsky, D et al. 1992 [93] Ref. [83]:	–
	The Utrecht Coping List for Adolescents (UCL-A) Questionnaire	Self-administered (7–18 y)	No	47	Verkleij, M et al. 2016 [66]	–
	Asthma Responsibility Questionnaire (ARQ)	Proxy-administered Self-administered	No	10	McQuaid, E et al. 2001 [74] Ref. [33, 94, 95]:	–

*PROMIS: *Patient-Reported Outcomes Measurement Information System*

VAS: Visual Analogue Scale

the license from the EuroQol group, multiple screenshots and very specific conditions were required (font size, bold or underlined words, and colors) before obtaining the final approval.

Since the data collected in the ARCA application include personal information, it was important to specify who will have access authorization. Likewise, the applicable digital data protection regulation must be specified, as well as server security procedures (such as firewalls, access control, and cryptographic mechanisms) in order to prevent unauthorized access to data.

Table 2 Terms and conditions: most relevant contents

Concept	Information included
General description	• Description of the application's purpose, who the application is intended for, and how participants can access it • Institutional liability and reminder of the informed consent signed to participate in the study
Information collected	• Type of information that is not collected (none that could identify the user, such as name, email, date of birth, postal code…) • Type of technical information of the device that is collected in order to solve possible technical difficulties
System Requirements	• Minimum specifications for mobile device compatibility • Operating systems required by the software for running the application
License transfers and intellectual property rights	• Ownership of intellectual property and related content • Conditions under which the use of the application is granted: the license is non-exclusive, free, limited and revocable, for non-commercial use • The user is not granted any right to use trademarks, logos, etc
Limitation of Liability	• Stipulation of responsibilities, the Owner and any of its employees or positions shall be not reliable for any direct and indirect damage or loss arising through the use or access of the application
User Responsibility	• The User's responsibility of fair use of the application according to the law, morality, public order • The conditions of use of the application
End of application use period, duration and termination	• End of application use corresponds to the duration of the study • The Owner of the application has the right to suspend, terminate or interrupt unilaterally at any time and without prior notice the service provided by the application
Applicable courts and jurisdiction	• Establishment of the applicable courts and jurisdiction in case of dispute or conflict between the User and the Owner of the ARCA application

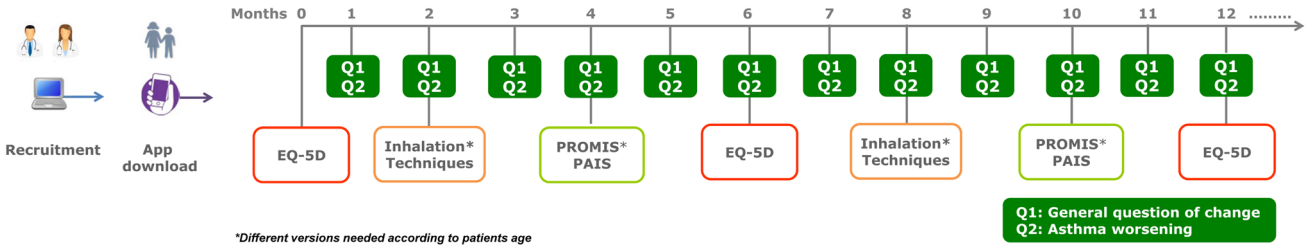

Fig. 2 Timeline of the ARCA application for the first year of follow-up

The 'terms and conditions' section is an agreement between application users and the application owner. Table 2 shows the main aspects of this section, which used a clear and easy language, without technical expressions. It provides a detailed description of what is considered appropriate and inappropriate use of the application, clarifying what patients can expect.

3. Assessment scheduling phase

The timeline for the first year of follow-up is shown in Fig. 2. It included a monthly administration of the two questions considered most suitable for frequent monitoring of patients, with a recall period of one month: global rating of change and experience of asthma worsening.

Further questionnaires were only administered in alternate months: the EQ-5D at baseline and month 6, inhalation techniques scale at months 2 and 8, and PROMIS Pediatric Asthma Impact Scale at months 4 and 10. Thus, we obtained repeated measurements administrating each questionnaire every 6 months.

Two rules were stipulated for patients who did not answer upon receiving the application notification: (1) monthly questions were available during the whole month, and (2) 6-month cycle questionnaires remained available to answer during the following five months, being administered after the scheduled content.

4. Image and user interface development phase

The purpose of this phase was to generate the application's general image and user interface following good practice guidelines for m-Health applications [98–100]. To be easily distinguishable and to avoid similarities with other applications, we performed a search in the Apple and Google stores. A logo with a simplified lung and the study acronym (ARCA) was selected after showing several mockups to children. The technical team initially provided a prototype of the login screen and user interface, which required some revisions until agreeing on which represented the application concept and target population: the background image with children playing outdoors, to help them identify and to convey a positive and playful message.

The dashboard for pediatricians was planned jointly with them, through face-to-face and remote meetings, and reviewed in several rounds until the final version was approved. This dashboard presented especially relevant design aspects to show patients' responses clearly and easily, in order to facilitate interpretation and to contribute to enhancing the quality and experience of care. Functionality was prioritized over design in the project manager dashboard.

5. Technical phase

The technical team developed the application architecture using Appcelerator Titanium for iOS and Android. The backend of the application was developed using node.js, and the architecture was designed using containers (Docker sets), which allowed keeping the different elements of the platform isolated, to facilitate its maintenance and possible updates. This application architecture allows editing the contents and their schedule when needed. The pediatricians' dashboard/interface was developed using React.js.

6. Testing and launch phase

Firstly, pediatricians ($n = 14$) of the Respiratory Tract Group of the Spanish Association of Primary Care Pediatricians (AEPAP), from seven Spanish autonomous communities, tested the dashboard to check the fields of the recruitment form and how their patients' responses were displayed. The project manager tested all the online platform functionalities specified for managing the study and the databases.

Secondly, to test the ARCA application's timeline, it was necessary to reduce the cycle from 1 month to 1 day, which allowed testing an entire year period in 12 days. The team checked on different mobile devices (operative systems, brands, and sizes) the proper display of the questionnaires, notifications, reminders and postponing options.

Once all these functionalities were confirmed, we performed a pilot test of the e-Health tool by semi-structured phone interviews of the first fifty participants included in the ARCA study. Patients were consecutively recruited from 8 primary care pediatricians if they fulfilled the ARCA inclusion criteria and accepted to participate. The purpose of the pilot test was to find out if participants received the Short Message Service (SMS) notifications and downloaded the application without problems and to know their impressions about the application, their understanding of the content, and the reasons for not downloading the application in the cases when this happened. Of the 53 participants (three of them parents), 34 had downloaded the application and qualified it as easy and fun to complete, but four deleted it after responding the EQ-5D, thinking that they only had to use the application once. The other 19 participants gave the following reasons for not downloading the application: technical issues (space, old devices), forgetfulness, or being afraid of application-related fees. To solve these issues detected, pediatricians were trained to emphasize that the application required monthly answers and was free of charge.

7. Usability survey phase

After solving the problems detected in the previous phase, we launched version 1.1 of the ARCA application and conducted a usability survey [101]. Once the ARCA cohort reached one hundred participants, the System Usability Scale (SUS) was administered by telephone interview. The SUS was designed to obtain subjective feedback on

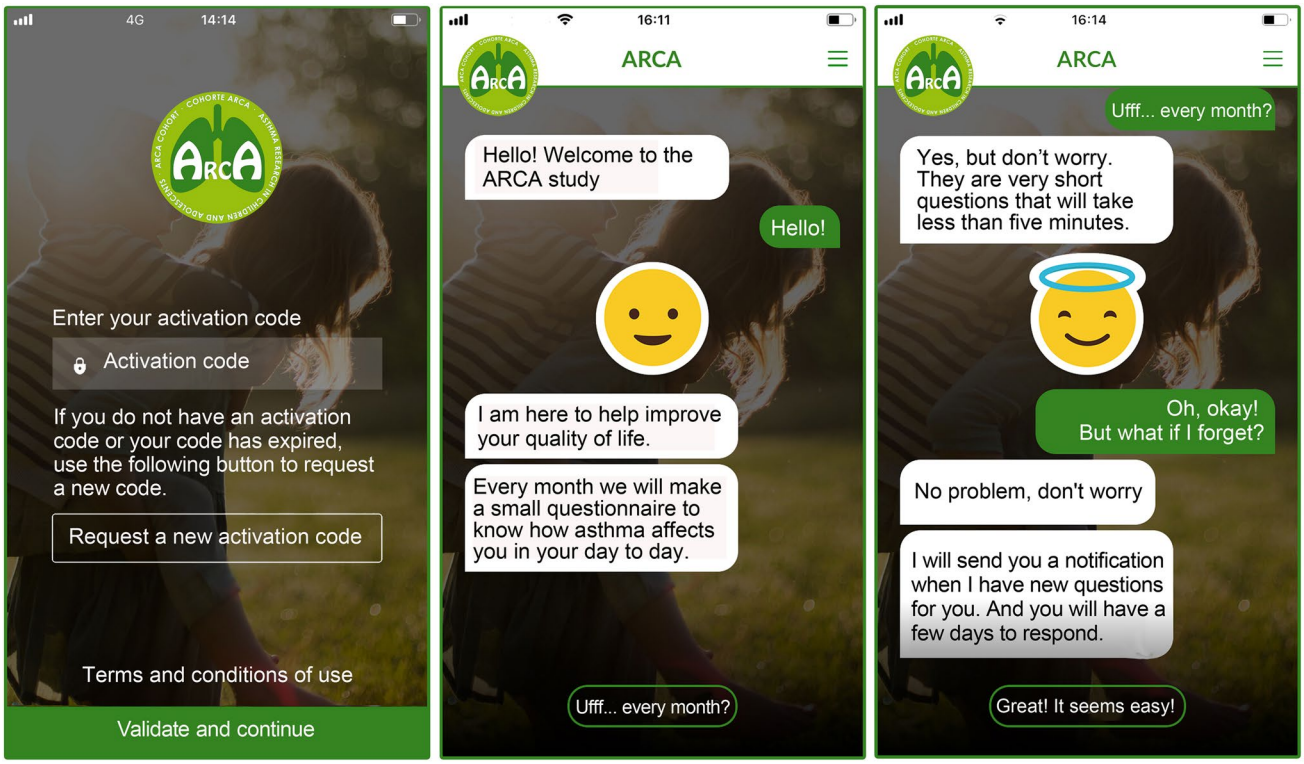

Fig. 3 Screenshot of the application's login and chat design of the ARCA application. Since the ARCA application was designed in Spanish, the text has been translated into English for these figures. The original ARCA application's screenshots are shown as supplementary material

perceived usability and user satisfaction [102, 103]. It is a reliable 10-item questionnaire with a 5-point Likert scale and global scores ranging from 0 (negative) to 100 (positive), considering the average score 68 [103]. The SUS questionnaire was modified to be more youth-friendly through age-appropriate language and customized for assessing a smartphone application. Usability differences among age groups were assessed using Kruskal–Wallis test.

The pediatricians' dashboard usability was assessed through several meetings, and their feedback was useful to detect mistakes and to improve the design and format of the patients' data visualization.

Results

Application downloading process

Recruitment of ARCA patients was carried out through the pediatricians' platform, after obtaining the informed consent, checking the inclusion and exclusion criteria, and requesting a mobile phone number. The participant received an automated SMS with an activation code and a direct link to the Apple and Google stores to download the application (Fig. 3).

Application use

The first contact with the application consists in an interactive chat, simulating a conversation by SMS or WhatsApp with someone in real time. The chat has predetermined answer options to choose from, to make interaction easier, and it celebrates certain answers with emoticons, GIFs, and animations. The first questionnaire that patients have to answer is the EQ-5D. Figure 4 shows the dimension of 'doing usual activities' and the 'health thermometer' of the EQ-5D-5L. The thermometer allows users to grade their health from 0 to 100 by sliding a green circle.

The users receive every month a notification from the application to answer the global rating of change and the asthma worsening questions (Fig. 5). The global rating of change [72] includes 15 answer options grouped according to the sense of the change: first, users select among improvement, stability, and worsening; then, they select the qualifier. The timeline of the questionnaires administered via application is shown in Fig. 2.

Application usability

Of the 104 participants contacted for the usability survey, the 85 patients who responded had a mean age of 11.3 years

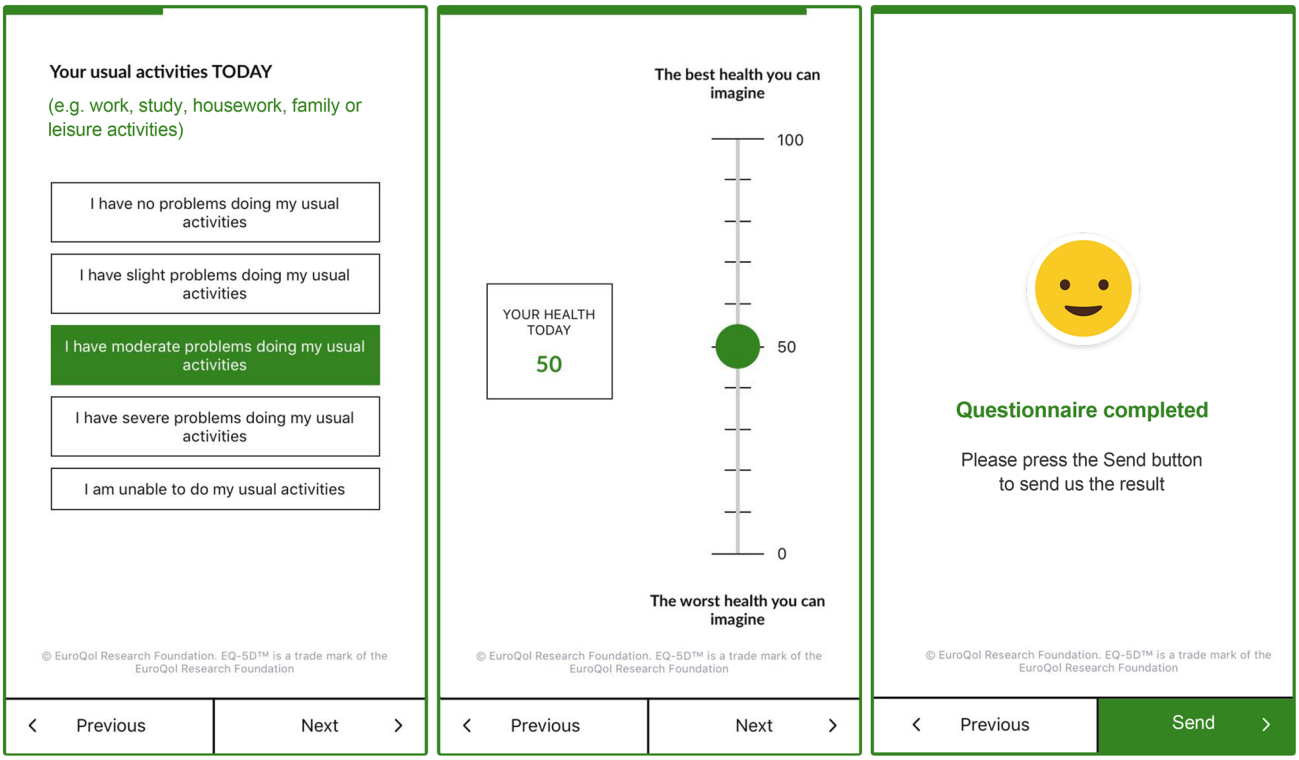

Fig. 4 Screenshots of the 'Doing usual activities' dimension and health thermometer of the EQ-5D-5L in the ARCA application. Since the ARCA application was designed in Spanish, the text has been translated into English for these figures. The original ARCA application's screenshots are shown as supplementary material

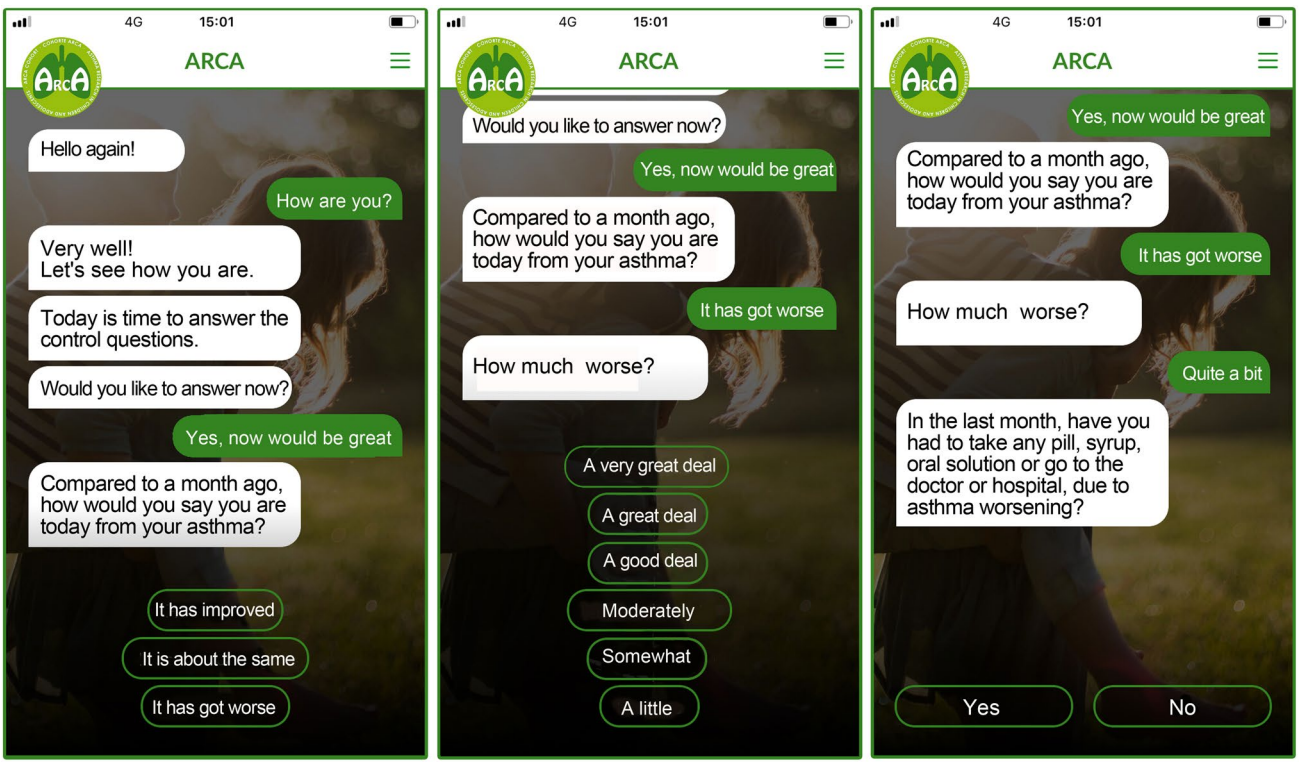

Fig. 5 Screenshot of the global rating of change and the asthma worsening question. Since the ARCA application was designed in Spanish, the text has been translated into English for these figures. The original ARCA application's screenshots are shown as supplementary material

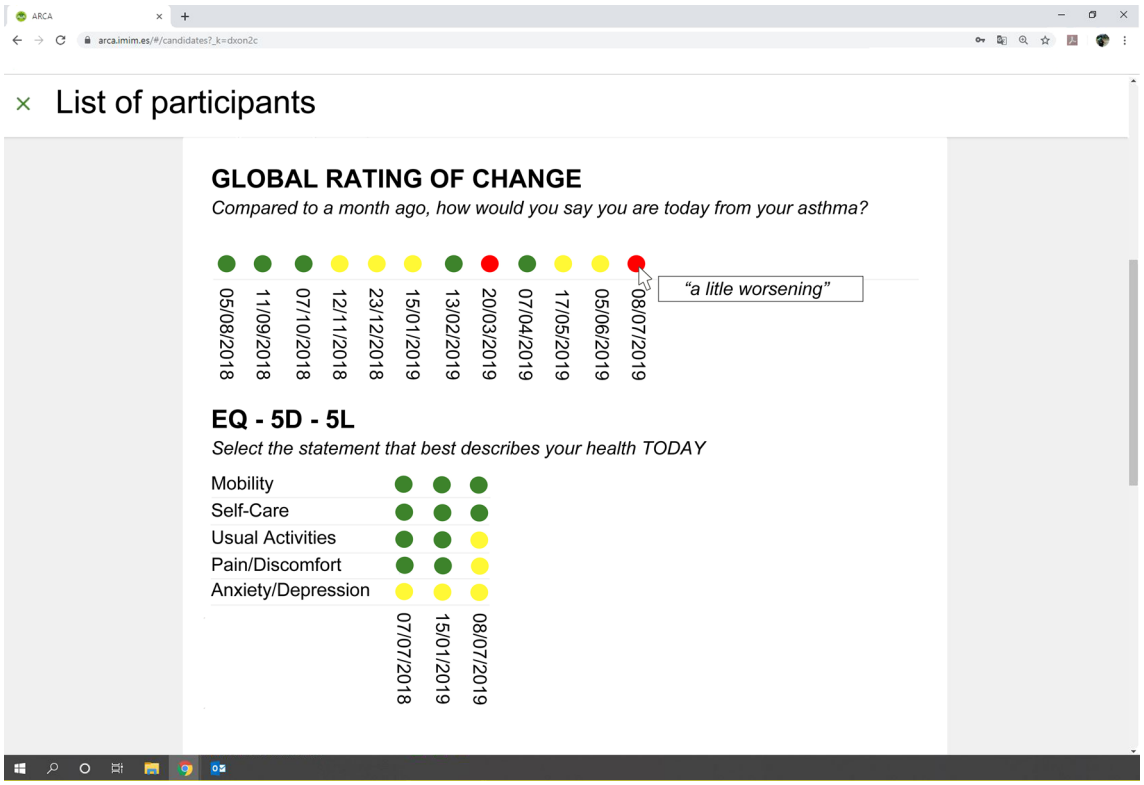

Fig. 6 Example of the visualization of a patient's results in the pediatricians' dashboard

(SD = 2.3) and 67% were males. The mean for overall SUS score was 92.9 (95% confidence interval 91.7–94.1). No differences were observed among users of different age versions ($p = 0.351$). The median of the overall SUS score was 95.0 in parents/guardians, 95.0 in children, and 93.8 in adolescents, all of them clearly higher than the recommended threshold of 68 [103].

Pediatricians' dashboard

The pediatricians accessed all the information from their patients, as collected through the application, on their dashboard (Fig. 6). Charts reflected the patient's answers over time using the traffic lights code: green for good outcomes, amber for intermediate, and red for poor. In the example in Fig. 6, the participant reported worsening at the global rating of change in July 2019, and the specific response option—'A little worsening'—was automatically displayed when hovering over the color-coded circle.

Discussion

Developing an m-Health application for the first time was a big step towards the advantages of new techniques, but a complex challenge due to the inevitable learning curve, even when having previous experience in online platforms development. Lack of knowledge of certain technical and legal issues was discouraging during the first phases, and it considerably lengthened the process. The ARCA application's development was more time consuming, and required more resources, than initially expected; however, it is a promising tool for patient monitoring.

The results obtained with the System Usability Scale indicated that the ARCA application presented an excellent usability for parents, children, and adolescents, since median scores were > 93 in the three age versions of the application. However, this good usability result is not sufficient to ensure long-term engagement reporting PROs, which will need to be evaluated. Functional problems were only detected when children first changed from the proxy to the self-response version due to their age range, which did not occur during the faster (daily cycle) project team pre-test. The pilot test provided relevant information about major application misunderstandings (thinking it only had to be answered once, or avoiding its download due to possible fees). Thus, the pilot test feedback was especially relevant to improve the implementation strategy by reorienting the information that the pediatricians provided about the application to achieve a better engagement. Similarly, several m-Health applications for patients

with asthma based their implementation strategy [24, 104] on the patient's own doctor inviting them to participate.

Since the ARCA application was specifically designed for patient monitoring, it presented major differences both in contents and in features when compared with other asthma m-Health applications for adolescents, which were focused on self-management. In addition to monitoring, these other applications included the following: action plans [23, 24, 27, 105], educational materials [23, 25], medication adherence [25, 27, 105], or communication and social support [26]. Two systematic reviews [20, 21] highlighted that future applications should better evaluate the contribution of each content and restrict features to those that attract and encourage patients to use the application. Although our application was not designed as an intervention program, we are aware that every action may have an effect. To evaluate the impact of the ARCA application, we applied the following two strategies: (1) randomization among application users so that 50% answer the inhalation technique quality scale, to assess if monitoring the inhalation technique improves its practice; and (2) to assess the effect of patient monitoring on pediatricians, by blinding patients' results to some of the pediatricians as a control group.

There are numerous m-Health applications monitoring PROs in daily clinical practice for patients with chronic conditions [106], such as asthma [19, 22]. A study evaluating the strengths and weaknesses of asthma applications based on the participants' preferences [27] concluded that adolescents gave greater relevance to interactive and informative features, since they seemed to increase both self-observation and self-judgment. The application features providing direct feedback, such as charting [23, 24], self-check [23], and reminders of doctors' appointments and medication intake [24], were considered especially relevant. These features providing direct feedback to patients were not included in the ARCA application because in our study the feedback is provided during the clinical visit by pediatricians, considering they were responsible of interpreting and discussing the follow-up information with patients and relatives. Physicians are the most suitable for assessing the importance of health changes in terms of treatment and management of the disease [107, 108]. Inclusion of some direct feedback for self-management in our application merits consideration for future developments.

Another major difference in the ARCA application is the frequency of interaction. Periodicity was considered a key aspect to achieve both short- and long-term engagement and fidelity. A monthly cycle for the long-term follow-up of the ARCA cohort was selected, as a balance between low response burden and enough frequency for monitoring a seasonal disease such as asthma. In contrast, most of the identified applications used daily notifications (reminders, questions…) [23–25]. Although it is important to highlight that this decision was made by the project team without the children's and adolescents' participation, notification periodicity was not identified as a barrier for engagement in the pilot test. An application with weekly cycles developed by Rudin et al. [109] programed the expiration of the questionnaires after 48 h, forcing prompt response. Flexibility was prioritized in the ARCA application, giving users the option to postpone answers, while recording the real date of the users' responses. Unfortunately, notifications and reminders could be ignored or disabled by the participants.

Evidence [110–112] supports that m-Health applications allow carrying out larger studies with faster results and better participant compliance. The immediate data transfer to pediatricians may allow better and timelier care decisions [27, 105, 113]. Besides, remote monitoring systems can increase the patients' and the caregivers' self-confidence, improving their attitude towards asthma [114]. However, smartphone data collection could also introduce new unintended and unknown barriers, such as the need for a smartphone with Internet or Wi-Fi access, or the possible loss of follow-up when patients change their phone number or device. Finally, the ongoing technical maintenance and updates required by applications threatens their sustainability.

Specifically, the ARCA application presented some advantages compared to others. First of all, a project manager online platform was developed in parallel for content editing. This feature would permit addressing future research questions by introducing the new measurements needed. Second, we chose to display the patients' application responses item by item in the pediatricians' dashboard, not the scores. Following available recommendations for displaying PRO data [115], we used colors (traffic lights code) and labels to reduce cognitive burden, propitiating easier interpretation and detection of change over time. Third, the communication with the user was designed simulating a WhatsApp chat, thought to be friendlier for children and adolescents; when a message is sent to the user, the phone will automatically display a push notification and a number appears on the application icon (badge). Fourth, the existence of three age versions within the same application (compatible with switching to the next one when needed) is also a specific advantage that allows following users from age 6 to 16 years, avoiding having to download different applications and the loss to follow-up when patients change age group. Finally, the ARCA application works without the need of mobile data: users can answer the questionnaires whenever suits them better, and when they are connected to Wi-Fi, this information is sent to the server. It is also worth mentioning that not only the application, but also the two related online platforms that make the functionalities of ARCA possible, followed a strict protocol of data protection.

Although the ARCA application has been well accepted by children and adolescents, it is necessary to comment some limitations. First, it would have been important to involve children and adolescents since the beginning, throughout the development process, as was the case with pediatricians. Decisions not being patient-led could affect the application's long-term engagement and monitoring, hindering its potential to enhance the quality and experience of care. However, the results of both the pilot test and the usability survey indicated a positive reception and short-term commitment. Second, the ARCA application was not linked with electronic medical records, which would clearly maximize efficiency by its integration into the providers' routine workflows, because it was beyond the scope of the project. Finally, although 66% of the Spanish population aged 10 to 15 had access to a mobile phone in 2019 [116], there is still a percentage of children and adolescents that belong to families without access to smartphones who could not be included in this study and therefore could not be monitored. To minimize this digital divide, other approaches could be adopted, such as making a web version of the application to collect information at home (80.9% of households in Spain have at least one computer or tablet [116]), at the doctor's office or at digital access centers in the community (e.g., libraries, schools [117]).

Conclusions

Technology has the capability of transforming the application of PROs and other patient-reported variables, especially in children and adolescents. This paper describes and shares our experience in developing the e-Health ARCA tool, which aimed to monitor children and adolescents with asthma. Monthly notifications are sent to the users to complete questionnaires, and responses are available for review on an online dashboard that gives real-time information to pediatricians. Describing all the development phases, from conceptualization to the usability assessment, may increase the knowledge on how to design applications for monitoring patients with different chronic conditions.

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Compliance with ethical standards

Conflict of interest All authors declare that they have no competing interests.

Ethical approval The study has the approval of the Parc de Salut Mar ethical committee of clinical research (nº 2015/62/12l), and it was conducted in accordance with the ethical standards of the institutional research committee and the 2000 revision of the Declaration of Helsinki. Informed consent was obtained from the parents or legally authorized representatives of participants, as well as from the children or adolescents.

Transparency The lead authors (KM and MF) affirm that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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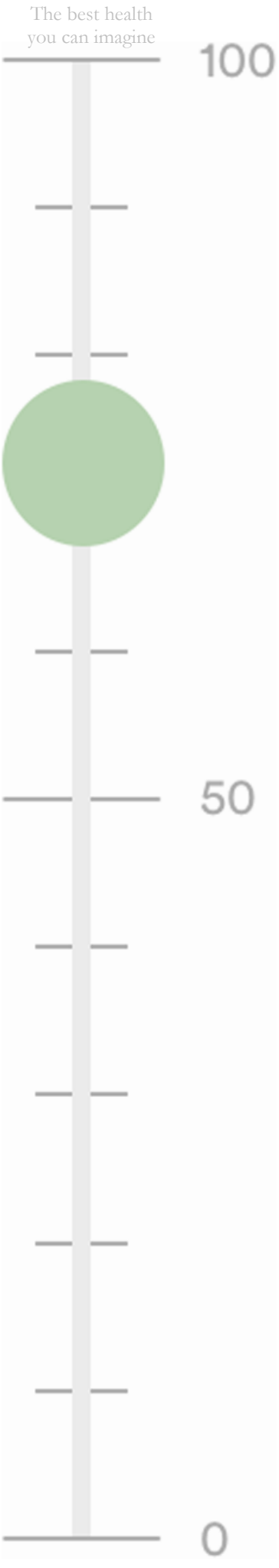

4.3. ARTICLE 3:

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Health and Quality of Life Outcomes

RESEARCH Open Access

Measurement properties of the EQ-5D-Y administered through a smartphone app in children with asthma: a longitudinal questionnaire study

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Abstract

Background: Asthma impacts children's physical, emotional, and psychosocial Health-Related Quality of Life (HRQL). The EQ-5D-Y is a generic econometric instrument developed to measure HRQL in children.

Objective: Evaluation of feasibility, validity, reliability, and responsiveness of EQ-5D-Y descriptive system and utility index to allow the assessment of HRQL in children with asthma, aged 8–11 years (self-response version) or under 8 years old (proxy-response version).

Methods: We used data from baseline to 10 months of follow-up of an observational, prospective study of children with persistent asthma recruited by pediatricians in Spain (2018–2020). HRQL instruments were administered through a smartphone application: ARCA app. The EQ-5D-Y is composed of a 5-dimension descriptive system, a utility index ranging from 1 to − 0.5392, and a general health visual analogue scale (EQ-VAS). The Pediatric Asthma Impact Scale (PROMIS-PAIS) includes 8 items, providing a raw score. Construct validity hypotheses were stated a priori, and evaluated following two approaches, multitrait–multimethod matrix and known groups' comparisons. Reliability and responsiveness subsamples were defined by stability or change in EQ-VAS and the Asthma Control Questionnaire (ACQ), to estimate the intraclass correlation coefficient (ICC) and the magnitude of change over time.

Results: The EQ-5D-Y was completed at baseline for 119 children (81 self-responded and 38 through proxy response), with a mean age of 9.1 (1.7) years. Mean (SD) of the EQ-5D-Y utility index was 0.93 (0.11), with ceiling and floor effects of 60.3% and 0%, respectively. Multitrait–multimethod matrix confirmed the associations previously hypothesized for the EQ-5D-Y utility index [moderate with PROMIS-PAIS (0.38) and weak with ACQ (0.28)], and for the EQ-5D-Y dimension "problems doing usual activities" [moderate with the ACQ item (0.35) and weak with the PROMIS-PAIS item (0.17)]. Statistically significant differences were found in the EQ-5D-Y between groups defined by asthma control, reliever inhalers use, and second-hand smoke exposure, with mostly moderate effect sizes (0.45–0.75). The

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ICC of the EQ-5D-Y utility index in the stable subsamples was high (0.81 and 0.79); and responsiveness subsamples presented a moderate to large magnitude of change (0.68 and 0.78), though without statistical significance.

Conclusions: These results support the use of the EQ-5D-Y as a feasible, valid, and reliable instrument for evaluating HRQL in children with persistent asthma. Further studies are needed on the responsiveness of the EQ-5D-Y in this population.

Keywords: Health-Related Quality of Life, Asthma, EQ-5D-Y, Validity, Reliability, Responsiveness, Smartphone app

Introduction

Asthma is a chronic condition that affects more than 300 million people worldwide [1], and it is the most common chronic disease during childhood, affecting around 14% of children globally [2]. Patient-reported outcome measures (PROMS), such as symptom control or Health-Related Quality of Life (HRQL), have been shown to be useful for clinical management, in combination with clinical measures, providing relevant information to understand the impact of the disease on patients' functional status and well-being [3–5]. Given its heterogeneous nature and symptoms burden, asthma has physical, emotional, and psychosocial impact on children's lives, as has been shown through diverse generic HRQL instruments [6–10]. The most affected dimensions of asthma-specific HRQL instruments are peer relationships, feeling of dependence on medication, shortness of breath, and activity limitations [11–13]. There is consistent evidence that HRQL and asthma control are independent predictors of future exacerbation [14–17]. Furthermore, a systematic review [18] found that asthma severity was significantly related to the child's HRQL in most of the studies. International guidelines [19–22] have emphasized that treatment goals should focus on improving the day-to-day symptoms of the patient, preventing exacerbations, and improving patients' HRQL.

HRQL instruments are generic or specific according to their target population, and they can in turn be classified as psychometric profiles or econometric indexes according to their measurement model [23]. Psychometric instruments generate scores on different dimensions in order to describe them (profiles). Econometric measures provide a single global score (index) which incorporates societal preferences for health states (utilities) that can be used to calculate quality-adjusted life years for use in economic evaluations [24]. The EQ-5D has probably been the most widely used econometric instrument in adults, and the EuroQol Group developed in 2010 the EQ-5D-Y to enable young individuals from 8 years onwards to self-report their health [25–28]. An EQ-5D-Y proxy version was also developed [29] for children under 8 years old.

There are few other econometric questionnaires for children, such as the Health Utility Index (HUI) and the Child Health Utility 9D (CHU-9D). The HUI [30] has a self-administered version and a proxy version (children 5–12 years old), but its administration burden is substantially greater than for the EQ-5D-Y. The interviewer-administered EQ-5D-Y showed high feasibility and agreement with the CHU-9D among 6–7 years old children [31], and several studies supported the acceptability [32], feasibility [32, 33], reliability [33], validity [33, 34], and responsiveness [35] of the EQ-5D-Y self-administered version in children and adolescents from the general population aged 8–18 years. Furthermore, the psychometric properties of the EQ-5D-Y have already been tested in several pathologies, such as chronic kidney disease [36], cystic fibrosis [37], juvenile idiopathic arthritis [38], type 1 diabetes mellitus [39], idiopathic scoliosis [40], and chronic or acute conditions [41]. As far as we know, there is only one study centered on the psychometric properties of the EQ-5D-Y in patients with asthma [42], supporting its feasibility and its convergent validity with the Pediatric Asthma Quality of Life Questionnaire. Other studies in heterogeneous samples that included children and adolescents with asthma [43, 44] also supported the EQ-5D-Y's feasibility, reliability, and construct validity.

There is extensive evidence on the reliability [45], construct validity [45, 46] and responsiveness [47] of EQ-5D in adults, both for the descriptive system and the utility index. However, all previous studies on EQ-5D-Y in children evaluated only the dimensions of the descriptive system, or an equally weighted summary score. None of them evaluated the EQ-5D-Y utility index, because the value set for children has just been published [48]: first for the Slovenian [49] and then for the Spanish [50] population.

To the best of our knowledge, this is the first study evaluating the psychometric properties of the EQ-5D-Y utility index, and also the first one assessing the psychometric properties of the EQ-5D-Y proxy version for children with asthma < 8 years of age. We have found only two studies supporting the reliability and construct validity of the EQ-5D-Y proxy version, both performed in the general population [29, 51].

Our aim was to evaluate the feasibility, validity, reliability, and responsiveness of the EQ-5D-Y descriptive system and utility index to allow the assessment of

Health-Related Quality of Life in children with asthma aged 8–11 years old (self-response version) or under 8 years old (proxy-response version).

Methods

Participants and study design

The Asthma Research in Children and Adolescents (ARCA) is a longitudinal prospective multicenter observational study (NCT04480242), designed to provide evidence about the evolution of young patients with persistent asthma through a regular follow-up.

Patients were recruited in 3 outpatient pediatric pulmonology hospital units and 8 primary care pediatric centers in Spain, from January 2018 to July 2020. Families were informed about the project and asked to participate if their children fulfilled the following inclusion criteria: aged 6–14, with clinical diagnosis of asthma, undergoing treatment with inhaled corticosteroids (alone or combined with long-acting beta-agonists) for more than 6 months in the previous year, and with access to a smartphone (their own, or their parents'). Exclusion criteria were: chronic obstructive pulmonary disease, cystic fibrosis, pulmonary fibrosis, bronchiectasis, active tuberculosis, or/and immunodeficiency associated with alpha 1 antitrypsin deficiency, ciliary diseases.

Study variables

The ARCA study collects information through different sources: medical records, computer-assisted telephone interviews performed by trained interviewers, and the ARCA smartphone application [52]. The EQ-5D-Y and the Patient-Reported Outcomes Measurement Information System-Pediatric Asthma Impact Scale (PROMIS-PAIS) were administered through the ARCA app, while all the variables to define known groups for validity assessment were collected through telephone interviews, and clinical characteristics came from medical records.

The ARCA app development has been described elsewhere [52]. Briefly, HRQL questionnaires are administered every 6 months: the EQ-5D-Y at baseline and month 6 of follow-up, and the PROMIS-PAIS at months 4 and 10. The ARCA app is available in 3 age versions (6–7, 8–11, and ≥ 12 years old) following the EQ-5D age cut-off points. The version for the younger age group was designed to be answered by parents or guardians (proxy response), and the other two versions for children's and adolescents' self-response. For the evaluation of the EQ-5D-Y, 12–14 years old adolescents were excluded because the EQ-5D-5L is administered in this age version.

The EQ-5D-Y was developed to measure HRQL in children [25]. It includes a descriptive system [26] of 5 dimensions and a visual analogue scale (EQ-VAS) of general health. The dimensions measure "mobility", "looking after myself", "doing usual activities", "having pain or discomfort" and "feeling worried, sad or unhappy" with 3-level Likert response scales (no problems, moderate problems, and serious problems). The EQ-VAS ranges from 0, worst health possible, to 100, best health possible. The time frame for both the dimensions and the EQ-VAS is "today". The EQ-5D-Y proxy version 1, which asked proxies to rate the child's HRQL in their own opinion, has the same characteristics as the self-reported version. Evidence on the Spanish EQ-5D-Y's validity, feasibility, and reliability has been reported [33].

From the three digital versions of the EQ-5D-Y, laptop/desktop, tablets, and PDA/smartphone, we administered the latter through a smartphone app [52] with its original generic content, without including any expression for asthma-specific attribution. The preference value set to generate the EQ-5D-Y utility index for Spain [48] was obtained from adults thinking as a hypothetical 10-year-old child, as recommended in the international protocol. A single preference-based index was calculated ranging from 1 (the best health state) to negative values (health states valued by society as worse than death), where 0 is equal to death.

The Patient-Reported Outcomes Measurement Information System (PROMIS) developed a disease-specific item bank to measure the HRQL of children with asthma [53]: the Pediatric Asthma Impact Scale (PROMIS-PAIS). The short form 8a version of the PROMIS-PAIS (v2.0) contains the item set that provides the maximum test information with the least items [52]. It has demonstrated a higher precision [53] than other asthma-specific instruments [54, 55], while presenting a lower administration burden. Each item of the PROMIS-PAIS is attributed to asthma with the expression "because of my asthma", except for the last one which states "My asthma bothered me". The items [56] ask about the past seven days in a 5-level Likert response scale (1–5) with the options: never, almost never, sometimes, often, and almost always. It is available for self-response in ages 8–17, and for proxy response in children starting at age 5. The total raw score is calculated by adding the values of the response to each question, the lowest possible score is 8 and the highest is 40. Missing items were imputed by a simple allocation method from the mean of those items that were available in each dimension of the questionnaire [57].

The information collected through telephone interviews included, among other, the Asthma Control Questionnaire (ACQ), exacerbations occurring in the previous 6 months, treatments for asthma, and secondhand smoke exposure. Two versions of telephone interviews were developed, one designed to be answered by parents or

guardians of children under 8 years old (proxy response) and the other for self-response (participants aged 8 and older).

The Asthma Control Questionnaire ACQ-symptoms only [58] assesses the frequency of 5 asthma symptoms (night-time waking, symptoms on waking, activity limitation, shortness of breath, and wheeze) during the previous week on a 7-level Likert scale from 0 (no impairment) to 6 (maximum impairment). The overall score, calculated as the mean of item responses, ranges from 0 to 6. Cut-off points of 1.5 and 0.75 are established to define not well- and well-controlled asthma, respectively [59]. Results generated by this short version have shown to be very similar to those of the complete ACQ, as were its measurement properties (reliability, responsiveness, internal consistency, construct validity, and interpretability) [58]. The ACQ has been validated [60] using self-administration in children 11 years and older and interviewer-administration in 6- to 10-year-olds.

Asthmatic exacerbations during the last 6 months were assessed through three questions constructed applying the definitions by the American Thoracic Society and the European Respiratory Society [61]: *Did you visit or phone your family doctor or outpatient emergency department because your asthma got worse? Did you call an ambulance or go to the hospital because of your asthma? Did you take steroids tablets or syrup (such as Prednisolone or Deltacortril) for at least 2 days because of your asthma?* If the participant answers "yes" to at least one of the three questions, an asthma exacerbation is confirmed.

To measure the frequency of Short-Acting Beta-Agonists (SABA) inhaler use during the previous 4 weeks, the following question was asked to patients with SABA therapy prescription: *How often have you usually taken your "reliever medication" (brand name) in the past 4 weeks?* (Every day; almost every day; once or twice every week; less than once a week; or I don't know).

Secondhand smoke exposure was measured through a single question taken from the High School Risk Factors Survey [62]: *How many people out of those who stay in your house regularly smoke indoors?* (No one smokes indoors; 1 person; 2; 3; 4; 5 people and more than 5 people).

Ethics considerations

The study was approved by the ethics committee of participant centers in accordance with national and international guidelines (code of ethics, Helsinki Declaration) as well as legislation on data confidentiality (Spanish Organic Law 3/2018 of December 5 on the Protection of Personal Data and the Guarantee of Digital Rights). The collection and transfer of data was carried out according to strict security and data encryption. Written informed consent was required from the parents or legally authorized representatives of all participants, and additionally oral consent was obtained from children.

Analytical strategy

Considering the ARCA sample of 119 patients, a statistical power of 80% (using a two-side test with a type I error of 5%) was calculated to detect moderate differences (0.5 SD) in the EQ-5D-Y utility index between two equally distributed known groups, or to detect moderate to large differences (0.65 SD) between two known groups unequally distributed into 85% and 15% of the sample [63].

Characteristics of the sample were described by calculating percentages, or means and standard deviations, according to the type of variable. To evaluate the feasibility of the EQ-5D-Y, we calculated the completion rate, the distribution of the response options, and the proportion of missing values. Distribution of the EQ-5D-Y utility index, EQ-VAS, and the PROMIS-PAIS raw score were examined by calculating the observed range, the floor and ceiling effects (proportion of participants with the worst and best possible score, respectively), and statistics of central tendency and dispersion.

Construct validity of the EQ-5D-Y was assessed by applying two different approaches: multitrait-multimethod matrix, and comparison of known groups. The multitrait-multimethod matrix between the EQ-5D-Y, the PROMIS-PAIS, and the ACQ was constructed with Spearman correlations due to the scores' distribution. Besides their scores, the dimension or item on activities was also included in the matrix, since it was covered by all three questionnaires. The strength of the correlations was defined [64] as weak (≤ 0.30), moderate (0.31–0.60), or strong (0.61–0.90).

The relationships between instruments can be categorized as convergent (different instruments measuring a similar concept) or discriminant (different instruments measuring different traits or constructs). For convergent validity, we hypothesized a moderate correlation between the PROMIS-PAIS raw score and the EQ-5D-Y utility index, since both instruments intend to measure HRQL though from different perspectives (generic and asthma-specific). Also, we expect moderate correlations between the EQ-5D-Y dimension "problems doing usual activities", and the ACQ item "how limited were you in your activities because of your asthma?". On the other hand, for divergent validity, we expected a weak correlation between the EQ-5D-Y utility index and the ACQ, since they differ on the construct being measured (HRQL and disease control). A weak correlation was also expected between the EQ-5D-Y dimension "problems doing usual activities" and the PROMIS-PAIS item "it was hard for

me to play sports or exercise because of my asthma", due to differences in the type of activities considered.

Known groups were defined according to the ACQ (well-controlled, intermediate, and not well-controlled asthma) [59], asthmatic exacerbation during the last 6 months (yes or no), frequency of SABA inhaler use during the previous 4 weeks (less than once vs once or more per week), and secondhand smoke exposure (exposed or not). The hypotheses raised a priori, based on available evidence, were that patients with worse control of asthma [65], asthmatic exacerbations [66], higher frequency of SABA use [65], and second-hand smoke exposure [67] present worse HRQL. In particular, we expected the EQ-5D-Y to present worse discriminant capacity than the disease-specific PROMIS-PAIS because of its generic nature. To assess differences among groups we used Chi-square test for proportions of participants with problems, and U-Mann Witney or Kruskall-Wallis nonparametric test for the HRQL scores. The magnitude of the differences between groups was assessed by the Cohen effect size (difference of mean/pooled SD) [68]. General guidelines define an effect size of 0.2 as small, 0.5 as moderate, and 0.8 as large [69].

To assess reliability and responsiveness, patients were divided into three subsamples defined according to stability, worsening or improvement between the two administrations of the EQ-VAS and the ACQ. On one hand, patients who changed in EQ-VAS ± 0.3 SD or less (small magnitude) were included in the stable subsample, and those with a change larger than 0.3 SD (moderate or large magnitude) in the negative and positive direction were considered for the worsening and improvement subsamples respectively. The cut-off point of 0.3 SD [69] was selected following the established interpretation of the magnitude of change. On the other hand, according to the ACQ, patients that remained in the same asthma control category were included in the stable subsample, while those which moved to a worse or better category were included in the worsening or improvement subsample.

Since our hypothesis was that a stable EQ-VAS or ACQ indicates health stability over time, test–retest reproducibility of the EQ-5D-Y and PROMIS-PAIS was assessed in the stable subsamples by measuring the agreement between the two administrations with the Intra-class Correlation Coefficient (ICC). Regarding responsiveness, our hypothesis was that the EQ-5D-Y is able to detect change over time, though with a lower sensitivity than the asthma-specific instrument PROMIS-PAIS. Responsiveness was evaluated in the worsening and improvement subsamples by testing differences between the two administrations in the EQ-5D-Y or PROMIS-PAIS with the Wilcoxon paired test. The magnitude of change was measured by the effect size coefficient (mean of change/SD of change) for the worsening and improvement subsamples analyzed together. IBM SPSS Statistics software, version 22, was used to analyze the data.

Results

Of the 189 participants recruited (see Fig. 1), 55 patients aged 12–14 years were excluded because they were administered the EQ-5D-5L, 15 did not download the ARCA app, and 119 in total were included in the study: 81 were 8–11 years old children who completed the self-response version, and 38 were 6–7 years old children whose parents or guardians completed the proxy response version of the EQ-5D-Y. Table 1 shows the characteristics of the sample at baseline. Around 60% of the participants were boys and had well-controlled asthma. Differences between age groups were only found for asthmatic exacerbation, which was more frequent among 6 to 7-year-olds.

Very few patients reported problems in the EQ-5D-Y dimensions (Table 2), especially for "mobility" (5.1%) and "looking after myself" (2.6%). The dimension showing the highest percentage of participants with problems was "doing usual activities" (28.8%) where there was 1 participant reporting "a lot of" problems. Very few missing values were observed in some EQ-5D-Y dimension ("mobility", "looking after myself", and "doing usual activities").

At month 4 after recruitment (when the PROMIS-PAIS was administered through the app), 44 participants were lost to follow-up, and 75 answered the PROMIS-PAIS. Table 3 shows the results of the participants who answered the PROMIS-PAIS (self-response n = 59; proxy response n = 16). Patients reported more frequently "my asthma bothered me" and "it was hard to play sports or exercise because of asthma". The PROMIS-PAIS was completed entirely by the responders, with no missing values for any of the items.

As shown in Table 4, the mean (SD) of the EQ-5D-Y utility index in the total sample was 0.93 (SD = 0.11). This high mean is explained by the accumulation of patients in 1, the highest score (best HRQL). This ceiling effect of 60.3% is caused by the high number of participants reporting "no problems" in all dimensions. Despite this accumulation in the highest score, the observed range (1–0.5095) indicates a high variance. The EQ-VAS mean (SD) was 84.3 (17.1) among the whole sample. There were three patients with a missing value in the EQ-5D-Y utility index, while the EQ-VAS was completed by all responders. The PROMIS-PAIS raw score mean (SD) was 11.9 (4.9), and its ceiling effect was 32%.

Table 5 presents the multitrait-multimethod matrix between EQ-5D-Y, PROMIS-PAIS, and ACQ. For the

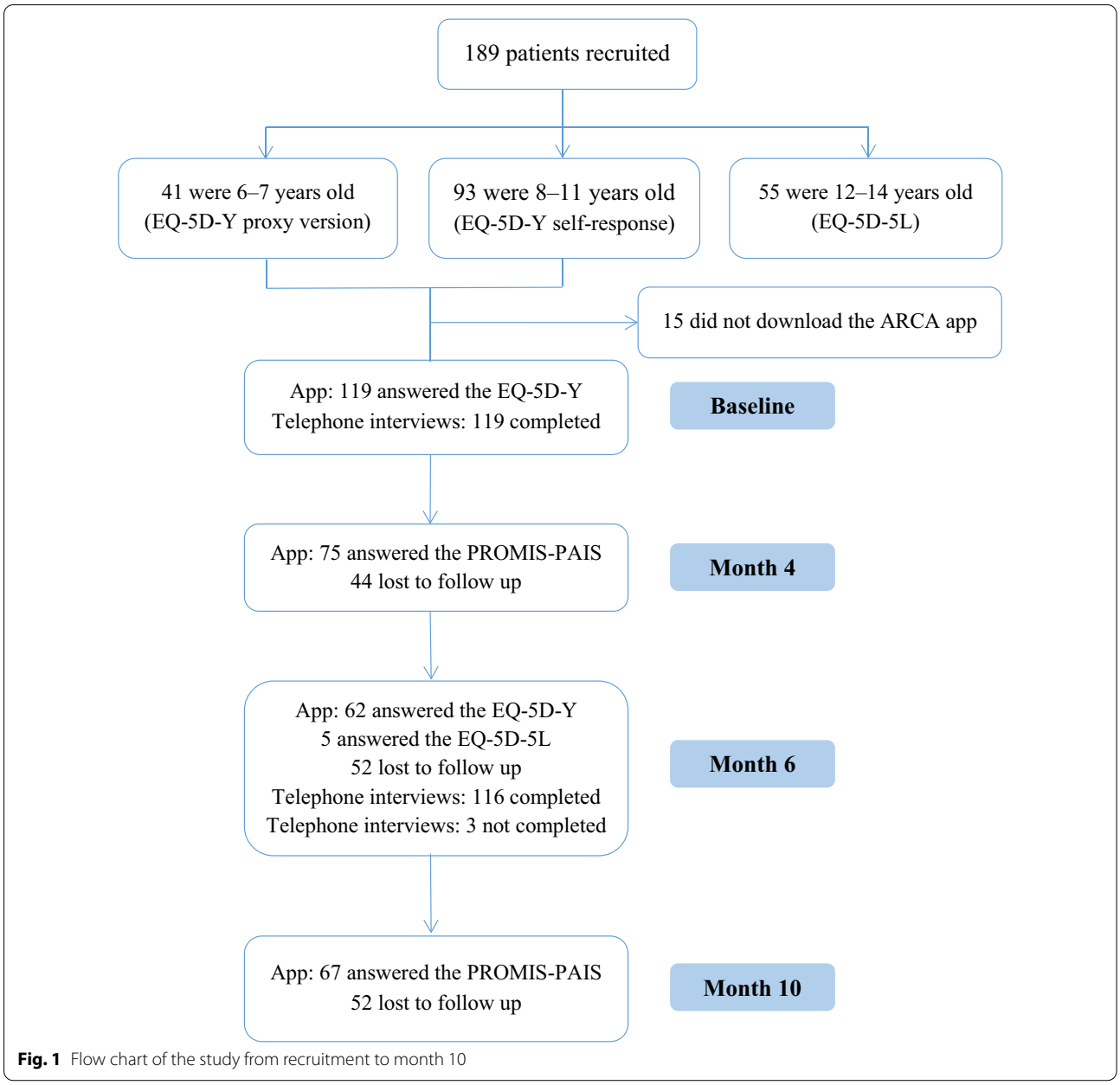

Fig. 1 Flow chart of the study from recruitment to month 10

two correlations previously hypothesized as moderate (convergent validity) we obtained a coefficient of 0.38 between the PROMIS-PAIS' raw score and the EQ-5D-Y utility index, and of 0.35 between the EQ-5D-Y dimension "problems doing usual activities" and the ACQ item "how limited were you in your activities because of your asthma?". Regarding discriminant validity, the two relationships hypothesized as weak obtained a correlation of 0.28 between the ACQ and the EQ-5D-Y utility index, and 0.17 between the EQ-5D-Y dimension "problems doing usual activities" and the PROMIS-PAIS item "it was hard for me to play sports or exercise because of my asthma". The correlation of the EQ-VAS with the other two asthma-specific instruments was lower than that obtained with the EQ-5D-Y utility index.

Table 6 shows statistically significant differences in some dimensions of the EQ-5D-Y, the utility index, and the EQ-VAS, among known groups defined by their asthma control with the ACQ, frequency of SABA use in the last 4 weeks, and second-hand smoke exposure. The effect size of almost all these differences in both the EQ-5D-Y utility index and the EQ-VAS was ≥ 0.5, indicating moderate magnitude. The largest magnitude of the

Table 1 Demographic and clinical characteristics of participants at baseline

	All (n = 119)	EQ-5D-Y Self response (n = 81)	EQ-5D-Y Proxy response (n = 38)	*P* value
Age, mean (SD)	9.1 (1.7)	10.1 (1.1)	7.0 (0.6)	< .001
6–7	38 (31.9%)	0 (0.0%)	38 (100.0%)	< .001
8–11	81 (68.1%)	81 (100.0%)	0 (0.0%)	
Sex				
Girls	48 (40.3%)	29 (35.8%)	19 (50.0%)	.14
Boys	71 (59.7%)	52 (64.2%)	19 (50.0%)	
Asthma control				.99
ACQ[a], mean (SD)	0.81 (0.93)	0.81 (0.88)	0.81 (1.06)	
Well controlled (< 0.75)	68 (58.6%)	43 (54.4%)	25 (67.6%)	.37
Intermediate (0.75–1.5)	23 (19.8%)	18 (22.8%)	5 (13.5%)	
Not well controlled (> 1.5)	25 (21.6%)	18 (22.8%)	7 (18.9%)	
Asthmatic exacerbations (last 6 months)				
Yes	53 (44.5%)	27 (33.3%)	26 (68.4%)	< .001
No	66 (55.5%)	54 (66.7%)	12 (31.6%)	
Number of prescribed SABA[b]				
0	9 (7.8%)	6 (7.6%)	3 (8.1%)	.72
1	103 (88.8%)	71 (89.9%)	32 (86.5%)	
2	4 (3.4%)	2 (2.5%)	2 (5.4%)	
Frequency of SABA inhaler use (previous 4 weeks)				
No use	9 (7.8%)	6 (7.6%)	3 (8.1%)	.99
Less than once per week	62 (53.4%)	43 (54.4%)	19 (51.4%)	
Once or twice per week	29 (25.0%)	19 (24.1%)	10 (27.0%)	
Almost every day/Every day	16 (13.8%)	11 (13.9%)	5 (13.5%)	
Secondhand smoke exposure				
Not exposed	81 (83.5%)	55 (84.6%)	26 (81.3%)	.92
Exposed	16 (16.5%)	10 (15.4%)	6 (18.7%)	
Missing	22	16	*6*	

[a] ACQ: Asthma Control Questionnaire

[b] SABA: Short-Acting β-Agonists

Table 2 Distribution of EQ-5D-Y dimensions in the entire sample at baseline

EQ-5D-Y dimensions	No problems n (%)	Some problems n (%)	A lot of problems n (%)	Missing values n (%)
Mobility	111 (94.9%)	6 (5.1%)	0 (0.0%)	2 (1.7%)
Looking after myself	114 (97.4%)	3 (2.6%)	0 (0.0%)	2 (1.7%)
Doing usual activities	84 (71.2%)	33 (28%)	1 (0.8%)	1 (0.8%)
Having pain or discomfort	98 (82.4%)	21 (17.6%)	0 (0.0%)	0 (0.0%)
Feeling worried, sad or unhappy	110 (92.4%)	9 (7.6%)	0 (0.0%)	0 (0.0%)

difference with the PROMIS-PAIS raw score was 1.11 among asthma control groups (p = 0.02).

Table 7 shows test–retest reproducibility results for the subsamples of stable patients and responsiveness results for the subsamples of patients with worsening and improvement, defined according to the changes on the EQ-VAS or the ACQ. Of the 62 participants who answered the EQ-5D-Y twice, after excluding three for missing values, 59 were finally distributed into the subsamples (24 stable, 17 worsened and 18 improved). Only 46 participants answered both the PROMIS-PAIS and the EQ-5D-Y twice. The subsamples defined according

Table 3 Distribution of the Pediatric Asthma Impact Scale (PROMIS-PAIS) items' responses at month 4 after recruitment

PROMIS-PAIS[a] items	Never n (%)	Almost never n (%)	Sometimes n (%)	Often n (%)	Almost always n (%)
I felt scared that I might have trouble breathing because of my asthma	60 (80.0%)	8 (10.7%)	6 (8.0%)	1 (1.3%)	0 (0.0%)
My chest felt tight because of my asthma	53 (70.7%)	13 (17.3%)	7 (9.3%)	1 (1.3%)	1 (1.3%)
I felt wheezy because of my asthma	52 (69.3%)	8 (10.7%)	14 (18.7%)	1 (1.3%)	0 (0.0%)
I had trouble breathing because of my asthma	52 (69.3%)	12 (16.0%)	9 (12.0%)	2 (2.7%)	0 (0.0%)
I had trouble sleeping at night because of my asthma	56 (74.7%)	9 (12.0%)	10 (13.3%)	0 (0.0%)	0 (0.0%)
It was hard for me to play sports or exercise because of my asthma	48 (64.0%)	12 (16.0%)	9 (12.0%)	5 (6.7%)	1 (1.3%)
It was hard to take a deep breath because of my asthma	52 (69.3%)	13 (17.3%)	8 (10.7%)	2 (2.7%)	0 (0.0%)
My asthma bothered me	46 (61.3%)	14 (18.7%)	13 (17.3%)	2 (2.7%)	0 (0.0%)

[a] PROMIS-PAIS: Patient-Reported Outcomes Measurement Information System-Pediatric Asthma Impact Scale

Table 4 Distribution of Health-Related Quality of Life (HRQL) scores

Distribution of scores	EQ-5D-Y Utility Index	EQ-VAS[a]	PROMIS-PAIS[b] Raw score
Sample	119	119	75
Theoretical Range	+1, −0.5392 Best–worst	100, 0 Best–worst	8, 40 Best–worst
Observed Range	+1, +0.5095	100, 25	8, 29
Floor effect	0.0%	0.0%	0.0%
Ceiling effect	60.3%	23.5%	32.0%
Mean (SD)	0.93 (0.11)	84.3 (17.1)	11.9 (4.9)
Missing	3 (2.5%)	0 (0.0%)	0 (0.0%)

[a] EQ-VAS: EuroQol-Visual Analogue Scale

[b] PROMIS-PAIS: Patient-Reported Outcomes Measurement Information System-Pediatric Asthma Impact Scale

to the ACQ were smaller, since we excluded nine patients whose telephone interview was more than 90 days apart from their app response. For the stable EQ-VAS subsample, the mean change was of 0.01 in the EQ-5D-Y utility index and -0.5 in the PROMIS-PAIS raw score with ICCs of 0.81 and 0.89 respectively, indicating high agreement between both evaluations (reproducibility). Regarding responsiveness, though change of means was not statistically significant, the effect size was of moderate and large magnitude for the EQ-5D-Y utility index and PROMIS-PAIS raw score (0.68 and 1.08 respectively) among patients in the worsening or improvement subsamples, analyzed together.

The agreement (reproducibility) in the stable subsample defined according to ACQ for the EQ-5D-Y utility index, EQ-VAS and the PROMIS-PAIS raw score measured with the ICC was 0.79, 0.70 and 0.68, respectively; and regarding responsiveness, the effect size of change was large (0.78, 1.15 and 1.28) among patients from the worsening or improvement subsamples, analyzed together.

Discussion

We found the EQ-5D-Y to be feasible and easy to administer via a smartphone application, but with a high ceiling effect (60.3% of participants reported no problem in any dimension). This generic preference-based instrument showed good validity, considering the moderate correlation between the EQ-5D-Y utility index and the PROMIS-PAIS raw score, and the discrimination among known groups based on the ACQ, frequency of Short-Acting Beta-Agonists (SABAs), and second-hand smoke exposure. Test–retest reproducibility among the stable subsamples indicated high reliability; and the magnitude of change observed between the first and second evaluation in the worsening or improvement subsamples may suggest its responsiveness, but the differences were not statistically significant.

Feasibility of the EQ-5D-Y was indicated by its high response rate at baseline (97.5%): of the 119 participants who downloaded the app, 116 responded the EQ-5D-Y entirely. These results are similar to the 96% response rate reported in the abovementioned cross-sectional Swedish study on children and adolescents with asthma [42]. The flexibility of the administration through the app benefits our completion results, especially for the EQ-VAS with a completion rate of almost 100%, compared with 91% and 86.2% reported in studies where the EQ-5D-Y was administered in paper format to children with chronic conditions [43] and schoolchildren [44], respectively. The losses to follow-up (44 participants who downloaded the app but did not follow until month 6) are likely related to major misunderstandings regarding the app, such us patients thinking that it only had to be answered once and then deleted [52]. On the other hand, 8 patients who continued using the app did not answer the EQ-5D-Y at month 6, which is a response rate of 88.5%. This high level of completion in both administrations could be explained by its low response burden: response times have been estimated on 1.25 min for EQ-5D-Y web

Table 5 Multitrait-multimethod matrix between the EQ-5D-Y, the Pediatric Asthma Impact Scale and the Asthma Control Questionnaire

	EQ-5D-Y Utility index	EQ-VAS[c] Visual Analogue Scale	EQ-5D-Y Dimension (Problems doing usual activities)	ACQ[d] Global Score	ACQ Item (Limited in activities because of asthma)
PROMIS-PAIS Global Score	0.38[a] n = 74 (p = .001) CI [0.56 to 0.16]	0.16 n = 75 (p = .158) CI [0.38 to 0.06]	0.33 n = 75 (p = .003) CI [0.12 to 0.52]	0.37 n = 73 (p = .001) CI [0.15 to 0.55]	0.29 n = 73 (p = .014) CI [0.06 to 0.48]
PROMIS-PAIS[e] Item (Hard to play sports or exercise because of asthma)	0.25 n = 74 (p = .033) CI [0.45 to 0.02]	0.16 n = 75 (p = .158) CI [0.38 to 0.06]	0.17[b] n = 75 (p = .151) CI [0.06 to 0.38]	0.31 n = 73 (p = .008) CI [0.08 to 0.50]	0.30 n = 73 (p = .011) CI [0.07 to 0.49]
ACQ Global Score	0.28[b] n = 113 (p = .002) CI [0.44 to 0.10]	0.26 n = 116 (p = .004) CI [0.43 to 0.09]	0.30 n = 115 (p = .001) CI [0.12 to 0.46]	1	0.79 n = 116 (p = .000) CI [0.71 to 0.85]
ACQ Item (Limited in activities because of asthma)	0.36 n = 113 (p = .000) CI [0.51 to 0.18]	0.26 n = 116 (p = .005) CI [0.42 to 0.08]	0.35[a] n = 115 (p = .000) CI [0.18 to 0.50]	0.79 n = 116 (p = .000) CI [0.71 to 0.85]	1

Correlation coefficients are presented without a sign, since it only reflects that instruments' scores are in the same or in the opposite direction

[a] Correlation hypothesized as moderate (0.31–0.60)

[b] Correlation hypothesized as weak (≤ 0.30)

[c] EQ-VAS: EuroQol-Visual Analogue Scale

[d] ACQ: Asthma Control Questionnaire

[e] PROMIS-PAIS: Patient-Reported Outcomes Measurement Information System-Pediatric Asthma Impact Scale

version [34]. These results support the feasibility of the EQ-5D-Y when it is administered through a smartphone application.

Regarding the distribution of EQ-5D-Y results, the ceiling effect in the sample was high for the utility index (60.3%) and for three out of its five dimensions, which exceeded 90% of participants reporting no problem ("mobility", "looking after myself", and "feeling worried/sad/unhappy"). This high ceiling effect in our sample could be partly explained by the considerable proportion of participants with well-controlled symptoms of asthma (58.6%). Furthermore, a similar ceiling effect, above 80%, has been also reported for the "mobility" and "looking after myself" dimensions in other studies with children or adolescents with asthma [42] and other chronic conditions [43, 44]. These ceiling effects are very high considering the established recommendation of 15% for HRQL scores [70]. However, this is a general standard, as there are none specifically for children. A higher ceiling effect could be expected in children, taking into account their capacity of adaptation to chronic diseases and treatment routines, known as the well-being paradox or response shift effect [71, 72]. The prevalence of problems reported in the dimensions of "doing usual activities" (29.6%) and "having pain or discomfort" (18.1%) are consistent with previous studies [42, 44, 73] where the EQ-5D-Y has been used to describe the impact of asthma on children and adolescents. Studies using the Pediatric Asthma Quality of Life Questionnaire (PAQLQ) [42, 74] or the Child Health Questionnaire (CHQ-CF87) [8] also highlighted the physical activity limitation, while another study measuring HRQL with the PedsQL™ [10] concludes that asthma has an impact on physical, emotional, and school performance. In our study, participants reported a low percentage of problems in the dimension of "Feeling worried, sad or unhappy" (7.6%).

Construct validity of the EQ-5D-Y was evaluated by exploring its relationships as a generic measure with the asthma-specific PROMIS-PAIS, as there is no gold standard for HRQL assessment in pediatric asthma. The correlation between the EQ-5D-Y utility index and the PROMIS-PAIS raw score is moderate in our study, showing that both instruments are capturing the HRQL impact of asthma although not similarly, mainly due to differences between generic and asthma-specific approaches, and to a lesser extent due to differences between the psychometric and econometric development. In our study, these questionnaires were administered at different

Table 6 Comparison of Health-Related Quality of Life (HRQL) between known groups measured at baseline

	% of participants reporting problems in each dimension (n of participants with problems/n of participants without problems)					EQ-5D-Y Utility Index	EQ-VAS[a]	PROMIS PAIS[b] raw Score
	Mobility	Looking after myself	Doing usual activities	Having pain/ discomfort	Feeling worried/sad/ unhappy	Mean (SD) n = 116	Mean (SD) n = 119	Mean (SD) n = 75
Asthma control—ACQ[c]								
Well controlled	4.4% (3/65)	1.5% (1/67)	20.6% (14/54)	14.7% (10/58)	7.4% (5/63)	.94 (.12)	88.2 (14.4)	10.9 (4.4)
Intermediate	0.0% (0/23)	4.3% (1/22)	39.1% (9/14)	21.7% (5/18)	8.7% (2/21)	.91 (.11)	78.6 (20.6)	11.3 (3.3)
Not well controlled	13.0% (3/20)	4.3% (1/22)	45.8% (11/13)	24.0% (6/19)	8.0% (2/23)	.89 (.12)	77.9 (18.5)	16.2 (6.2)
P value	.12	.64	.04	.52	.98	.06	< .006	.002
ES[d] [95% CI[e]]	N/A[f]	N/A[f]	N/A[f]	N/A[f]	N/A[f]	− 0.38 [− 0.87 to 0.1]	0.66 [0.19 to 1.13]	1.11 [0.45 to 1.76]
Asthmatic exacerbations (last 6 months)								
No	6.3% (4/60)	1.5% (1/64)	23.1% (15/50)	13.6% (9/57)	6.1% (4/62)	0.94 (0.11)	84.6 (18.3)	11.3 (4.8)
Yes	3.8% (2/51)	3.8% (2/50)	35.8% (19/34)	22.6% (12/41)	9.4% (5/48)	0.91 (0.12)	84.0 (15.6)	12.9 (5.0)
P value	.55	.43	.13	.20	.49	.12	.46	.15
ES [95% CI]	N/A[f]	N/A[f]	N/A[f]	N/A[f]	N/A[f]	− 0.24 [− 0.61 to 0.13]	0.03 [− 0.33 to 0.4]	0.35 [− 0.13 to 0.82]
Frequency of SABA[g] use reported by patients (last 4 weeks)								
Less than once per week	4.3% (3/66)	1.4% (1/69)	18.6% (13/57)	11.3% (8/63)	5.6% (4/67)	0.95 (0.09)	88.4 (14.2)	11.4 (4.9)
Once or more per week	6.7% (3/42)	4.5% (2/42)	46.7% (21/24)	28.9% (13/32)	11.1% (5/40)	0.88 (0.14)	77.2 (19.4)	12.7 (5.0)
P value	.59	.31	.001	.02	.28	.004	.001	.27
ES [95% CI]	N/A[f]	N/A[f]	N/A[f]	N/A[f]	N/A[f]	− 0.59 [− 0.98 to − 0.2]	0.68 [0.30 to 1.07]	0.26 [− 0.21 to 0.73]
Second-hand smoke exposure								
Not exposed	5.1% (4/75)	1.3% (1/79)	27.5% (22/58)	17.3% (14/67)	9.9% (8/73)	0.92 (0.11)	85.6 (15.4)	11.6 (4.7)
Exposed	12.5% (2/14)	13.3% (2/13)	43.8% (7/9)	37.5% (6/10)	6.3% (1/15)	0.87 (0.16)	73.5 (19.7)	13.7 (6.6)
P value	.27	.01	.20	.07	.65	.35	.02	.21
ES [95% CI]	N/A[f]	N/A[f]	N/A[f]	N/A[f]	N/A[f]	− 0.45 [− 1.01 to 0.1]	0.75 [0.21 to 1.30]	0.42 [− 0.23 to 1.07]

[a] EQ-VAS: EuroQol-Visual Analogue Scale

[b] PROMIS-PAIS: Patient-Reported Outcomes Measurement Information System-Pediatric Asthma Impact Scale

[c] ACQ: Asthma Control Questionnaire

[d] ES: effect size

[e] CI: interval confidence

[f] N/A: not applicable

[g] SABA: Short-Acting β-Agonists

periods (EQ-5D-Y at baseline and PROMIS-PAIS at month 4), which may have produced an underestimation of their correlations. Previous studies have remarked that asthma-specific HRQL instruments measure similar contents to those covered by asthma control questionnaires [75, 76], with a high correlation between them (0.78) [76], proposing generic HRQL instruments to add broader domains which are also important to patients with asthma [77]. However, in our study the correlation of the ACQ with the PROMIS-PAIS was moderate (0.37,

Table 7 Evaluation of reproducibility and responsiveness of EQ-5D-Y's utility index and PROMIS-PAIS

	Stable subsample	Worsening subsample	Improvement subsample
Subsamples defined according to the EQ-VAS[a]			
EQ-5D-Y utility Index			
n	24	17	18
1st administration, mean (SD)	0.94 (0.11)	0.98 (0.04)	0.90 (0.12)
2nd administration, mean (SD)	0.95 (0.09)	0.95 (0.10)	0.94 (0.10)
Change, mean (SD)	0.01 (0.08)	− 0.04 (0.09)	0.04 (0.11)
P value	.50	.12	.18
Effect size	0.14	0.68[d]	
ICC[b]	0.81	N/A[c]	N/A[c]
PROMIS-PAIS raw score[e]			
n	19	12	15
1st administration, mean (SD)	39.0 (7.4)	41.4 (7.8)	38.0 (6.6)
2nd administration, mean (SD)	39.5 (9.8)	36.5 (5.8)	37.6 (6.0)
Change, mean (SD)	− 0.5 (5.5)	5.0 (8.7)	0.4 (10.1)
P value	.71	.07	.88
Effect size	0.09	1.08[d]	
ICC[b]	0.89	N/A[c]	N/A[c]
Subsamples defined according to the ACQ[f]			
EQ-5D-Y utility Index			
n	29	6	16
1st administration, mean (SD)	0.94 (0.10)	0.92 (0.15)	0.95 (0.08)
2nd administration, mean (SD)	0.96 (0.09)	0.88 (0.14)	0.95 (0.08)
Change, mean (SD)	0.02 (0.08)	− 0.04 (0.13)	0.00 (0.11)
P value	.31	.50	.94
Effect size	0.19	0.78[d]	
ICC[b]	0.79	N/A[c]	N/A[c]
EQ-VAS[a]			
n	30	6	16
1st administration, mean (SD)	88.9 (14.1)	78.5 (22.3)	80.4 (16.3)
2nd administration, mean (SD)	90.8 (11.7)	83.0 (19.3)	83.1 (18.1)
Change, mean (SD)	2.0 (12.5)	4.5 (24.0)	2.7 (20.2)
P value	.40	.67	.59
Effect size	0.16	1.15[d]	
ICC[b]	0.70	N/A[c]	N/A[c]
PROMIS-PAIS raw score[e]			
n	25	6	11
1st administration, mean (SD)	36.5 (4.0)	48.0 (10.1)	42.1 (9.0)
2nd administration, mean (SD)	36.7 (5.2)	46.6 (11.8)	38.5 (7.1)
Change, mean (SD)	− 0.2 (4.6)	1.4 (13.8)	3.7 (10.3)
P value	.83	.82	.27
Effect size	0.04	1.28[d]	
ICC[b]	0.68	N/A[c]	N/A[c]

[a] EQ-VAS: EuroQol-Visual Analogue Scale

[b] ICC: Intra-class Correlation Coefficient

[c] N/A: not applicable

[d] Effect size of change calculated for the worsening and improvement subsamples together

[e] PROMIS-PAIS: Patient-Reported Outcomes Measurement Information System-Pediatric Asthma Impact Scale

[f] ACQ: Asthma Control Questionnaire

95% CI 0.15–0.55), and not significantly stronger than that of the ACQ with the EQ-5D-Y index (0.28, 95% CI 0.44–0.10).

As we hypothesized, the correlation of the EQ-5D-Y dimension "problems doing usual activities" with the ACQ item "how limited were you in your activities because of your asthma?" was moderate, and with the PROMIS-PAIS item "it was hard for me to play sports or exercise because of my asthma" was insignificant. This was similar to the correlation of 0.21 between "mobility" (EQ-5D-Y) and "physical wellbeing" (KIDSCREEN) reported in children with diabetes [39], arguing that some KIDSCREEN items consider high energy activities such as "have you been physically active (e. g. running, climbing, biking)?".

Furthermore, the results on discrimination capacity of the EQ-5D-Y utility index and EQ-VAS among most of the selected known groups confirm the hypothesized direction. Although these groups are well known in adults, as far as we know there are no EQ-5D-Y studies evaluating them in children: the EQ-5D was able to detect differences between groups defined by the ACQ [65], and presented a significant association with second-hand smoke exposure [67]. These findings provide evidence of the EQ-5D-Y's ability to detect differences in these known groups, indicating a good construct validity of the instrument, which presented a similar discriminant capacity to the PROMIS-PAIS among groups except for those defined by the ACQ. The PROMIS-PAIS raw score showed, as expected, greater differences than EQ-5D-Y between patients with well- and not well-controlled asthma defined by ACQ (large effect size of 1.11).

Regarding content validity, it is important to mention that the EQ-5D-Y does not cover key aspects of children's HRQL such as social, emotional, or school impact, unlike other generic HRQL instruments that do include them. For example, the KIDSCREEN [78] considers "autonomy and relationships with parents", "social support", "relationship with friends", and "school environment"; the Child Health Questionnaire [79] includes "role/social emotional and behavioral functioning"; and the Child Health Utility 9D [80] asks about "school, daily routine and activities".

Our study shows good reproducibility of the EQ-5D-Y utility index and EQ-VAS according to the established standard [70] (ICC equal or greater than 0.70), which was consistent with the ICC of the EQ-5D-Y unweighted summary score (0.83) reported in a study with children with type 1 diabetes mellitus for the EQ-5D-Y summary score [39]. Two studies reported from poor to substantial agreement according to the EQ-5D-Y dimension, with Kappa coefficients ranging from 0.003 to 0.67 [33] and from 0.199 to 0.653 [41]. The period of time between test and retest in these two studies was short (7–10 days and 48 h). In our case, a 6-month time interval between evaluations could underestimate the reproducibility, but this effect could be compensated by the selection of stable patients. Reproducibility of the PROMIS-PAIS raw score was high in the stable subsample defined with the EQ-VAS (ICC of 0.89) and acceptable in the subsample defined with the ACQ (ICC of 0.68). We did not find previous studies evaluating reproducibility of the PROMIS-PAIS.

Regarding responsiveness of the EQ-5D-Y utility index, we obtained a moderate to large capacity of the instrument to detect change over time. As expected, a larger capacity of detecting change was observed with the asthma-specific instrument PROMIS-PAIS. The EQ-5D-Y unweighted summary score has demonstrated its ability to detect improvement of a moderate magnitude in children and adolescents with type 1 diabetes mellitus (n = 58) [39]. A study of children with idiopathic scoliosis (n = 110) [40] demonstrated the responsiveness of the EQ-5D-Y index constructed with adult value sets, obtaining a large worsening and a small improvement in subsamples defined according to the global rating of health scale.

Strengths and limitations

The Asthma Research in Children and Adolescents (ARCA) study provides a complete database with repeated administration of HRQL instruments and disease-related variables that allow the assessment of EQ-5D-Y's (self-response and proxy version) psychometric properties. The administration of the PROMIS-PAIS allowed us to assess the construct validity of the generic EQ-5D-Y, comparing it with an asthma-specific HRQL instrument. To the best of our knowledge, this is the first study evaluating the psychometric properties of the EQ-5D-Y using the value sets for children, and also the first one including the proxy version to collect HRQL of children with asthma younger than 8 years old.

The effect of the SARS-CoV-2 pandemic on this study deserves a comment. Of the 119 patients included in this study, there were only 8 patients recruited after the SARS-CoV-2 lockdown (between March 2020 and the closing of the data base in June 2020). Of the patients recruited before lockdown, 19 should have responded the 6-month follow-up during this 4-month period, but only 6 answered the EQ-5D-Y. Considering the low number of participants who had to answer during the SARS-CoV-2 lockdown, results are not likely to be affected by the pandemic. On the other hand, 18 participants reported during the telephone interviews having suffered SARS-CoV-2, but only two had been diagnosed before closing the data base of this analysis.

Some limitations should be mentioned. First, this is a secondary objective of the ARCA study, primarily designed for purposes other than the evaluation of the psychometric properties of EQ-5D-Y. Second, the small sample size in the proxy response (n = 38) prevented an independent, complete analysis for self-response and proxy-response versions. However, the examination of the distribution of each version showed a similar pattern (see Tables S1 and S2 in the Additional file 1). Third, the skewness (high ceiling effect) of the EQ-5D-Y utility index could have affected the construct validity results and also hinder the detection of improvement. The EuroQol research foundation's younger populations working group recently developed the new version with 5 levels (EQ-5D-Y-5L) [81], since expanding the number of severity levels might reduce ceiling effects and improve sensitivity. Fourth, responsiveness results should be interpreted with caution considering the low number of participants evaluated due to the classification into two subsamples (stable and changed), and also in part the losses to follow-up (n = 44). The latter could have introduced an attrition bias; in fact, differences found in the asthmatic exacerbations in the last 6 months reported at baseline suggest that the participants could be healthier than those who dropped out (see Table S3 in the Additional file 1). Fifth, because the ARCA project only included patients with mild-to-moderate persistent asthma, the generalizability of our results to those with intermittent or severe persistent asthma is uncertain. Its generalizability is also uncertain to other chronic conditions.

Conclusion

Despite the limitations discussed above, our results provide considerable evidence supporting the appropriate psychometric properties of the EQ-5D-Y in children with persistent asthma. In conclusion, these findings suggest that the EQ-5D-Y is a feasible, valid, and reliable instrument for evaluating HRQL in children and adolescents with mild-to-moderate persistent asthma when it is self-responded by 8–12 years old patients and through proxy response by parents of children under 8 years old. However, the EQ-5D-Y's high ceiling effect found in our sample suggests that it may be more suitable for patients with severe asthma and a higher presence of problems. Further head-to-head comparisons of the three-level and the new five-level version of the EQ-5D-Y in children with asthma are needed to examine to what extent expanding the number of response levels decreases ceiling effect and increases responsiveness. The recent development of the value sets for Spanish children [50] following the international protocol [48] will allow calculating quality-adjusted life-years (combining both the quantity and quality of life) for economic evaluations, since it is a preference-based health status measure. It is a promising instrument to compare the efficiency of different programs or treatment strategies, helping prioritization and investment at different levels. Given its short and easy administration, the EQ-5D-Y is a practical instrument to be used for monitoring patients through the use of smartphone applications.

Abbreviations

ARCA: Asthma Research in Children and Adolescents; HRQL: Health-Related Quality of Life; ACQ: Asthma Control Questionnaire; CHQ-CF87: Child Health Questionnaire; CHU-9D: Child Health Utility 9D; EQ-VAS: EuroQol-Visual Analogue Scale; HUI: Health Utility Index; SMS: Short Message Service; ICC: Intraclass Correlation Coefficient; PedQL: Pediatric Quality of Life Inventory; PROMIS PAIS: Patient-Reported Outcomes Measurement Information System-Pediatric Asthma Impact Scale; PROMS: Patient-Reported Outcome Measures; SABA: Short-Acting β-Agonists; SD: Standard deviations; PAQLQ: Pediatric Asthma Quality of Life Questionnaire.

Supplementary Information

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Additional file 1: Table S1. Distribution of Health-Related Quality of Life (HRQL) scores, self-response version (n=81). **Table S2**. Distribution of Health-Related Quality of Life (HRQL) scores, proxy-response version (n = 38). **Table S3**. Demographic characteristics of participants who completed the 6-month follow-up evaluation and those who did not.

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Authors' contributions

K.M. contributed to the conception and design of the article and wrote the article; M.F. conceived the study, oversaw all aspects, contributed to the conception and design of the article, contributed to the statistical analyses, carried out the interpretation of data, and contributed to the writing of the article; O.G., C.L.B. contributed to the conception and design of the article, conceptualized and oversaw analyses, and contributed to the interpretation of data; A.P. contributed to the analysis and provided statistical support; A.C.-R., M.P., L.V.-N., M.T.G., J.A.C., I.dM., E.T., participated in the design of the study and carried out the fieldwork; J.A., Y.P., V.S.S., revised important intellectual content and the draft versions of the manuscript. All the co-authors critically revised

the manuscript and approved the final draft before submission, and can attest to the validity and legitimacy of the data in the manuscript and agree to be named as author of the manuscript.

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Availability of data and materials
The datasets used and/or analysed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethical approval and consent to participate
The study has the approval of the Parc de Salut Mar ethical committee of clinical research (nº 2015/62/12l), and it was conducted in accordance with the ethical standards of the institutional research committee and the 2000 revision of the Declaration of Helsinki. Informed consent was obtained from the parents or legally authorized representatives of participants, as well as from the children.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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6. DISCUSSION

6.1. MEASUREMENT PROPERTIES OF THE EQ-5D-Y

The EQ-5D-Y was found to be acceptable and easy to administer online for children and adolescents with T1DM. Validity of the EQ-5D-Y was supported by results from the known groups' analysis based on general health, acute diabetic decompensations, mental health, and family function, as well as from the multitrait, multimethod matrix with KIDSCREEN. The test-retest reproducibility was high, indicating good reliability, and the moderate-large change observed between the first and fourth visits among the selected subsample of "improvement" supports its responsiveness.

Similarly, for children and adolescents with persistent asthma, the EQ-5D-Y was found to be feasible and easy to administer via a smartphone application. The EQ-5D-Y showed good validity, with moderate correlation to the Patient-Reported Outcomes Measurement Information System-Paediatric Asthma Impact Scale raw scores, and discrimination among known groups based on the Asthma Control Questionnaire, frequency of Short-Acting Beta-Agonists (SABAs), and second-hand smoke exposure. The test-retest reproducibility indicated high reliability, and while the magnitude of change observed between the first and second evaluation in the worsening or improvement subsamples may suggest its responsiveness, the differences were not statistically significant.

In both chronic conditions, high ceiling effects were observed in the EQ-5D-Y, although a higher percentage was observed in the cohort of patients with asthma (60.3%) compared to the ceiling effect in the sample of T1DM patients (50.7%).

To obtain a comprehensive and current perspective of the evidence on the metric properties of the EQ-5D-Y, a thorough search was conducted in Medline (May 2023), utilizing various terms such as EQ-5D-Y, child, adolescents, and validation, to identify all studies on the metric properties of the EQ-5D-Y across different conditions. Out of the 154 articles that were identified, 27 studies had the specific purpose of evaluating the metric properties of the EQ-5D-Y. These studies, ranging from the first publication in 2009 to the most recent one in 2023, are listed in **Table 8**.

The majority of the identified studies were conducted in China (189–194), Spain (160,163,195–199), and South Africa (163,200–205). There have been articles providing evidence of the metric properties of the EQ-5D-Y-3L in children and adolescents from school settings (191,198,199,206–209), as well as those with specific conditions, including T1DM (197), respiratory illness (196,203,210), orthopaedic or musculoskeletal conditions (189,193,194,200,201,204,211), cancer (192,195,212); and acute illnesses (201,202,205). Only three articles evaluated the EQ-5D-Y proxy versions, specifically in paediatric patients with idiopathic scoliosis (190), beta-thalassemia, haemophilia, and leukaemia (213), and in patients with persistent asthma under 8 years old (196).

There have been no further articles published so far measuring the metric properties of the EQ-5D-Y in patients with T1DM and asthma, apart from the two papers included in this thesis. Some descriptive studies have been published in these two chronic conditions where the EQ-5D-Y was used only to evaluate the impact of these diseases on HRQL (214,215), without assessing its metric properties.

As the EQ-5D-Y questionnaire was initially developed with three response levels (3L), the first articles made use of this version. However, since the design of the EQ-5D-Y with five levels of response (5L) in 2019 (206), there has been a significant increase in recent publications utilizing both versions, the EQ-5D-Y-3L and EQ-5D-Y-5L. The identified studies administered the EQ-5D-Y-3L alone (n=10) or in combination with EQ-5D-Y-5L (n=15).

Overall, the EQ-5D-Y-5L has been found to have better acceptability, convergent validity, and discriminatory power than the EQ-5D-Y-3L, and is recommended for studies where a ceiling effect is anticipated. For instance, the EQ-5D-Y-5L was found to be feasible, presenting a lower ceiling effect and a higher discriminative power that the 3L in Spanish patients with cancer (195). Also, studies that extended the number of levels in the proxy versions to EQ-5D-Y-5L concluded that it increased accuracy, responsiveness, and was associated with closer agreement between proxy-report and self-report in children with various health conditions in Indonesia (213). One study (216) recommended the 3L to be more suited for use in younger children and the 5L in adolescents. In the EuroQol website (217) there is no information available regarding the five-level version, and the user guide and valuation information are only available for the 3-level version.

Since the international valuation protocol for the EQ-5D-Y-3L was published in 2020 (169), value sets have been published for Slovenia (218), Japan (219), Spain (170), Belgium (220), China (221), Germany (222), Hungary (223), Indonesia (224), and Netherlands (225). As value sets were made available in Spain in 2022, it was only possible for us to apply them in the asthma article, published in the same year (196).

Regarding the EQ-5D-Y administration mode used in the studies, there were variations among countries. Despite the widespread adoption of technology among young people, the EQ-5D-Y questionnaire has mostly been administered in paper format (n=13), with fewer administrations through web-based platforms (n=4). We are the only ones who administer EQ-5D-Y through an app. During the design of the ARCA app, we took advantage of the age-based successive versions of the EQ-5D-Y by creating corresponding versions to follow up a person through the different stages of childhood and adolescence. It seems challenging to transition from paper to other electronic administrations in children aged 8-15, despite the fact that electronic administration of PROMs offers several theoretical advantages. Besides being an attractive alternative to traditional methods of data collection, electronic administration offers streamlined and automated data entry and checking processes, which increase efficiency and enhance accuracy. Additionally, skip logic options can be implemented, reducing patient burden and improving response precision, and validation checks can be integrated and programmed to ensure no items are missed (226).

Table 8. Summary of published studies evaluating the psychometric properties of the EQ-5D-Y in different paediatric populations.

First Author, Publication Year	Country	Type of EQ-5D-Y	Administration mode	Diagnosis	Conclusions
EQ-5D-Y-3L and EQ-5D-Y-5L					
Ngwira LG (216), et al., 2023 36892714	Malawi	EQ-5D-Y-3L EQ-5D-Y-5L	Not specified	- Healthy and sick children and adolescents	For both versions convergent validity, discriminant validity with respect to gender and age, and known-group validity of both measures were met for use among children and adolescents in this population. The EQ-5D-Y-3L was found particularly suited for use in younger children (8-12 years) and the EQ-5D-Y-5L in adolescents (13-17 years).
Xu RH (189), et al., 2022 36156120	China	EQ-5D-Y-3L EQ-5D-Y-5L	Web-based	- Osteogenesis imperfecta	The results confirmed that the EQ-5D-Y and CHU-9D are reliable and valid in paediatric OI patients. The EQ-5D-Y-5L performed better than EQ-5D-Y-3L regarding acceptability, convergent validity, and discriminatory power.
Verstraete J (200), et al., 2022 35177084	South Africa	EQ-5D-Y-3L EQ-5D-Y-5L	Paper format	- Traumatic or chronic congenital/ acquired orthopedic condition	The English version of the EQ-5D-Y-5L appears to be a valid and responsive extension of the EQ-5D-Y-3L for children receiving acute orthopaedic management. The expanded levels notably reduce the ceiling effect and has greater discriminatory power. Concurrent validity of the EQ-5D-Y-3L and EQ-5D-Y-5L was low to moderate. The EQ-5D-Y-5L generally showed greater change than the EQ-5D-Y-3L across all dimensions with the greatest change observed for 0–48 h. Responsiveness was comparable across the EQ-5D-Y-3L and EQ-5D-Y5L for those with improved self-rated health.
Verstraete J (201), et al., 2022 35429927	South Africa	EQ-5D-Y-3L EQ-5D-Y-5L	Paper format	- Acute or chronic health condition - General population	The Y-5L is a valid, reliable extension of the Y-3L for children or adolescents across health conditions and healthy children/adolescents. The expanded levels reduced the ceiling effect. The relative informativity of report across dimensions increased on the Y-5L compared with the Y-3L with retention of the evenness of reporting. The convergent validity and test-retest reliability of the Y-5L was comparable with the Y-3L.
Perez-Sousa MA (195), et al., 2022 36141694	Spain	EQ-5D-Y-3L EQ-5D-Y-5L	Paper format	- Cancer	EQ-5D-Y-5L is feasible, presenting a lower ceiling effect than the 3L and high discriminative power.
Lin J (190), et al., 2022 35122171	China	Proxy EQ-5D-Y-5L Proxy EQ-5D-Y-3L	Not specified	- Juvenile or adolescent idiopathic scoliosis	Both the proxy-reported Y-5L and Y-3L are valid (ceiling effects, discriminative power, construct validity) and test-retest reliable instruments for assessing the HRQL in idiopathic scoliosis.
Mayoral K (196), et al., 2022 35346225	Spain	EQ-5D-Y-3L	PDA- Smartphone app	- Persistent asthma	These results support the use of the EQ-5D-Y as a feasible, valid, and reliable instrument for evaluating HRQL in children with persistent asthma. Further studies are needed on the responsiveness of the EQ-5D-Y in this population.
Verstraete J (202)**, 2022** 35708825	South Africa	EQ-5D-Y-3L EQ-5D-Y-5L	Paper format	- Acute or chronic health condition - General population	When considering the choice between the PedsQL, Y-5L and Y-3L these study results indicate that the EQ-5D-Y instruments (Y-3L and Y-5L) are recommended for studies assessing known-group validity or where missing data should be minimised. The PedsQL generic measure may be preferable in future studies including the general population where a ceiling effect is anticipated.
Fitriana TS (213)**, 2022** 35659313	Indonesia	EQ-5D-Y-5L EQ-5D-Y-3L Proxy EQ-5D-Y-5L	Paper format	Parents of children and children with: - Beta-thalassemia	Extending the number of levels in the proxy version of the EQ-5D-Y benefttd its performance in terms of classifcation accuracy, and in the ability to detect health changes over time. Furthermore,

First Author, Publication Year	Country	Type of EQ-5D-Y	Administration mode	Diagnosis	Conclusions
		Proxy EQ-5D-Y-3L		- Hemophilia, - Acute lymphoblastic - Leukemia - Acute ill	the level structure of the EQ-5D-Y-5L was associated with a closer agreement between proxy-report and self-report.
Fitriana TS (212)**, 2021** 34781978	Indonesia	EQ-5D-Y-3L EQ-5D-Y-5L	Paper format	- Beta-thalassemia - Hemophilia, - Acute lymphoblastic - Leukemia - Acute ill	Extending the number of levels did not give clear superiority to EQ-5D-Y-5L over EQ-5D-Y-3L based on the criteria assessed in this study. However, increasing the number of levels benefitted EQ-5D-Y performance in the measurement of moderate to severe problems and especially in longitudinal study designs.
Pei W (191), et al., 2021 33893889	China	EQ-5D-Y-3L EQ-5D-Y-5L	Paper format	- General population	The Y-5L, Y-3L, and KIDSCREEN-10 questionnaires are feasible and valid for measuring HRQL among children/adolescents in China. It also appears that the advantages of Y-5L over Y-3L were modest.
Krig S (227), et al., 2021 32815186	Sweden	EQ-5D-Y-5L	Paper format	- Psychiatric	Results indicate that these patients in general could self-report their health in a meaningful way with the EQ-5D-Y-5L instrument
Zhou W (192), et al., 2021 33950465	China	EQ-5D-Y-3L EQ-5D-Y-5L Proxy EQ-5D-Y-3L	Face-to-face interview	- Leukaemia or other Haematological malignancies	The Y-3L and Y-5L descriptive systems showed acceptable patient-caregiver agreement and test–retest reliability when used to assess the HRQL of children and adolescents with haematological malignancies
Wong CKH (193), et al., 2019 31634302	China	EQ-5D-Y-3L EQ-5D-Y-5L	Web-based	- Idiopathic scoliosis	The 5LY is demonstrated as responsive as the 3LY for patients with idiopathic scoliosis
Kreimeier S (207), et al., 2019 31378708	Germany	EQ-5D-Y-3L EQ-5D-Y-5L	Cognitive interviews - focus groups	- Healthy children - Children with a health condition	German EQ-5D-Y version with five severity levels was developed (EQ-5D-Y-5L) that can be used in children and adolescents aged 8 to 15 years. However, the psychometric properties of the instrument need further investigation.
Kreimeier S (206)**, 2019.** 30739287	Germany Spain Sweden UK	EQ-5D-Y-3L EQ-5D-Y-5L	Cognitive interviews - focus groups	- General population	This multinational study has provided a version of the EQ-5D-Y with 5 severity levels in each dimension. This extended version (EQ-5D-Y-5L) requires testing its psychometric properties and its performance compared to that of the original EQ-5D-Y-3L.
Wong CKH (194)**, 2019** 30600469	China	EQ-5D-Y-3L EQ-5D-Y-5L	Interviewer-administered (IA) Telephone interview	- Adolescent idiopathic scoliosis (AIS)	Through this head-to-head comparison, the 5LY had significant improvements in ceiling effects in two dimensions when compared to 3LY but other measurement properties of 3LY and 5LY performed similar in the idiopathic scoliosis patient group.

First Author, Publication Year	Country	Type of EQ-5D-Y	Administration mode	Diagnosis	Conclusions
EQ-5D-3L					
Amien R, et al., 2023 (203) 36814254	South African	EQ-5D-Y-3L	Interviewer-administered (IA)	- Chronic respiratory illnesses - Functional disabilities - Orthopaedic conditions - General population	The EQ-5D-Y-3L IA showed acceptable convergent validity and test-retest reliability for measuring health in children aged 5-7-years.
Mayoral K (197), et al., 2019 31714252	Spain	EQ-5D-Y-3L	Web-based	- Type 1 diabetes mellitus	These results support the use of the EQ-5D-Y administered online as an acceptable, valid, reliable, and responsive instrument for evaluating HRQL in children and adolescents with T1DM.
Scott D (204), et al., 2019 31392295	South Africa	EQ-5D-Y-3L	Paper format	- Juvenile idiopathic arthritis	This study showed that the EQ-5D-Y is valid and feasible in measuring HRQL in JIA children and adequately responsive to detect change over time.
Shiroiwa T (208), et al., 2019 31243620	Japan	EQ-5D-Y-3L Proxy EQ-5D-Y-3L	Paper format	- General population	The EQ-5D-Y demonstrates reliability and validity among children/adolescents and their parents in Japan. Construct validity of the EQ-5D-Y by self-report was confirmed through comparisons with the PedsQL
Scott D (205), et al., 2017 28103872	South Africa	EQ-5D-Y-3L	Not specified	- Acutely ill children - Chronic health condition - Disability - Healthy children	The EQ-5D-Y could be used with confidence as an outcome measure for acutely-ill children, but demonstrated poorer psychometric properties in children with no health condition or chronic conditions.
Robles N (198), et al., 2015 26037720	Spain	EQ-5D-Y-3L	Paper format Web-based	- General population	The digital EQ-5D-Y showed almost identical VAS scores and acceptable levels of agreement on dimensions. Both formats demonstrated acceptable levels of construct validity. Availability of the Spanish and Catalan web-version will facilitate its use in HRQOL assessment and in economic evaluation.
Gusi N (199), et al., 2014 24411558	Spain	Proxy EQ-5D-Y-3L	Paper format	- General population	The results obtained show the reliability and validity of the proxy version of the EQ-5D-Y.
Burström K (211), et al., 2014 24761459	Swedish	EQ-5D-Y-3L	Paper format	- Functional motor - orthopaedic - Medical disabilities - General population	Even though feasibility and discriminative validity of the EQ-5D-Y were supported in our study, further studies are needed including more patients and patient groups.
Ravens-Sieberer U (209), et al., 2010 20401552	Germany Italy South Africa Spain Sweden	EQ-5D-Y-3L	Not specified Sweden (paper format)	- General population	Results provide preliminary evidence of the instrument's feasibility, reliability and validity.
Eidt-Koch D (210), et al, 2009 19715563	Germany	EQ-5D-Y-3L	Not specified	- Cystic fibrosis	The EQ-5D-Y can be considered a cross-sectional valid instrument which reflects differences in health according to the progression of the life-long chronic disease cystic fibrosis.

6.2. TOWARDS THE STANDARDIZATION OF THE USE OF PROMS

The standardization of outcomes measurement will open up new possibilities to compare performance globally and improve care. Since 2012, the International Consortium for Health Outcomes Measurement ICHOM (228) is committed to achieving value-based healthcare by working with patients and professionals, measuring outcomes to globally improve care quality. ICHOM organizes working groups on specific medical conditions with different stakeholders from around the world, facilitating collaboration among patients, health professionals, researchers, outcomes measurement experts, and policymakers. The aim of the working groups is to develop a globally agreed-upon set of outcomes that truly represents what matters most to the majority of patients. The results obtained may guide healthcare practices, research, and policy-making efforts to improve care and address the most important concerns for patients (228).

In 2021, ICHOM developed the Overall Paediatric Health Standard Set (OPH-SS) which included, physical health and psychosocial well-being as essential for young people. In the context of diabetes, the ICHOM diabetes working group has identified the core set for adults (for both type 1 and type 2), which include the assessment of well-being, depression, and diabetes-related emotional distress. However, ICHOM has not included yet core sets for paediatric populations with diabetes or asthma.

Efforts for standardization of asthma patients' assessment have been made from the COMSA (Core Outcome Measures sets for paediatric and adult Severe Asthma) working group, which have sought to develop Core Outcome Measures (COM) sets to facilitate a better synthesis of data and appraisal of biologics in paediatric and adult asthma clinical studies. The COM sets include forced expiratory volume in 1 s (FEV1) as z-scores, annual frequency of severe exacerbations, and maintenance oral corticosteroid use. PROMs included in the COM are the Paediatric Asthma Quality of Life Questionnaire and Asthma Control Test or Childhood Asthma Control Test, while the adult COM set includes the Severe Asthma Questionnaire and the Asthma Control Questionnaire-6 (symptoms and rescue medication use reported separately).

Treatment for chronic conditions is constantly evolving, influenced by a broader understanding of their safety due to post-marketing studies, the generation of new evidence on their effectiveness, and the adoption of new digital technologies. An example of this evolution is the inclusion of inhaled insulin in the market for T1DM as an alternative method of administration. In asthma, changes in treatments have been driven by the identification of adverse drug events (such as in the case of montelukast), or the new combinations of drugs to enhance the effectiveness. Montelukast's neuropsychiatric adverse reactions (including nightmares, depression, insomnia, aggression, anxiety, and abnormal behaviour or changes in behaviour) led the FDA to issue a warning. To contribute to a better comprehension of this problem, we conducted a systematic review with meta-analysis summarizing the available evidence on the impact of montelukast in paediatric patients with asthma and/or allergic rhinitis, measured with PROMs, included as annex 1 of this thesis.

6.3. DIGITAL HEALTH TECHNOLOGIES

It is crucial to start to use technologies that enable a close follow-up of patients, encompassing clinical parameters, the evaluation of treatment effect, and the natural changes of the transition from childhood to adolescence which, as mentioned above, can have an influence on the course of the condition and its management. Innovations in personalized health technology provide a unique opportunity to develop connected healthcare models that are built around the patients' individual needs (177).

The use of mHealth apps has indeed rapidly increased, and there are now thousands of apps available for numerous health conditions. Mobile apps collect PROMs in a feasible and a well-received way among diverse populations (229). Additionally, these apps enable systematic monitoring of symptoms on a large scale by gathering PROMs between medical visits, and facilitate communication between patients and healthcare providers in case of worsening symptoms (230–232).

In 2019 there were over 500 asthma-related apps (233), with only a few reporting research on their ability to improve asthma management (233). Most of them have been used to track or collect overall health status (234) or symptoms (232,234–237), some with specific PROMs such as the Asthma Control Test (ACT) (234,235) or with visual analogue scales assessing daily symptoms and their impact (237). As far as we are aware, there are no apps besides ARCA app specifically designed with the aim of monitoring HRQL in children and adolescents with asthma. However, apart from mobile apps, monitoring can also be performed through web-based survey platforms such as RED Cap or Qualtrics, as is the case with the EQ-5D-Y instrument (238).

In the ARCA app, HRQL questionnaires are administered every 6 months, specifically the EQ-5D-Y, and the Patient-Reported Outcomes Measurement Information System-Pediatric Asthma Impact Scale. Questionnaires assessing the participant's inhaler technique, social support, self-perceived health change, and asthma exacerbations are also administered through this app.

Electronic monitoring devices can be paired with mobile apps on smartphones, offering various features such as audio-visual reminders for medication intake and the ability to correlate medication use with environmental exposures (177). Considering the significance of self-management in assessing symptoms and adhering to medication regimens, individuals with asthma may find apps paired with inhaler sensors particularly beneficial for monitoring symptoms and inhaler usage (177,233).

Additionally, devices capturing breathing sounds through microphones placed on the skin can provide information about asthma-related breathing patterns (respiratory rate, flow rate, tidal volume) and symptoms like wheezing and coughing. Moreover, chest movement signals can be acquired using an accelerometer or a belt-shaped device (239). However, it is important to note that the use of these wearable continuous monitoring systems is still an emerging field and requires further investigation to determine its clinical impact (233).

In the field of diabetes, mHealth apps have become increasingly popular (240). In 2019, diabetes-related mHealth apps downloads were approximately 46.3 million, which represented approximately 11% of patients with diagnosed diabetes mellitus worldwide in the same year (241). Of the mHealth apps installed, 35.8% focused on T1DM (242) and the rest in type 2 diabetes. Diabetes mHealth apps present a great variety and include very different features (243), being used mainly for self-management, lifestyle modification, and medication adherence motivation (244).

Specifically, apps designed for T1DM have functions such as logging blood glucose values, providing blood glucose graph analyses for feedback to promote reflection and behavioural change, setting reminders for insulin injection, blood glucose checks or exercise, carbohydrate counting, and insulin dose calculation (245). Additionally, some continuous glucose monitoring sensors and glucometers can automatically connect to smartphone apps, helping in logging blood glucose or giving updates to parents or health care professionals. Also, with the help of artificial intelligence and machine learning, patient data on diabetes can now be analysed for automated generation of recommendations for therapy adjustment. Software systems have been developed that can automatically generate decision-support recommendations for insulin dose (246).

In summary, all these digital health innovations have the potential of measuring PROMs together with traditional clinical and functional indicators, which are both complementary to guide the management of patient with chronic conditions.

7. FUTURE LINES OF RESEARCH

Evidence on metric properties of the instruments is accumulative. In this sense, additional studies are necessary to corroborate and extend the evidence regarding the acceptability, validity and responsiveness of the EQ-5D-Y for evaluating Health-Related Quality of Life (HRQL) in children and adolescents with both type 1 diabetes mellitus (T1DM) and asthma. These studies should involve larger sample sizes and encompass different levels of disease severities to enhance the generalizability of the findings.

The use of proxy-response versions is especially useful in paediatric chronic conditions for the youngest patients or when patients experience severe impairments, making self-response difficult. To ensure an appropriate assessment of the performance of all EQ-5D-Y versions, it is recommended that future studies conduct separate analyses for the self-response and proxy-response versions. Helping to provide evidence on how the instrument performs according to the response mode. Considering the scarcity of studies evaluating the EQ-5D-Y proxy version, it is important to guide research efforts towards the assessment of its metric properties, which can help to address the underrepresentation of the group of children who are younger than 8 years old.

The head-to-head studies comparing the EQ-5D-Y-3L with the EQ-5D-Y-5L have been performed in cancer, juvenile idiopathic scoliosis, osteogenesis imperfecta, and traumatic or chronic orthopaedic conditions but, so far, none have been performed in asthma and T1DM. It is important to perform head-to-head comparisons between the three-level and the newer five-level versions of the EQ-5D-Y in children with T1DM and asthma, to investigate to which extent expanding the number of response levels reduces the EQ-5D-Y-3L's ceiling effect and increases its responsiveness. On the other hand, more research is needed to establish if the 3L version suits the younger children better, and the 5L version is best for the adolescents.

Taking into account that value sets are currently only available for the 3L version, cost-utility analysis can only be performed with this version. Therefore, developing value sets for the country versions of the EQ-5D-Y-5L will help to compare the efficiency of different programs or treatment strategies and aid in prioritization and resource allocation in these two important paediatric conditions.

Further research is needed to evaluate the feasibility and the impact of using eHealth tools, including PROMs in routine clinical care for monitoring and management, especially through the use of smartphone applications. There is a clear potential benefit of incorporating electronic administration of PROMs in research and rutinary health care, as it can improve completion rates, provide real-time feedback for patients and health care professionals, reduce missing data, and streamline data entry and management processes. However, evaluation of new e-Health tools is needed to confirm the abovementioned theoretical benefits.

Patient education and awareness regarding security, data protection, and potential costs associated with downloading mobile apps for different health contexts should be prioritized. To obtain all the potential benefits of digital health, more research is needed in order to identify challenges and user experiences associated with digital health, without forgetting the limitations of underrepresentation in these results of patients with lower digital literacy and of those without smartphones or with outdated devices.

It is challenging for asthma and T1DM treatment guidelines to expand beyond the recommendations of symptoms questionnaires only. While acknowledging that the ultimate goal of treatment is to improve patients' HRQL, these guidelines fall short in providing specific recommendations regarding which questionnaires should be utilized. We strongly recommend conducting new systematic reviews that evaluate the metric properties of the available HRQL instruments in paediatric asthma and T1DM. These reviews should employ a checklist such as COSMIN (Consensus-based Standards for the selection of health Measurement INstruments) to assess the methodological quality of individual studies, with the primary goal of providing updated evidence-based guidance for selecting HRQL instruments in both research and clinical practice. This will help to close this existing gap and address the lack of clear recommendations.

Working group initiatives such as ICHOM (International Consortium for Health Outcomes Measurement) and COMSA (Core Outcome Measures sets for paediatric and adult Severe Asthma) continue to make valuable contributions in standardizing outcomes measurement for diabetes and asthma patients, respectively. To ensure a comprehensive assessment of outcomes for paediatric populations, it is essential for ICHOM to consider developing core sets specifically designed for Type 1 diabetes (T1DM) in children and adolescents. Currently, these core sets are exclusively proposed for adults with diabetes. Additionally, it is crucial to prioritize the inclusion of asthma core sets in the future, given its status as one of the most common non-communicable diseases in young people. Expanding their scope to include paediatric patients will guide healthcare practices, research, and policy-making efforts to improve care and address the concerns that are most important for patients.

Treatment for chronic conditions is constantly evolving, influenced by the collection of evidence regarding effectiveness, safety, and by the adoption of new digital technologies. Studies based on real world data from health care registries will be in the near future one of the most quick and efficient designs to answer these research questions. Thus, the incorporation of PROMs in routine clinical care is a promising strategy, not only to improve the management of children and adolescents with chronic conditions, but also to test hypotheses on emerging research questions.

8. CONCLUSIONS

1.1 Our results provide considerable evidence supporting the appropriate metric properties of the EQ-5D-Y in patients with type 1 diabetes mellitus, suggesting that the EQ-5D-Y administered online is an acceptable, valid, reliable, and responsive instrument for evaluating health-related quality of life in children and adolescents with this condition.

1.2 Since it is a preference-based health status measure, it will allow calculating quality-adjusted life-years (combining both the quantity and quality of life) for economic evaluations. Given its short and easy administration, the EQ-5D-Y is a practical instrument to implement in primary care to routine monitoring children and adolescents with type 1 diabetes mellitus.

2.1 Technology has the capability of transforming the application of patient-reported outcomes measures and other patient-reported variables, especially in children and adolescents, as shown in our experience developing the e-Health ARCA tool to monitor paediatric patients with asthma.

2.2 Having described all the development phases of the ARCA app, from conceptualization to the usability assessment, may increase the knowledge on how to design applications for monitoring patients with different chronic conditions. This app sends monthly notifications to the users to complete questionnaires, while responses are available for review on an online dashboard that gives real-time information to paediatricians.

3.1 Our findings support the appropriate psychometric properties of the EQ-5D-Y in children with persistent asthma, suggesting that the EQ-5D-Y is a feasible, valid, and reliable instrument for evaluating health-related quality of life in children and adolescents with mild-to-moderate persistent asthma when it is self-responded by 8–12 years old patients and through proxy response by parents of children under 8 years old.

3.2 The EQ-5D-Y's high ceiling effect found in our sample of paediatric patients with persistent asthma suggests that it may be more suitable for those with severe asthma and a higher presence of problems. Further head-to-head comparisons of the three-level and the newer five-level version of the EQ-5D-Y in children with asthma are needed, to examine to what extent expanding the number of response levels decreases ceiling effect and increases responsiveness.

4. Due to its low burden of administration and robust metric properties, the EQ-5D-Y is a practical instrument to be used for monitoring patients through the use of smartphone applications and other e-health tools in type 1 diabetes mellitus and persistent asthma. Moreover, the EQ-5D-Y is a promising instrument to compare the efficiency of different programs or treatment strategies, helping prioritization and investment at different levels for paediatric patients with chronic conditions.

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10. OTHER PUBLICATIONS OF THE PhD CANDIDATE RELATED TO THE THESIS

1. Hernandez G, Dima AL, Pont À, Garin O, Martí-Pastor M, Alonso J, Van Ganse E, Laforest L, de Bruin M, **Mayoral K**, Ferrer M*, ASTRO-LAB group. Impacto f asthma on women and men: Comparison with the general population using the EQ-5D-5L questionnaire. PLoS One. 2018;13(8):e0202624.

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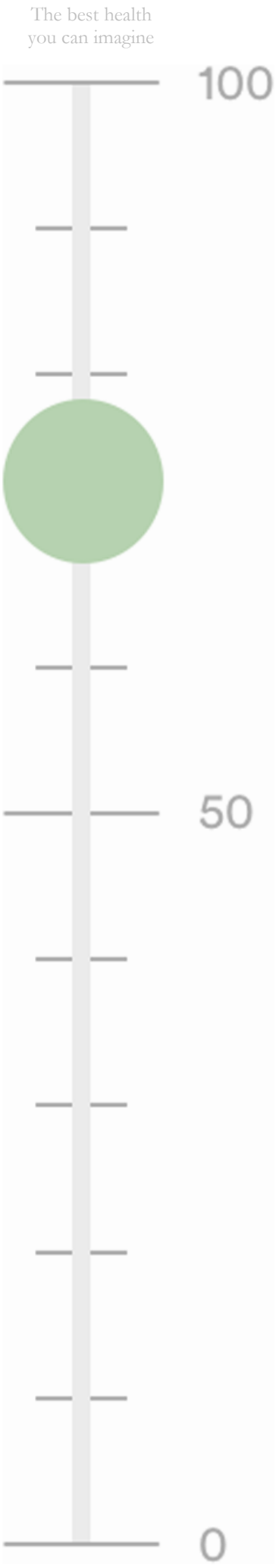

ANNEX 1:
Non-published article

Mayoral K., Lizano-Barrantes C, Zamora V, Pont A., Miret C, Barrufet C., Caballero-Rabasco M.A, Praena-Crespo M., Bercedo A, Valdesoiro-Navarrete L, Guerra M.T, Pardo Y, Martínez Zapata M.J, Garin O, Ferrer M, ARCA Group. ***Impact of montelukast in paediatric asthma and allergic rhinitis from the patients' perspective: a systematic review and meta-analysis.***

REVIEW ARTICLE

Impact of montelukast in paediatric asthma and allergic rhinitis from the patients' perspective: a systematic review and meta-analysis

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Abstract

Background: We aim to assess the impact of montelukast on paediatric patients with asthma/allergic rhinitis, measured with Patient-Reported Outcome Measures (PROMs), when compared with other treatments or placebo. We also aim to synthesize the evidence about adverse drug events and withdrawals.

Methods: Protocol registration number CRD42020216098 (www.crd.york.ac.uk/PROSPERO). The Ovid Medline and Ovid Embase databases were used to conduct the search. Two authors independently selected studies for inclusion and extraction of data, and a third reviewer resolved discrepancies. Meta-analyses were constructed to test the impact of montelukast on PROMs, estimating the standardised mean difference (SMD), with random effects model. Subgroup analyses according to type of asthma were performed.

Results: Out of 3937 articles identified, 265 articles were fully read, and 49 studies met the inclusion criteria. Most studies were randomized clinical trials with sample sizes ranging from 21 to 689 patients. The SMD of change pooled estimators for the global, mental, and physical domains of HRQL were not statistically significant. For daytime and night-time symptoms scores, the SMD was in favour of Inhaled Corticosteroids (-0.12 [95%CI -0.20; -0.05] and -0.23 (95%CI [-0.41; -0.06], respectively). The pooled estimator for global asthma symptoms was 0.90 (95%CI 0.44, 1.36) in favour of montelukast when compared with placebo.

Conclusions: The synthesis of the available evidence suggests that in children and adolescents, montelukast was effective in controlling asthma symptoms when compared with placebo, but Inhaled Corticosteroids were superior in controlling symptoms, specially at night-time. These findings of our systematic review are in accordance with current guidelines for asthma treatment.

KEY WORDS

Asthma; Allergic Rhinitis; Montelukast; Children; Adolescents; Patient-Reported Outcome Measures, Health-Related Quality of Life, Meta-analysis.

1. Introduction

Asthma and allergic rhinitis affect over 300 million people globally [1, 2], comprising 10% to 30% of all adults and up to 40% of children. Montelukast, a leukotriene receptor antagonist (LTRA), was approved by the United States' Food and Drug Administration (FDA) in 1998 for the treatment of asthma and in 2002 for allergic rhinitis [3]. Currently, asthma treatment guidelines [4, 5] include LTRAs in the category of other controller options (in monotherapy or in combination with inhaled corticosteroids), highlighting their limited indications and the lack of evidence for efficacy or safety. The guideline for allergic rhinitis [6] limit montelukast only as a treatment option for patients who are not effectively treated with alternative therapies.

In 2009 the FDA requested a review of the clinical trials with montelukast performed by Merck KGaA, whose results indicated that suicidality and behaviour-related adverse experiences were infrequent and similar to those seen in control subjects [7, 8]. Nonetheless, several cases were notified between 2014 and 2018 as suspected adverse neuropsychiatric events [9]. In 2019, a European Medicines Agency (EMA) review [10] identified some cases in which there had been a delay in recognizing neuropsychiatric events as possible adverse drug reactions, and the United Kingdom's Medicines and Healthcare products Regulatory Agency (MHRA) activated a warning including nightmares, depression, insomnia, aggression, anxiety, and abnormal or changed behaviour. In 2020, the FDA required a boxed warning advising healthcare providers to avoid prescribing montelukast for patients with mild symptoms [11]. The majority of systematic reviews evaluating montelukast adverse events were performed before the FDA's warning release [12–14]. To the best of our knowledge, after the release there was only one systematic review aimed to identifying montelukast adverse drug reactions reported in the medical literature [15], which found a wide range of suspected reactions, predominantly gastrointestinal and neuropsychiatric, and a study reviewing in the World Health Organization's database (VigiBase) the reports of suspected adverse drug reactions to [16], which found 1118 reports of nightmares, two thirds concerning children aged 5–10 years.

The impact of montelukast adverse reactions could be captured through Patient-Reported Outcomes Measures (PROMs), which cover a variety of constructs from the patient's perspective, including symptoms and health-related quality of life (HRQL) among others [17]. Asthma and rhinitis guidelines recommend the use of PROMs to monitor symptom control and to measure the impact of the disease on daily activities and health-related quality of life (HRQL) [4, 5, 18, 19].

We found five systematic reviews evaluating the efficacy of montelukast or LTRA specifically on paediatric asthma patients [13, 20–23], confirming the superiority of ICs in symptoms control [20, 21, 24], symptoms scores [13], symptoms-free days [24], night-time awakening [24], and HRQL [24]. Other systematic reviews compared LTRA with placebo [12], or as an addition to usual care [23]. PROMs were secondary endpoints in most of these systematic reviews and no meta-analyses were constructed with them. We identified three systematic reviews including adolescents and adults with allergic rhinitis that compared montelukast with placebo, antihistamines, and intranasal corticosteroid [25–27], all considering PROMs as primary and secondary outcomes (symptoms and HRQL, respectively), but none included a metanalysis with paediatric patients.

There are few systematic reviews in children and adolescents evaluating montelukast with PROMs, especially for HRQL in asthma patients. Our primary aim was to evaluate the impact of montelukast on paediatric patients with asthma and/or allergic rhinitis, measured with PROMs, when compared with other treatments or with placebo, through a systematic review and meta-analysis. We also considered to synthesize the evidence about adverse drug events and withdrawals in the selected studies.

2. Methods

2.1 Protocol and registration

We conducted a systematic review of the literature on the impact of montelukast in children and adolescents with asthma and/or allergic rhinitis, measured with PROMs (CRD42020216098 in https://www.crd.york.ac.uk/PROSPERO), following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) methodological standards [28].

2.2 Eligibility criteria

We consider as inclusion criteria: studies including children and adolescents (<18 years old) with a diagnosis of asthma or allergic rhinitis, comparing montelukast with other treatments or placebo, with or without randomization, and with at least one endpoint measured with a validated PROM. No limitation of language, region, or year of publication was considered.

Studies were excluded if samples were composed by patients with multimorbidity, were case-control, a longitudinal design without a comparison group, comparison groups with non-pharmacological intervention, data not stratified for patients <18 years old, with a small sample size ($n \leq 30$), or not published as original articles.

2.3 Information sources and search

The search was conducted in Ovid Medline and Ovid Embase databases on 1/06/2022, and updated last on 31/01/2023. We searched for both MeSH and text word terms including 'asthma', 'rhinitis', 'leukotriene antagonists', and 'patient-reported outcome measures'. The detailed search strategy can be found in the supplementary material (Figure S1). In addition, a manual search was performed in the reference list of selected articles and other published systematic reviews.

2.4 Selection process

Two members (KM, VZ) independently reviewed titles and abstracts using the Covidence® software (www.covidence.org). A pilot test was conducted to standardize criteria among reviewers. Two pairs of members (KM, CL; VZ, CM) reviewed the articles' full text, to select the articles for data extraction. Disagreements in all phases were resolved through discussion, with the participation of a third party (MF).

2.5 Data collection process and data items

Data extraction was carried out by one researcher (KM, CL, or VZ) with independent verification performed by a statistician (AP). We designed a predefined data collection form in Microsoft Excel with the information to be extracted: author and year of publication, study design, follow-up period, sample size and age, diagnosis and severity, intervention and control groups, PROMs administered, type of endpoint and central tendency and dispersion statistics, adverse events and withdrawals. Authors were contacted via email to request any PROM information not reported in the manuscript.

2.6 Study risk of bias assessment

To assess the risk of bias (RoB) we used RoB 2 version 2 [29], or ROBINS-I [30] tool (Risk Of Bias in Non-randomized Studies of Interventions), according to the study design. Both tools have a common set of domains of bias: deviations from intended interventions; missing outcome data; measurement of the outcome; and selection of the reported result. For the nonrandomized studies, the bias due to confounding, selection of participants, and classification of interventions was added and, for the RCTs, the bias arising from the randomization process. The risk of bias arising from each domain is classified for the RoB 2 as: 'low', 'high', or 'some concerns'; and for ROBINS-I 'serious', 'moderate', 'low', or 'no information'. We used the Robvis tool [31] for presenting the risk of bias results in graphics.

2.7 Summary measures

The primary outcome was defined as the difference between treatment groups on the mean change of the PROM score, which was standardized by applying the *escalc* function in R-4.2.0 [32]. Either this difference or the mean change of each group was used to estimate the standardised mean difference (SMD). Otherwise, we calculated the mean change through a basic subtraction of the means at baseline and at follow-up evaluations for each group and the pooled standard deviation. The magnitude (effect size) of the SMD [33] is considered small for 0.2 standard deviations (SD), moderate for 0.5 SD, and large for 0.8 SD.

2.8 Synthesis of results

Aggregated data was described as part of the general narrative synthesis. Meta-analyses for quantitative syntheses were constructed to test the impact of montelukast on PROMs, by performing subgroup analyses according to type of asthma (considering severity or chronicity). A random effects model (DerSimonian-Laird method) was employed due to expecting variation in study populations, diseases, and data collection. Heterogeneity among studies was evaluated using the I^2 statistic and categorized as: 25–50% low; 50–75% moderate; and >75% high [34]. To explore a possible publication bias, a funnel plot was planned when the number of studies pooled is ≥10. The statistical analysis software program used was RevMan version 5.4 [35].

Additional analyses

Sensitivity analyses by risk of bias were carried out: studies rated as high risk of bias using the tool RoB 2 or the ROBINS-I were excluded as they were considered a potential source of heterogeneity.

Table 1. Characteristics of the included studies

First author, Publication year Study funding (F)	Study design/ Follow-up period	Sample size: n Age: range (mean)	Diagnosis	Intervention (I) or Control (C) group	PROM Administered	PROM as primary, secondary, or tertiary outcome	Endpoint measure	Adverse events reported
LTRA vs ICs								
Bukstein DA [36], 2003 **F:** Merck & Co, Clinical Development, US Human Health	Observational 12 months	Total n: 104 6-15 yrs (9.6)	Mild persistent asthma	(I): Montelukast (10 mg) (C): Fluticasone (176 µg)	- ATAQ	Secondary	Mean (SD)	No
*Stelmach I [37], 2005 **F:** Medical University of Lodz, Poland	RCT 6 months	Total n: 51 6-18 yrs (11.8)	Newly diagnosed atopic asthma	(I): Montelukast (5 or 10 mg) (C): Budesonide (400 or 800 µg)	- Asthma symptom score (0-9) (Daytime/night-time/β2 use)	Secondary	Mean (SEM)	No
García-García ML [38], 2005 **F:** Merck & Co	RCT 12 months	Total n: 541 6-14 yrs (median 9)	Mild persistent asthma	(I): Montelukast (5 mg) (C): Fluticasone (200 µg)	- PATAQ – Overall	Tertiary	Mean change [95%CI]	Yes
*Ostrom NK [39], 2005 **F:** GlaxoSmithKline Inc	RCT 12 weeks	Total n: 342 6-12 yrs (9.35)	Chronic asthma	(I): Montelukast (5 mg) (C): Fluticasone (100 µg)	- Daytime symptom score (0-5) - Night-time symptom score (0-3) - Satisfaction with treatment‡	Not specified	Mean (SEM) Mean change (SEM)	Yes
Szefler S [40], 2007 **F:** AstraZeneca LP	RCT 52 weeks	Total n: 312 2-8 yrs (4.65)	Mild persistent asthma	(I): Montelukast (5 mg) (C): Budesonide (500 µg)	- CHQ-PF50 – General/ Activities - CSHA – Physical/ Activities/ Emotional - Asthma symptom score (AM/PM)	Secondary	Mean (SD) Mean (SEM) Adjusted mean change (SEM)	Yes
Olszowiec-Chlebna M [41], 2010 **F:** Medical University of Lodz, Poland	RCT 6 months	Total n: 60 5-18 yrs (8.53)	Newly diagnosed asthma	(I): Montelukast (5 or 10 mg) (C): Budesonide (400 and 800 µg)	- ATAQ	Not specified	Mean (SD)	No
Parisi G [42], 2022 **F:** University of Catania, Italy	RCT 12 weeks	Total n: 42 2-6 yrs (3.5)	Recurrent wheezing	(I): Montelukast (4 or 5 mg) (C): Beclomethasone (200 mcg)	- TRACK	Primary	Mean (SD)	=
LRA vs other treatment combinations								
°Malmstrom K [43], 1999 **F:** Merck Research Laboratories	RCT 12 weeks	Total n: 895 >15 yrs Paediatric n: 45 15-18 yrs	Chronic asthma	(I): Montelukast (10 mg) (C): Beclomethasone (400 µg) (C): Placebo	- Daytime asthma symptoms - Global evaluation question‡ - AQLQ‡	Primary	Mean (SD) Mean change (SD)	Yes
°Williams B [44], 2001 **F:** Merck Research Laboratories	RCT 16 weeks	Total n: 1055 15-85 yrs Paediatric n: 245 6-14 yrs	Chronic asthma	(I): Montelukast (5 or 10 mg) (C): Beclomethasone (300 µg) (C): Placebo	- PAQLQ – Activity/ Symptom/ Emotional	Not specified	Mean Adjusted mean change [95%CI]	No
Peters SP [45], 2007 **F:** GlaxoSmithKline - American Lung Association	RCT 16 weeks	Total n: 500 >15 yrs Paediatric n: 245 6-14 yrs	Mild persistent controlled asthma	(I): Montelukast (5 or 10 mg) (C): Fluticasone (200 µg) (C): Fluticasone (100 µg) + Salmeterol (50 µg)	- mini AQLQ - ASUI‡ - ACQ‡	Secondary	Adjusted mean (SD) [95%CI]	No

Máspero J [46], 2008 **F:** GlaxoSmithKline	RCT 12 weeks	Total n: 548 6-14 yrs (9.3)	Persistent uncontrolled asthma	**(I):** Montelukast (5 mg) **(C):** Salmeterol / Fluticasone (100/200 µg)	- PAQLQ - Asthma symptoms sore (0-5)‡‡	Secondary	Adjusted mean change (SEM)	No
Bérubé D [47], 2014 **F:** Merck Frosst Canada Ltd	Observational 12 weeks	Total n: 328 2-14 yrs (6.92)	Uncontrolled asthma	**(I):** Montelukast (4 or 5 mg) **(C):** Montelukast (4 or 5 mg) ICs (different doses)	- ACQ	Primary and secondary	Mean (SD) [95%CI] Mean change (SD)	No
LRA vs placebo								
Knorr B [48], 1998 **F:** Merck & Co Inc Becker A [49], 2004 **F:** Merck & Co Inc	RCT 8 weeks	Total n: 336 6-14 yrs (Median 11)	Mild asthma	**(I):** Montelukast (5 mg) **(C):** Placebo	- PAQLQ – Activity/ Symptom/ Emotional - Daytime symptom score (0-5) - Night-time symptom score (0-5)	Primary	Mean (SD) Mean change [95% CI]	No
°Knorr B [50], 2001 **F:** Merck Research Laboratories	RCT 12 weeks	Total n: 689 2-5 yrs (3.6)	Mild to severe persistent asthma	**(I):** Montelukast (4 mg) **(C):** Placebo	- Daytime-symptom score (0-5) - Overnight Asthma Symptoms	Secondary	Mean change [95%CI]	Yes
Stelmach I [51], 2002 **F:** Medical University of Lodz, Poland	RCT 6 weeks	Total n: 32 6-18 yrs (13.5)	Mild to moderate asthma	**(I):** Montelukast (5 or 10 mg) **(C):** Placebo	- Asthma symptom score (0-9) (Daytime/night-time/β2 use)	Secondary	Mean (SD) [95% CI]	No
*Stelmach I [52], 2002 **F:** Medical University of Lodz, Poland	RCT 8 weeks	Total n: 49 9-15 yrs (11.9)	Moderate atopic asthma	**(I):** Montelukast (5 or 10 mg) **(C):** Placebo	- Asthma symptom score (0-9) (Daytime/night-time/β2 use) - PAQLQ‡‡	Not specified	Mean (SD) [95% CI]	No
°Philip G [53], 2004 **F:** Merck Research Laboratories	RCT 2 weeks	Total n: 831 15-85 yrs Paediatric n: 102 15-18 yrs	Asthma and seasonal allergic rhinitis	**(I):** Montelukast (10 mg) **(C):** Placebo	- Daily rhinitis symptoms (0-3) - Daytime symptom score (0-3) - Night-time symptom score (0-3) - RQLQ‡‡	Primary	Mean change (SD)	No
Chen ST [54], 2006 **F:** Chung Shan Medical University Hospital, Taiwan	RCT 12 weeks	Total n: 40 2-6 yrs (4.4)	Rhinitis	**(I):** Montelukast (5 mg) **(C):** Placebo	- PRQLQ - Symptoms Score	Not specified	Mean (SD) Mean change (SD)	No
*Spahn JD [55], 2006 **F:** Merck & Co Inc	RCT 8 weeks	Total n: 21 9-18 yrs (13.1)	Mild to moderate asthma	**(I):** Montelukast (5 or 10 mg) **(C):** Placebo	- Daytime symptom score (0-3) - Night-time symptom scores (0-3)	Not specified	Mean (SEM)	Yes
Stelmach I [56], 2015 **F:** Medical University of Lodz, Poland. National Science Centre	RCT 30 weeks	Total n: 76 6-14 yrs (10.7)	Allergic asthma	**(I):** Montelukast (5 mg) **(C):** Placebo	- ACT scores	Not specified	Mean (SD)	No
Sahiner U [57], 2021 **F:** Merck Sharp and Dohme Company	RCT 4 weeks	Total n: 46 6-18 yrs (11)	Asthma	**(I):** Montelukast (10 mg) **(C):** Placebo	- ACT	Secondary	Mean (SD)	No

(*) Citations identified from other reviews; **(°)** Data obtained after contacting sponsor; **(/)** Combo (fixed dose); **(+)** added treatment; (‡‡) PROM information not available.

RCT Randomized controlled trial; **Y** Years; **I** Intervention group; **C** Control group; **G** Generic questionnaires; **S** Specific questionnaires; **CI** Confidence interval; **SD** Standard deviation; **SEM** Standard error of the mean; **ICs** Inhaled corticosteroids; **PAQLQ** Pediatric Asthma Quality of Life Questionnaire; **PRQLQ** Pediatric Rhinoconjunctivitis Quality of Life Questionnaire; **PATAQ** Pediatric Asthma Therapy Assessment Questionnaire; **ACT** Asthma Control Test; **CSHA** Children's Health Survey for Asthma; **CHQ-PF50** Child Health Questionnaire Parent Form-50; **ATAQ** Asthma Therapy Assessment Questionnaire for children; **TRACK** Test for Respiratory and Asthma Control in Kids; **AQLQ** Asthma Quality of Life Questionnaire; **Mini-AQLQ** Mini Asthma Quality of Life Questionnaire; **ACQ** Asthma Control Questionnaire; **RQLQ** Rhinoconjunctivitis Quality-of-Life Questionnaire; **ASUI** Asthma Symptom Utility Index.

3. Results

3.1 Study Selection

Figure 1 shows that 3937 articles were identified, 3250 titles and abstracts were reviewed, and a complete reading of 265 articles was carried out. Of them, 215 were excluded mostly due to 'only adult patients' (32.5%), 'other outcomes' (23.3%), and 'small sample size (n<30)' (15.8%). Finally, of the 50 articles that fulfilled the inclusion criteria, 28 did not report sufficient data to be included in the meta-analysis (see Supplementary Material – Table A) and 22 did. Data from five articles [43, 44, 50, 53, 57] were obtained by contacting the sponsor (a pharmaceutical company) or authors.

3.2 Study Characteristics

The 22 articles (21 studies) included in some of the meta-analyses (Table 1) [36–57] were published between 1998 and 2015, and all assessed asthma except for one study evaluating allergic rhinitis [54] and another one evaluating patients with both conditions [53]. All studies were performed only in paediatric samples except for four including adults, but with data stratified by age [43–45, 53]. Sample size ranged from 21 to 689, and the follow-up period was from 2 to 52 weeks. There were 7 studies using ICs in monotherapy as the comparator group [36–42], 5 studies using diverse treatments [43–47] and 9 studies (10 articles) comparing it only with placebo [48–57]. All administered PROMS were disease-specific except for a RCT which used the generic questionnaire Child Health Questionnaire Parent Form-50 (CHQ-PF50) [40]. The constructs collected were symptoms (differentiating between daytime and night-time, or considered globally) and HRQL.

3.3 Authors' judgements about each risk of bias item for each included study

Figure 2 shows that of 20 RCTs, 12 had a low risk of bias [37, 39, 41, 43–46, 48, 50, 52, 54, 57], 6 had high risk [38, 40, 42, 52, 55, 56], and one study presented some concerns [53] (Figure 2.A). The most frequent domain causing downgrading was the 'bias in measurement of the outcome' because the assessment of the outcome was probably being influenced by knowledge of the intervention received by patients [38, 40, 42, 52, 55, 56], and no information was reported in the articles. Figure 2.B shows two nonrandomized studies [36, 47] which presented moderate and serious risk of bias.

3.4 Results of syntheses

Figure 3 shows forest plots of studies comparing HRQL of patients with asthma treated with ICs in monotherapy or combined with LABAs vs montelukast. Figure 3A shows the forest plot of the SMD of change for the global HRQL, which included six studies with a sample size of 656 participants for the intervention group, and 535 for the control group (ICs in monotherapy), the pooled estimator was -0.06 (95% CI -0.14; 0.02). The subgroup analysis was statistically significant ($p<0.001$), showing that, in patients with mild persistent asthma and unspecified type of asthma, the change in HRQL was in favour of ICs, but there was one study in favour of montelukast including patients with mild persistent controlled asthma.

Similarly, the HRQL forest plot of the two studies comparing montelukast with ICs/LABA (Figure 3B) was in favour of the latter group without statistically significant differences: overall estimator -0.13 [95%CI -0.28, 0.02] with a moderate heterogeneity (I^2 of 69%). Both studies were carried out among patients with persistent asthma [45, 46]. Figures 3C and 3D show forest plots of mental and physical domains constructed with only two studies providing data at domain level (n=298 intervention, n=158 control), which used ICs in monotherapy as the comparator group. Pooled estimators were not statistically significant and heterogeneity was high in both cases.

Figures 4.A and 4.B show forest plots of studies comparing patients with asthma treated with ICs vs montelukast in terms of daytime (n=386 intervention, n=376 control) and night-time symptoms (n=363 intervention, n=363 control), which showed a statistically significant difference in favour of ICs. When assessing the symptoms globally (Figure 4.C), there were no differences between montelukast and ICs (-0.04 95%CI -0.55, 0.47). The subgroup analysis by type of asthma was statistically significant ($p<0.001$), and heterogeneity was high ($I^2>90\%$) for the three metanalyses. The change was statistically significant in favour of montelukast in a study among newly

diagnosed atopic asthma patients, while favouring ICs in a study among patients with recurrent wheezing.

Meta-analyses of studies comparing montelukast with placebo are shown in Figure 5. Pooled estimators of daytime, nigh-time symptoms, and global symptoms scores (Figures 5.A, 5.B and 5.C) showed a statistically significant difference in favour of montelukast: 0.11 (95%CI 0.05, 0.18); 0.15 (95%CI 0.09, 0.21); and 0.90 (95%CI 0.44, 1.36). The heterogeneity was high except for the night-time symptoms score (I^2 =38%). The subgroup analysis by asthma severity was not statistically significant in any of these three metanalyses.

Sensitivity analyses excluding studies with a high risk of bias are shown in the Supplementary Material Figure S2. Pooled estimators obtained in these sensitivity analyses were in the same direction and similar magnitude to the metanalyses constructed with all the studies.

Six studies [38–40, 47, 48, 50] provided information on adverse drug events and study withdrawals, and other three studies [37, 46, 55] provided information only on study withdrawals. (Supplementary Material - Table B). Most studies reporting adverse drug events concluded that those were not significantly different for montelukast when compared to other treatments [38–40, 48, 50], while some studies reported withdrawals more frequently in the montelukast group [38–40, 46, 48]. Asthma exacerbations, headaches, and upper respiratory tract infections were among the most commonly reported events [38–40, 48, 50]. After having requested them from the authors, one study [50] provided adverse effects for 60 participants, being the most frequent ones headache (n=35), irritability (n=7), nervousness (n=4), behaviour disturbance (n=4) and drug overdose (n=4, presenting thirst, mydriasis, and somnolence). There was one study [47] that reported both adverse events and withdrawals in general, but montelukast was included in both the intervention and control groups: nightmares and sleep terror (n = 6), abdominal pain (n = 5), insomnia (n = 2), and headache (n = 2). Another study [38] reported one death in the montelukast group, although it was not considered to be related to the drug.

4. Discussion

In this systematic review, we identified 50 articles (49 studies) evaluating the impact of montelukast on PROMs when compared with other treatments or placebo in children and adolescents with asthma/allergic rhinitis. The 21 studies finally included in some of the meta-analyses allowed for the construction of pooled estimators of montelukast impact on HRQL (global, mental and physical domains) and symptoms (daytime, night-time and globally) with high heterogeneity. Results were in favour of ICs without statistically significant differences, in the global, mental and physical HRQL mean changes. For daytime and night-time symptoms scores, the change was significant and in favour of ICs. The incidence of adverse events and withdrawals was only provided by 6 and 9 of these studies, respectively, showing infrequent adverse events, which were similar to those seen in the control group, and only one study reported neuropsychiatric ones, but withdrawals were slightly more frequent in the montelukast group.

In our systematic review, of the 49 studies that fulfilled inclusion criteria, 11 (22%) included PROMs as a primary outcome, 21 (43%) as a secondary outcome, 1 (2%) as tertiary outcome, and 16 (33%) did not specify. Furthermore, of the 21 studies included in the meta-analysis, six did not include complete data for all the PROMs administered [39, 43, 45, 46, 52, 53]. The 28 studies whose data could not be extracted for meta-analysis were predominantly RCTs in asthma patients comparing montelukast with ICs [58–64, 70, 77, 79] or placebo [64, 72, 74, 80–85] (see Supplementary Material – Table A). Reasons for non-inclusion in the meta-analyses were results not being segregated for children and adults [59, 60, 64, 65, 67–69, 71, 74, 76–79, 82–84], or PROM data not fully reported [58, 61–63, 66, 70, 72, 73, 75, 80, 81, 85]. These latter 12 studies with missing information on PROMs, that remained unavailable after contacting authors, suggest the poor relevance given to these endpoints. This is in line with reviews [86, 87] highlighting the small proportion of asthma clinical trials including PROMs: only 20 of 300 published RCTs [86], and only 27% of 96,736 registered trials [87]. There is growing evidence that PROM results are frequently omitted, non-reported, and data is presented with suboptimal reporting standards [88, 89]. Issues such as lack of PROMs training, poor understanding of the purpose of PROMs assessment, and questionnaire selection [90] should be contemplated to avoid research waste.

Global HRQL pooled results of our meta-analyses were in favour of ICs in monotherapy or combined with LABAs, but they were not statistically significant, with a negligible magnitude of difference. The study conforming the subgroup of mild persistent controlled asthma was the only one favouring montelukast, which is consistent with GINA's recommendation of using montelukast in patients with fewer frequency of symptoms (more than once a month but less than daily) [4]. The studies included in our systematic review of HRQL mostly administered asthma-specific questionnaires [36, 38, 40, 41, 43–46, 48, 52–54], similarly to findings of a review of PROMs in asthma [86], where the low use of generic questionnaires was highlighted. In fact, the National Asthma Education and Prevention Program [91] in the United States supported the use of generic HRQL instruments to capture patients' global health perceptions.

Results for both meta-analyses on mental and physical domains of HRQL were also in favour of ICs, without statistically significant differences; however, the first one achieves a small magnitude of the difference between treatment groups. No other systematic reviews were found summarizing mental and physical domains. The mental health is an important component of health in children with asthma [92, 93]. The USA National Survey of Children's Health [94] reported higher ORs for developmental or behavioural problems in children with asthma. Furthermore, considering the lack of screening tools for anxious and depressive symptomatology validated among asthma populations remarked by GINA [4], mental dimensions covered by PROMs could be a valuable proxy since they could capture mental adverse problems related to drugs or disease. Several studies included in our meta-analyses measured the mental health component of the HRQL, such as those administering the CSHA [40] (emotional health domain); the CHQ-PF50 (role/social emotional functioning, role/social behavioural functioning, mental health, and behaviour domains); the PAQLQ [44, 46, 48, 52], AQLQ [43], or Mini-AQLQ [45] (emotional function domain); the ATAQ [36, 41] and PATAQ [38] (attitude and behaviour domain); and the PRQLQ [53, 54] (feeling irritable item). Unfortunately, the majority of the articles identified only included total scores [36, 38, 41, 44, 45, 54], and none provided information at dimension and item level, which may have limited the possibility of finding the

real impact of montelukast on mental and physical components of health. Only three studies provided information on the dimension scores: one study that administered the CSHA [40], and two that administered the PAQLQ [44, 48]. The latter used placebo as the comparison group, and the first one used ICs.

The metanalysis of global symptoms shows opposite results according to the type of asthma used as inclusion criteria in the studies (newly diagnosed atopic asthma, chronic asthma, and recurrent wheezing). Results of daytime and night-time symptoms meta-analyses were statistically significant favouring ICs over montelukast, with only night-time achieving a small magnitude. Our results are consistent with previous systematic reviews of schoolchildren with mild to moderate asthma [13], preschool children [95], and paediatric patients [20], concluding that those treated with ICs had better symptoms control than those with montelukast. This is also in line with asthma guidelines recommendation of ICs therapy as the step one treatment for paediatric patients with mild-to-moderate persistent asthma [4, 18].

The synthesis of trials using placebo as a comparison group confirmed the efficacy of montelukast in terms of statistically significant improvement in symptoms daytime, night-time, and globally. However, the magnitude of the benefits was only large for symptoms when measured globally, but very small (<0.2 SD) for symptoms measured separately for daytime and night-time. The large magnitude for the global symptoms pooled estimator (0.9 SD) is explained by two [51, 52], of the five studies included. These studies [51, 52] measured asthma symptoms with an overall score covering daytime, night-time, and also the use of β2 agonist, differing from the other studies which did not include the use of rescue inhalers [48, 56, 57]. Results of studies using placebo as comparison group, without enough information to be included in the meta-analysis, did not show significant differences for HRQL [80] and symptoms score [85] in asthma patients using montelukast, except for one study which obtained a statistically significant higher HRQL improvement in this group [81]. Another study in children with allergic rhinitis found that montelukast's improvement of HQRL was significantly higher than in placebo [72].

In this systematic review, we have not found any PROMs aiming to measure treatment adverse events, and only 6 studies reporting them [38–40, 47, 48, 50]. Only one of these studies reported neuropsychiatry-related events [50] such as irritability, nervousness, behaviour disturbance, insomnia, dream abnormality, anxiety, bipolar disorder, and personality change, but they were more infrequent than in the control group (4.0% vs 5.1%). This is consistent with results of the FDA requested review of behaviour-related adverse experiences in montelukast clinical trials [14], but it is important to consider that some neuropsychiatric events could have been underreported, since patients/parents may have not associated the treatment with the adverse experience. On the other hand, study withdrawals, extracted as a proxy to adverse events, were more frequent in the montelukast group in 5 out of 8 studies [38–40, 46, 48]. This result is consistent with another systematic review [24] found LTRA associated with a 24% increased risk of overall withdrawals in paediatric patients, but also with no statistically significant group difference due to adverse effects. Although treatment may occasionally be discontinued for mild or moderate adverse events, withdrawals are especially important because they reflect the ultimate decision of the participant and/or physician to discontinue treatment.

The main limitation related to the systematic review process was that we may have failed to identify all articles assessing the impact of montelukast on PROMs in children/adolescents. However, we believe that this has been minimized due to the bibliographic database interphase used (OVID), the sensitive search strategy, and the additional hand search of references followed. Regarding limitation related to the studies included and pooled results obtained, first, heterogeneity was high (I^2>75%) in all meta-analyses comparing montelukast with ICs in monotherapy, and moderate (I^2= 69%) when compared with ICs combined with LABAs. Since we hypothesized asthma severity as a potential source of heterogeneity, we performed subgroup analyses according to this variable, but it was statistically significant only in one of the three meta-analyses where it could be tested: the one comparing HRQL between montelukast and ICs. It is important to remark the lack of uniform criteria across studies for asthma severity and classification types, which limited our subgroup analyses, but many other possible reasons could explain such heterogeneity. Second, the internal validity of the pooled estimator provided by a meta-analysis depends on the quality of primary studies. Results of the sensitivity analyses

excluding the 29.4% studies qualified as high risk of bias were consistent with those obtained by the meta-analyses constructed with all the studies. Third, the follow-up period in most of trials could be considered short to detect montelukast's adverse events, which could appear after stopping treatment [16]. In fact, 11 studies were conducted over 12 weeks or less [39, 43, 46–48, 50–55]. Fourth, the ability to generalize our findings in preschool children (<5 years) is limited because only two studies examined this population; likewise in paediatric patients with allergic rhinitis, for which there were five studies and most of them without data to be included in the metanalyses. Fifth, no funnel plot for publication bias assessment could be constructed because of the low number of studies pooled (n <10) in all forest plots. Finally, concerns about the sources of these studies are remarkable, as more than half of the studies included were sponsored by pharmaceutical companies.

Conclusion

To the best of our knowledge, this is the only systematic review focused on the impact of montelukast on children and adolescents with asthma, measured with PROMs. Our results suggest that the benefit of ICs on night-time symptoms was statistically higher than that of montelukast, although the magnitude of the difference was small. HRQL did not present statistically significant differences between montelukast and ICs, and the magnitude was small only for the mental domain (negligible for the rest). Compared with placebo, montelukast was effective in controlling asthma symptoms. These findings of our systematic review are in accordance with current guidelines for asthma treatment, which recommend the use of inhaled corticosteroids (ICs) therapy as first step treatment for paediatric patients with mild-to-moderate persistent asthma; and considering LTRAs in the category of other controller options, but taking into account the lack of evidence for safety. It is essential to achieve a broader understanding of the safety of montelukast by long-term post-marketing studies, and improving the collection of adverse events in clinical trials, specifically measuring them through validated PROMs.

Declarations

Competing interests
None declared.

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Authors' contributions
MF conceived the research question, contributed to the conception and design of the article, oversaw all aspects, contributed to the statistical analyses, carried out the interpretation of data, and contributed to the writing of the article; **KM, CLB, VZ**, participated in the conception of the research question, conducted the literature search and data extraction, as well as the quality assessment, conceptualized and oversaw analyses, and wrote the article; **CM, CB** conducted the literature search and data extraction, as well as the quality assessment; **AP** contributed to the analysis and provided statistical support and help in the interpretation of data; **MAC, MP, AB, LV-N, OC**, participated in the conception of the research question, ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved, and helped in the interpretation of data and drafting of the paper; **OG, YP, MJMZ** revised important intellectual content and the draft versions of the manuscript. All the co-authors critically revised the manuscript and approved the final draft before submission, and can attest to the validity and legitimacy of the data in the manuscript and agree to be named as author of the manuscript.

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List of abbreviations, in order of appearance:
RCT: Randomized Controlled Trial
LRA: Leukotriene Receptor Antagonists
ICs: Inhaled Corticosteroids
FDA: Food and Drug Administration
EMA: European Medicines Agency
MHRA: Medicines and Healthcare products Regulatory Agency
PROMs: Patient-Reported Outcomes Measures
PREMs: Patient-Reported Experiences Measures
HRQL: Health-Related Quality of Life
CI: Confidence Interval
Rob2: Revised tool for Risk of Bias in randomized trials
ROBINS-I: Risk of Bias in Non-randomized Studies of Interventions
AntiH1: Antihistamines against the H1 receptor
LABA: Long-acting beta-agonists
PAQLQ: Pediatric Asthma Quality of Life Questionnaire
PRQLQ: Pediatric Rhinoconjunctivitis Quality of Life Questionnaire
PATAQ: Pediatric Asthma Therapy Assessment Questionnaire
ACT: Asthma Control Test
CSHA: Children's Health Survey for Asthma
CHQ-PF50: Child Health Questionnaire Parent Form-50
ATAQ: Asthma Therapy Assessment Questionnaire for children
AQLQ: Asthma Quality of Life Questionnaire
Mini-AQLQ: Mini Asthma Quality of Life Questionnaire
ACQ: Asthma Control Questionnaire
PRQLQ: Paediatric Rhinoconjunctivitis Quality of Life Questionnaire
RQLQ: Rhinoconjunctivitis Quality-of-Life Questionnaire

Figure 1. PRISMA flowchart of systematic literature review

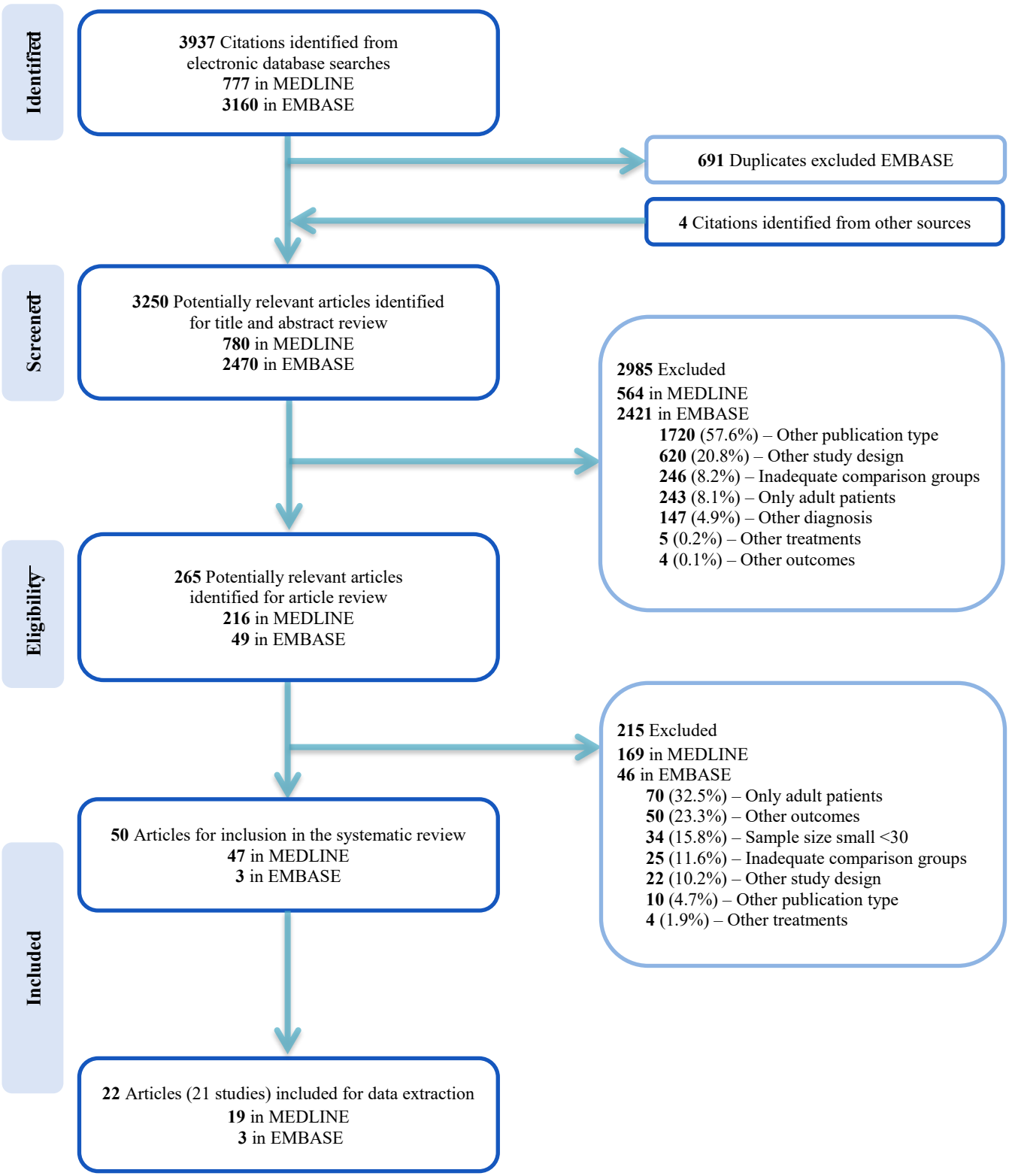


Figure 2. Risk of bias of included studies.

Figure 2.A. Risk of bias summary for RCTs using Rob2* tool.

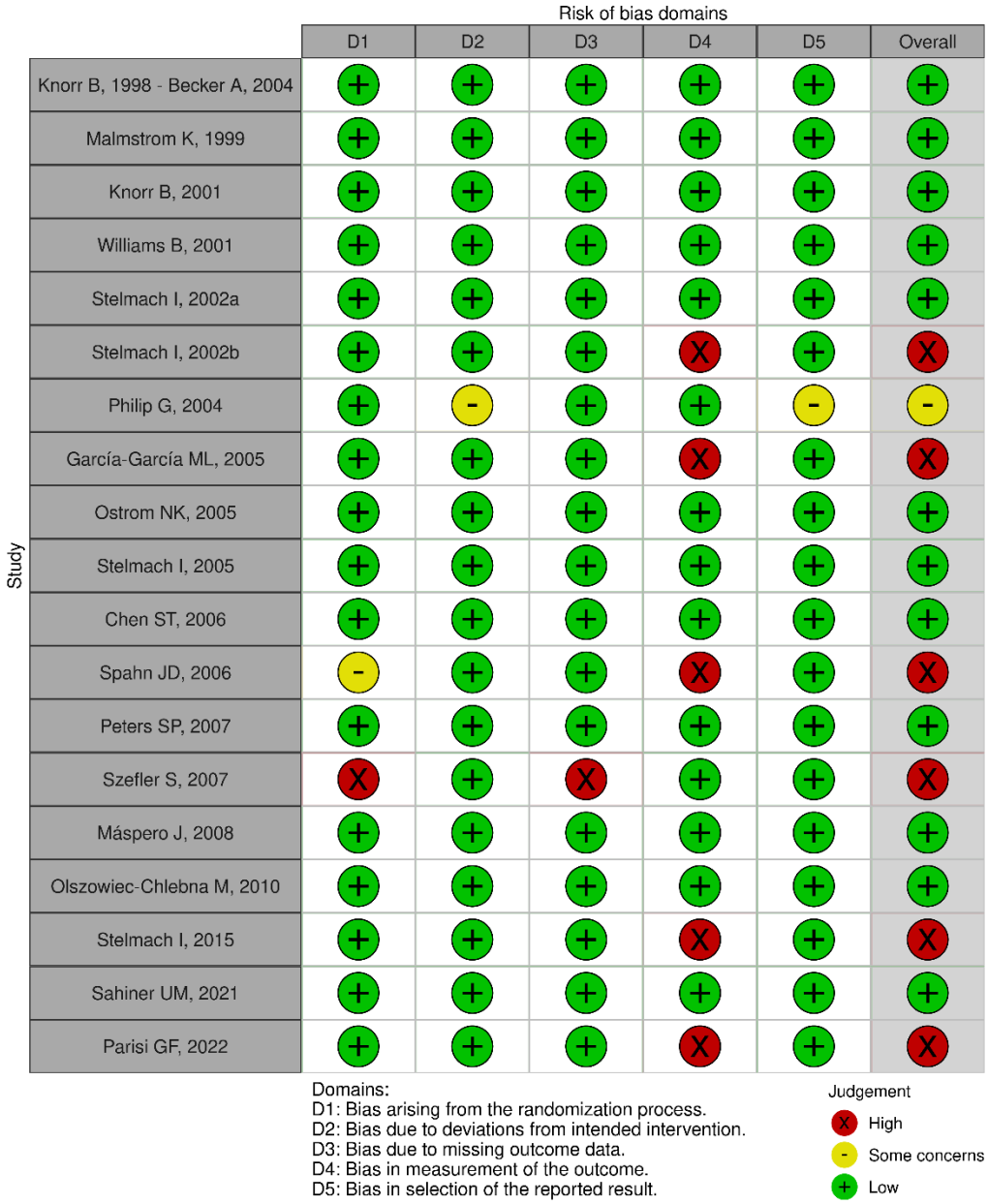
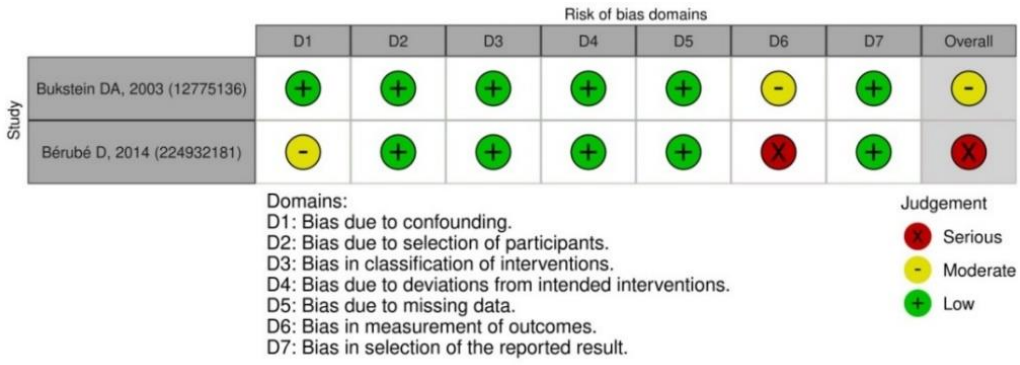


Figure 2.B. Risk of bias of nonrandomized studies assessed using ROBINS-I** tool.



Footnotes: ***Rob2** Revised tool for Risk of Bias in randomized trials; ****ROBINS-I** Risk of Bias in Nonrandomized Studies of Interventions

Figure 3. Forest plot of studies comparing patients with asthma treated with Inhaled Corticosteroids in monotherapy* or as a combined treatment with LABAs** vs Montelukast in terms of Health-related Quality of Life: global scores, mental and physical domains.

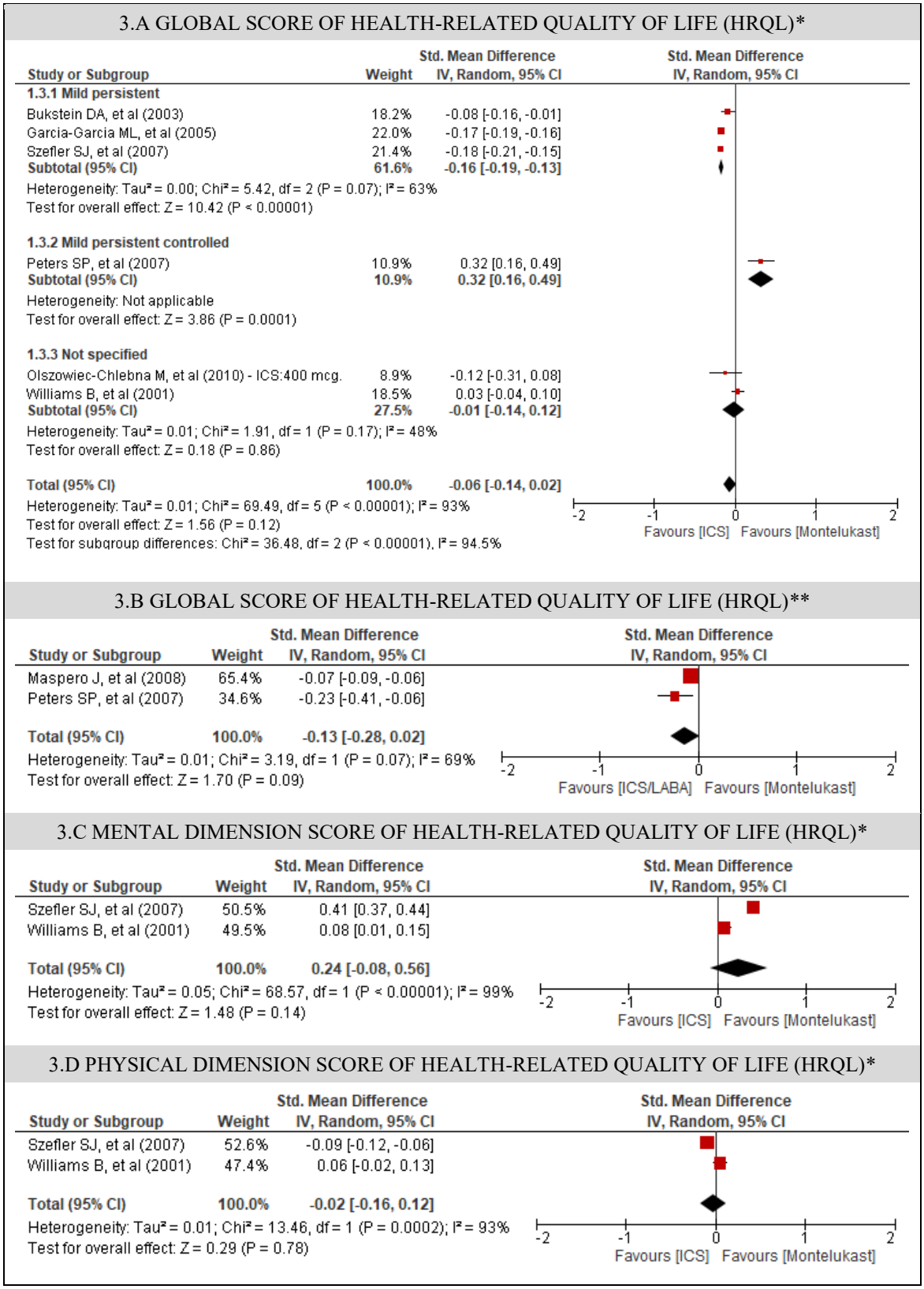


Figure 4. Forest plot of studies comparing patients with asthma treated with Inhaled Corticosteroids vs Montelukast in terms of symptoms.

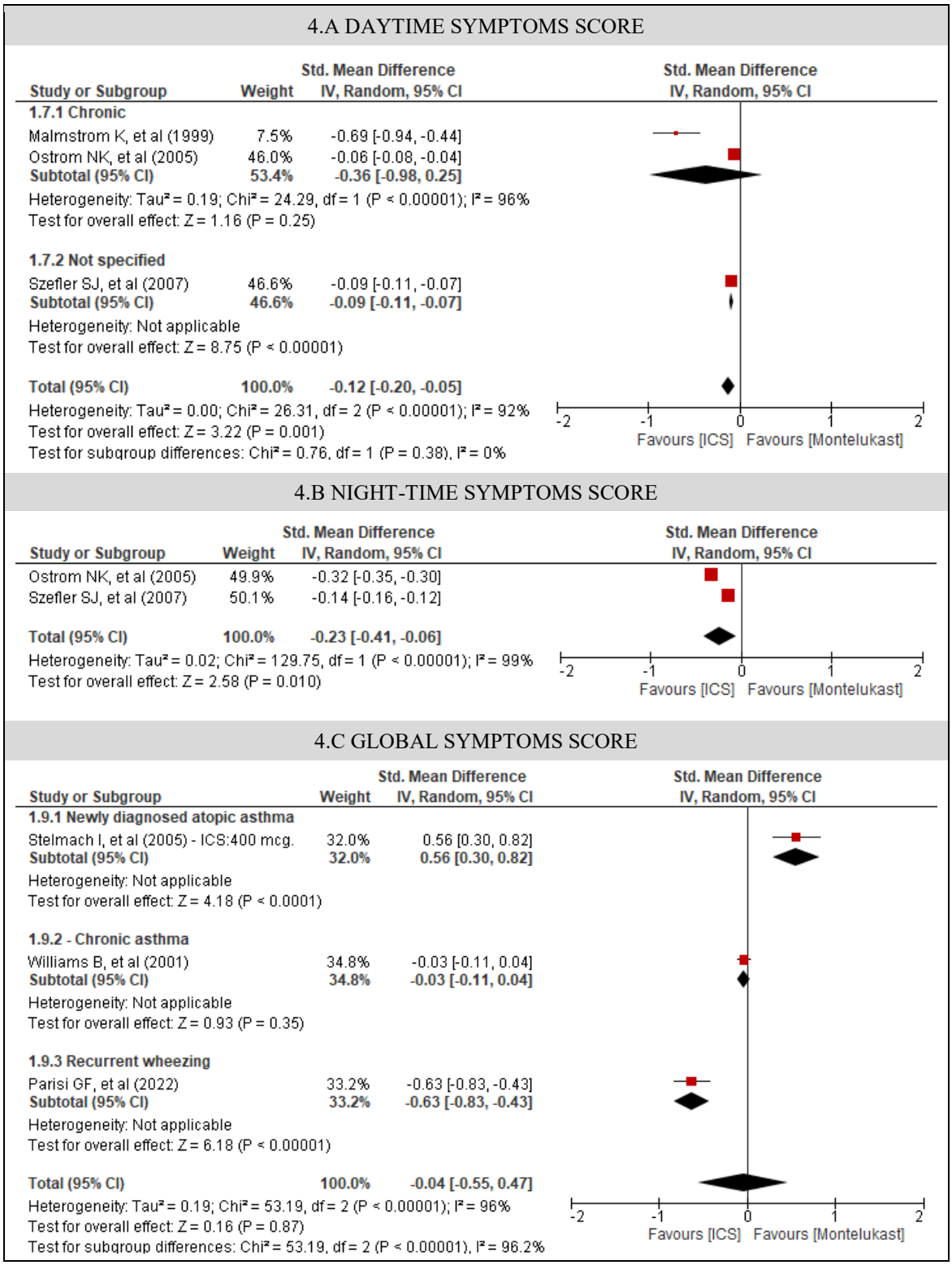
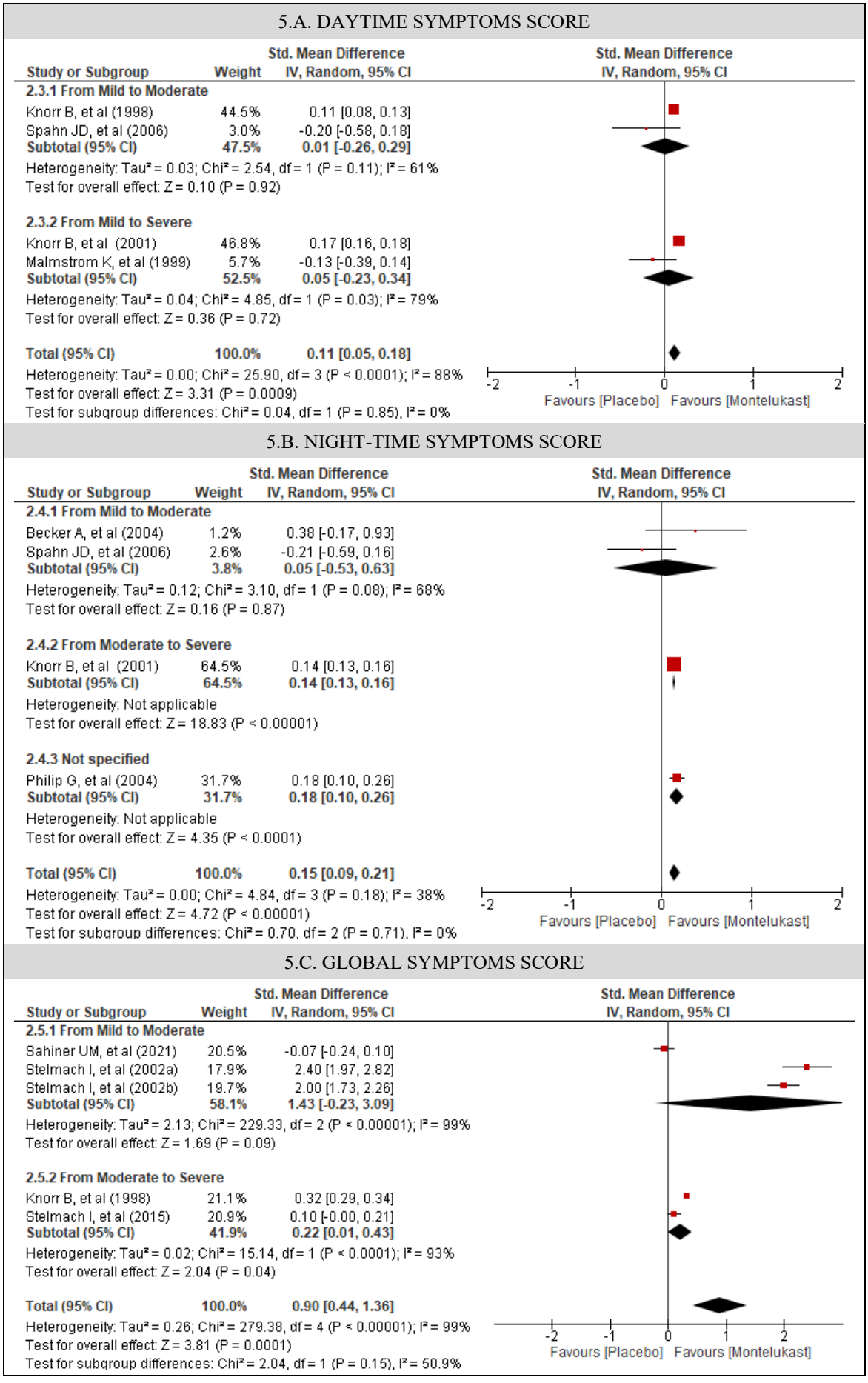


Figure 5. Forest plot of studies comparing patients with asthma treated with Placebo vs Montelukast in terms of symptoms.



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Supplementary material

Figure S1. Search strategy

MEDLINE - OVID

The search strategy applied was as follows: ("asthma"[MeSH Terms] OR "asthma"[Text Word] OR "Rhinitis"[MeSH Terms] OR "Rhinitis"[Text Word] OR "Rhinitis, Allergic"[MeSH Terms] OR "Allergic Rhinitis"[Text Word]) AND ("leukotriene antagonists"[MeSH Terms] OR "leukotrien"[Text Word] OR "leukotriene antagonists"[Text Word] OR Antileukotrien*[Text Word] OR Antileucotrien*[Text Word] OR Anti-leukotrien*[Text Word] OR Antileucotrien*[Text Word] OR "leukotrienes"[MeSH Terms] OR "leukotrienes"[Text Word] OR "leukotriene"[Text Word] OR "leukotriens"[Text Word] OR "montelukast"[Text Word] OR "singulair"[Text Word]) AND ("therapeutics"[MeSH Terms] OR Therap*[Text Word] OR "treatment*"[Text Word] OR "cortico*"[Text Word]) AND ("quality of life"[MeSH Terms] OR "quality of life"[Text Word] OR "health related quality of life"[Text Word] OR "patient reported outcome measures"[MeSH Terms] OR "patient reported outcome measures"[Text Word] OR "patient reported outcome"[Text Word] OR "asthma control"[Text Word] OR "symptoms control"[Text Word] OR "symptoms score"[Text Word]).

EMBASE - OVID

1. asthma/ or asthma.mp.
2. rhinitis/ or allergic rhinitis/ or rhinitis.mp. or allergic rhinitis.mp. or rhinitis, allergic.mp.
3. 1 or 2
4. (leukotriene antagonists or antileukotrien* or antileucotrien* or anti-leukotrien* or anti-leucotrien* or leukotriene or leukotrien or leukotrienes or leukotriens).mp. or leukotriene receptor blocking agent/ or leukotriene/
5. montelukast.mp. or montelukast/
6. singulair.mp.
7. 4 or 5 or 6
8. (therapeutics or treatment* or therap*).mp. or therapy/
9. cortico*.mp. or corticosteroid/
10. 8 or 9
11. (health related quality of life or quality of life).mp. or "quality of life"/
12. (patient reported outcome or patient reported outcome measures).mp. or exp Patient Reported Outcome Measures/
13. asthma control.mp.
14. symptoms control.mp.
15. symptoms score.mp.
16. 11 or 12 or 13 or 14 or 15
17. 3 and 7 and 10 and 16
18. remove duplicates from 17

Supplementary Material. Table A. Characteristics of the studies that data could not be extracted for meta-analysis

First author, Publication year	Study design, Follow-up period	Sample size: n Age: range (mean)	Diagnosis	Intervention (I) or Control (C) group	PROM Administered	PROM as primary, secondary, or tertiary outcome	PROM score	Adverse events reported	Study PROMs findings
LRA vs ICs									
Maspero JF [58], 2001	RCT 6 months	Total n: 124 6-11 yrs (9.5)	Stable asthma	(I): Montelukast (5 mg) (C): Beclomethasone (300 µg)	- Patients and parent satisfaction questionnaires	Not specified	+	No	Parents showed significantly higher satisfaction and numerically higher satisfaction scores in all categories with montelukast at 6 months than with inhaled beclomethasone. Asthmatic children receiving montelukast reported significantly greater overall satisfaction and had a significantly greater satisfaction score than children receiving beclomethasone.
Meltzer E [59], 2002	RCT 24 weeks	Total n: 522 (395 completed the study) >15-77 yrs (36)	Persistent asthma	(I): Montelukast (10 mg) (C): Fluticasone (176 µg)	- AQLQ (emotional function) - Symptoms score (0-5) - Satisfaction with medicine	Not specified	-	Yes	A low dose of fluticasone was more effective in improving asthma control. This was demonstrated by a significantly greater improvement in symptoms control, subject satisfaction, and asthma-related quality of life.
Zeiger RS [60], 2005	RCT 12 weeks	Total n: 400 15-85 yrs (35)	Mild persistent Asthma	(I): Montelukast (10 mg) (C): Fluticasone (176 µg)	- Asthma Symptom Questionnaire - ATAQ - AQLQ	Primary	=	No	Patient-reported asthma outcome measures, including scores for asthma symptoms, asthma control, and asthma-specific quality of life, significantly improved for both montelukast and fluticasone groups compared with baseline. Fluticasone treatment was associated with a significant decrease in night-time symptom frequency (P= 0.04).
Zeiger RS [61], 2006	RCT 16 weeks	Total n: 144 6-17 yrs	Mild-to-moderate persistent asthma	(I): Montelukast (5 or 10 mg) (C): Fluticasone (200 µg)	- ACQ	Not specified	-		The validated Asthma Control Questionnaire improved significantly more with fluticasone than with montelukast treatment.
Kumar V [62], 2007	RCT 12 weeks	Total n: 62 5-15 yrs	Mild persistent asthma	(I): Montelukast (5 mg) (C): Budesonide (800 µg)	- Symptom score	Secondary	=	No	No statistically significant difference in the average symptom score and symptom-free days for cough, wheezing and sneezing.
Knuffman J [63], 2009	RCT 48 weeks	Total n: 191 6-14 yrs	Mild moderate persistent asthma	(I): Montelukast (5 mg) (C): Fluticasone (200 µg)	- ACQ - Night-time awakenings	Primary	-	No	Poorer asthma control was found in the montelukast group.
LRA vs other treatment combinations									
°Laviolette M [64], 1999	RCT 16 weeks	Total n: 642 (39)	Intermittent or persistent asthma	(I): Montelukast (10 mg) (C): Beclomethasone (400 µg) (C): Montelukast (10 mg) + Beclomethasone (400 µg) (C): Placebo	- AQLQ - Daytime symptom score - Global evaluation question	Primary	-	Yes	Montelukast provided significant (p= 0.05) clinical benefit in addition to inhaled beclomethasone in terms of daytime asthma symptom scores, and nocturnal awakenings. Blind removal of beclomethasone in the presence of placebo tablets caused worsening of asthma control, and in the presence of montelukast resulted in less asthma control but not to the level of the placebo group.
Nelson H [65], 2000	RCT 12 weeks	Total n: 447 >15 yrs (42)	Asthma	(I): Montelukast (10 mg) + fluticasone (200 µg) (C): Fluticasone / salmeterol (200/ 100 µg)	- Daytime symptom score (0-5)	Secondary	-	Yes	Fluticasone/salmeterol provided clinically important and statistically significant improvement in overall asthma control compared with fluticasone + montelukast. **AE:** for both groups were oral candidiasis, sore throat, hoarseness, and headache.

°Narayanan S [66], 2002	Observational-prospective 4 weeks	Total n: 175 6-14 yrs (9.6)	Persistent asthma	(I): Montelukast (C): Montelukast / another controller medication	- ACI - Satisfaction with medication (0-6)	Primary	-	No	The results for the individual ACI items indicate that there were improvements in all four items. A fivefold reduction in loss of activity due to asthma was reported among patients for whom montelukast was prescribed alone, while a twofold reduction from baseline was observed among patients using montelukast in combination with another long-term controller. Patient satisfaction with montelukast at 1 month was markedly greater than with the asthma control medication used at baseline.
Pearlman D [67], 2002	RCT 12 weeks	Total n: 432 >15 yrs (36)	Persistent asthma	(I): Montelukast (10 mg) (C): Fluticasone / salmeterol (200/ 100 µg)	- AQLQ - Symptom scores (0-5) - Satisfaction with medicine	Secondary	-	No	The mean AQLQ increase (improvement) from baseline at endpoint in global and individual domain AQLQ scores was significantly greater for patients treated with Fluticasone compared with montelukast (P=0.001). Initial maintenance therapy with FSC provides greater improvement in asthma control and patient satisfaction than montelukast.
Price D [68], 2003	RCT 12 weeks	Total n: 889 15-75 yrs (43)	Optimally controlled Asthma	(I): Montelukast (10 mg) + budesonide (800 µg) (C): Budesonide (1600 µg)	- AQLQ - Daytime symptom score	Secondary	=	No	Both groups showed similar improvements with respect to 'as needed' B agonist use, mean daytime symptom score, nocturnal awakenings, exacerbations, asthma-free days, peripheral eosinophil counts, and asthma-specific quality of life.
°Bjermer L [69], 2003	RCT 52 weeks	Total n: 1490 15-72 yrs (41)	Chronic asthma	(I): Montelukast (10 mg)/ fluticasone (C): Salmeterol/ fluticasone	- AQLQ - Daytime symptom score	Secondary	=	No	Both treatments significantly decreased nocturnal awakenings compared with baseline (P ≤ 0.001). The asthma-specific quality of life score significantly improved from baseline for both treatments (P ≤ 0.001) with no significant difference between the two groups.
Karamana Ö [70], 2004	RCT 12 weeks	Total n: 63 8-14 yrs (120 months)	Mild persistent asthma	(I): Montelukast (5 mg) (C): Budesonide (800 µg) (C): Montelukast (5 mg) + budesonide (800 µg)	- Symptoms score (0-5)	Not specified	=	Yes	The beneficial effects of Montelukast were similar to those produced by inhaled corticosteroids. **AE**: There were no significant adverse effects requiring treatment discontinuation.
Ilowite J [71], 2004	RCT 48 weeks	Total n: 1059 14-73 yrs (38.5)	Moderate-to severe persistent asthma	(I): Montelukast (10 mg) + fluticasone (220 µg) (C): Salmeterol (84 µg) + fluticasone (220 µg)	- AQLQ	Secondary	-	No	Salmeterol significantly increased asthma-specific quality of life, morning peak expiratory flow rate, and decreased nocturnal awakenings compared with montelukast. Differences between treatments were small, and both treatments were generally well tolerated.
Hsieh J-C [72], 2004	RCT 12 weeks	Total n: 65 6-12 yrs (8)	Moderate to severe perennial allergic rhinitis	(I): Montelukast (5 mg) (C): Placebo (C): Cetirizine (10 mg)	- PRQLQ - Nasal symptom score (0-3)	Not specified	=C +P	Yes	Cetirizine has been shown to be more efficacious than montelukast as regards controlling the total symptom score after week 8. Compared with the placebo, cetirizine and montelukast significantly improved the quality of life of children suffering perennial allergic rhinitis. There appears to be no significant difference between cetirizine and montelukast in the scores of the PRQLQ.
O'Connor R [73], 2005	Observational prospective 12 months	Total n: 1270 15-18 yrs Total n: 107 (>15 yrs)	Asthma	(I): Montelukast (10 mg) (C): Fluticasone / salmeterol (100/ 50 µg)	- ACQ - AQLQ - Satisfaction with medication	Not specified	-	No	Fluticasone patients on average reported inferior asthma control and lower assessment of quality of life, compared to montelukast patients. Despite their poorer baseline status, patients treated with fluticasone demonstrated greater improvement in asthma control and asthma-related quality of life, higher satisfaction with treatment, and went to work or school with asthma symptoms less

									often, compared to patients treated with montelukast, 12 months after initiating therapy.
American Lung Association Asthma Clinical Research Centers [74], 2007	RCT 24 weeks	Total n: 489 >15 yrs (40)	Poorly controlled asthma	(I): Montelukast (10 mg)● (C): Theophylline (300 mg)● (C): Placebo●	- ASUI - ACQ - AQLQ	Secondary	-	No	For patients not using inhaled corticosteroids, low-dose theophylline improved asthma symptom control more than montelukast or placebo, and provides a safe and low-cost alternative asthma treatment.
Moeller A [75], 2008	Observational-prospective 8 weeks	Total n: 31 2-5 yrs (4)	Mild to moderate asthma	(I): Montelukast (4 mg) (C): Montelukast (4 mg) ● baseline treatment	- Symptom score (1-5)	Not specified	+	No	First-line or add-on treatment of oral montelukast in children with asthma improved symptom scores. The symptom scores were generally low in both groups and ranged between 1 and 5, with no differences between the two groups at visit 1 (P=0.26). Symptom scores in group 1 were reduced at visit 2 compared to visit 1 (P=0.034), whereas no change was observed for group 2.
Koenig SM [76], 2008	RCT 16 weeks	Total n: 647 >15 yrs (41)	Well controlled asthma	(I): Montelukast (10 mg) (C): Fluticasone / salmeterol (200/100 µg) (C): Fluticasone (200 µg) (C): Salmeterol (100 µg)	- Daily asthma symptom scores (0-5) - Satisfaction with medication	Secondary	-	No	Satisfaction with treatment was rated highest in the fluticasone treatment group, with 76% of subjects reporting being satisfied or very satisfied with therapy. Asthma symptom scores at endpoint showed an improvement from baseline following fluticasone treatment and a worsening from baseline in the salmeterol and montelukast treatment groups.
°Lu S [77], 2009	RCT 16 weeks	Total n: 406 15-65 yrs (34)	Asthma	(I): Montelukast (10 mg) (C): Loratadine (10 mg) (C): Beclomethasone (400 µg) (C): Montelukast (10 mg) + Loratadine (10 mg)	- AQLQ domains - Symptoms score - Patient global evaluation question	Secondary	=	Yes	When compared to montelukast, montelukast + loratadine significantly improved the tertiary endpoints of nocturnal asthma symptom score (p = 0.006), nocturnal awakenings (p = 0.045), and asthma-specific quality of life (p =0.029). There is no benefit of adding loratadine to montelukast for the treatment of asthma.
Katial R [78], 2010	RCT 4 weeks	Total n: 1081 >15 yrs (34.5)	Asthma with seasonal allergic rhinitis	(I): Montelukast (10 mg) (C): Fluticasone / salmeterol (200/100 µg) (C): Fluticasone / salmeterol (200/100 µg) + Montelukast (10 mg) (C): Fluticasone / salmeterol (200/100 µg) + Fluticasone nasal spray (50 µg)	- Symptoms score (0-5)	Not specified	-	No	Treatment with fluticasone alone achieves similar asthma control to concurrent treatment with fluticasone and LTRA. Fluticasone nasal spray was statistically superior in controlling active seasonal allergic rhinitis symptoms compared with montelukast. Treatment with FSC produced significant (p <0.001) improvements in all clinical and patient-reported measures versus montelukast. FSC+ fluticasone nasal spray was superior to fluticasone + montelukast (p < 0.001) in improving daytime and night-time total nasal symptom scores.
Price D [79], 2011	RCT 2 years	Total n: 650 12-80 yrs (47.5)	Uncontrolled Asthma	(I): Montelukast (10 mg) or Montelukast (10 mg) + Beclomethasone or budesonide or fluticasone (C): Beclomethasone or budesonide or fluticasone Beclomethasone or budesonide or fluticasone + Salmeterol or formoterol	- EQ-5D utility scores - MiniAQLQ - ACQ	Secondary	-	Yes	No significant between-group differences were found in ACQ score at either 2 months [adjusted difference 0.01 (–0.20 to 0.22)] or 2 years [0.13 (–0.07 to 0.33)]. MiniAQLQ scores were marginally over the equivalence threshold, favouring long-acting β2-agonist as an add-on therapy.

LRA vs placebo									
Simons F.E.R [80], 2001	RCT 4 weeks	Total n: 279 5-15 yrs (10.4)	Persistent asthma	(I): Montelukast (5 mg) (C): Placebo	- PAQLQ	Secondary	=	No	The effects of montelukast and placebo did not differ significantly. There was no significant difference between treatments groups in global evaluations or asthma attacks.
Strauch E [81], 2003	RCT 12 weeks	Total n: 36 6-14 yrs (11.9)	Moderate asthma	(I): Montelukast (5 or 10 mg) (C): Placebo	- PAQLQ	Secondary	+	No	Patients receiving montelukast showed a significant elevation in the QOL scores within the domains 'emotions' and 'overall quality of life score.' This might suggest a clinical effect of the add-on treatment with montelukast, which is in agreement with earlier reports from randomized controlled trials on montelukast.
Patel P [82], 2005	RCT 6 weeks	Total n: 1992 15-81 yrs (36.4)	Rhinitis	(I): Montelukast 10 mg (C): Placebo	- RQLQ - Daytime symptom score (0-3)	Primary	+	No	All domains of the RQLQ were statistically significantly improved with montelukast relative to placebo.
Wise R [83], 2009	RCT 4 weeks	Total n: 601 >15 yrs (37)	Inadequately controlled asthma	(I): Montelukast (10 mg) (C): Placebo	- ACQ - KASE-AQ - ASUI - Asthma treatment perceptions	Secondary	-	Yes	The improvement in the ASUI was most evident in the patients receiving placebo. Participants assigned to the neutral placebo group had more symptom-free days and fewer nocturnal awakenings than those assigned to usual care. Participants at baseline thought that montelukast was an effective drug for the treatment of asthma. Four weeks later, this perception was significantly improved for participants assigned to the enhanced expectancy presentation compared with the neutral presentation but was not different for most perceptions in those assigned to montelukast versus placebo.
Goh BS [84], 2014	RCT 8 weeks	Total n: 128 13-51 yrs (24.5)	Rhinitis	(I): Montelukast (10 mg) (C): Placebo	- RQLQ - Daytime symptom score (0-3)	Primary and secondary	+	No	The mean improvement in overall quality of life score was significantly greater for the montelukast group than the placebo group.
Kim JH [85], 2020	RCT 5 weeks	Total n: 30 6-8 yrs (7.1)	Clinical asthma	(I): Montelukast (4 or 5 mg) (C): Placebo	- C-ACT	Not specified	=	No	Compared to the montelukast group, the placebo group showed no significant changes in symptoms by the C-ACT.

(●) Added to existing medication; (/) Combo (fixed dose); (+) added treatment; (⁂) PROM information not available. **RCT** Randomized controlled trial; PROM score: **(+)** favours montelukast, **(-)** against montelukast, **(=)** no differences between treatments; **I** Intervention group; **C** Control group; **G** Generic questionnaires; **S** Specific questionnaires; **LRA** Leukotriene receptor antagonists; **ICS** Inhaled corticosteroids; **AntiH1** Antihistamines against the H1 receptor; **LABA** Long-acting beta agonists; **AQLQ** Asthma Quality of Life Questionnaire; **PAQLQ** Pediatric Asthma Quality of Life Questionnaire; **ACI** Asthma Control Index; **ATAQ** Asthma Therapy Assessment Questionnaire; **TRACK** Test for Respiratory and Asthma Control in Kids; **KASE-AQ** Knowledge, Attitude, and Self-Efficacy Asthma Questionnaire; **ASUI** Asthma Symptom Utility Index; **RQLQ** Rhinoconjunctivitis Quality-of-Life Questionnaire; **PRQLQ** The Pediatric Rhinoconjunctivitis Quality of Life Questionnaire; **ACT** Asthma Control Test; **C-ACT** Childhood Asthma Control Test; **ATAQ** The Asthma Therapy Assessment Questionnaire; **ACQ** Asthma Control Questionnaire.

Figure S2. Sensitivity analysis - forest plot of studies comparing patients with asthma treated with ICs vs Montelukast in terms of global Health-related Quality of Life and daytime symptoms scores.

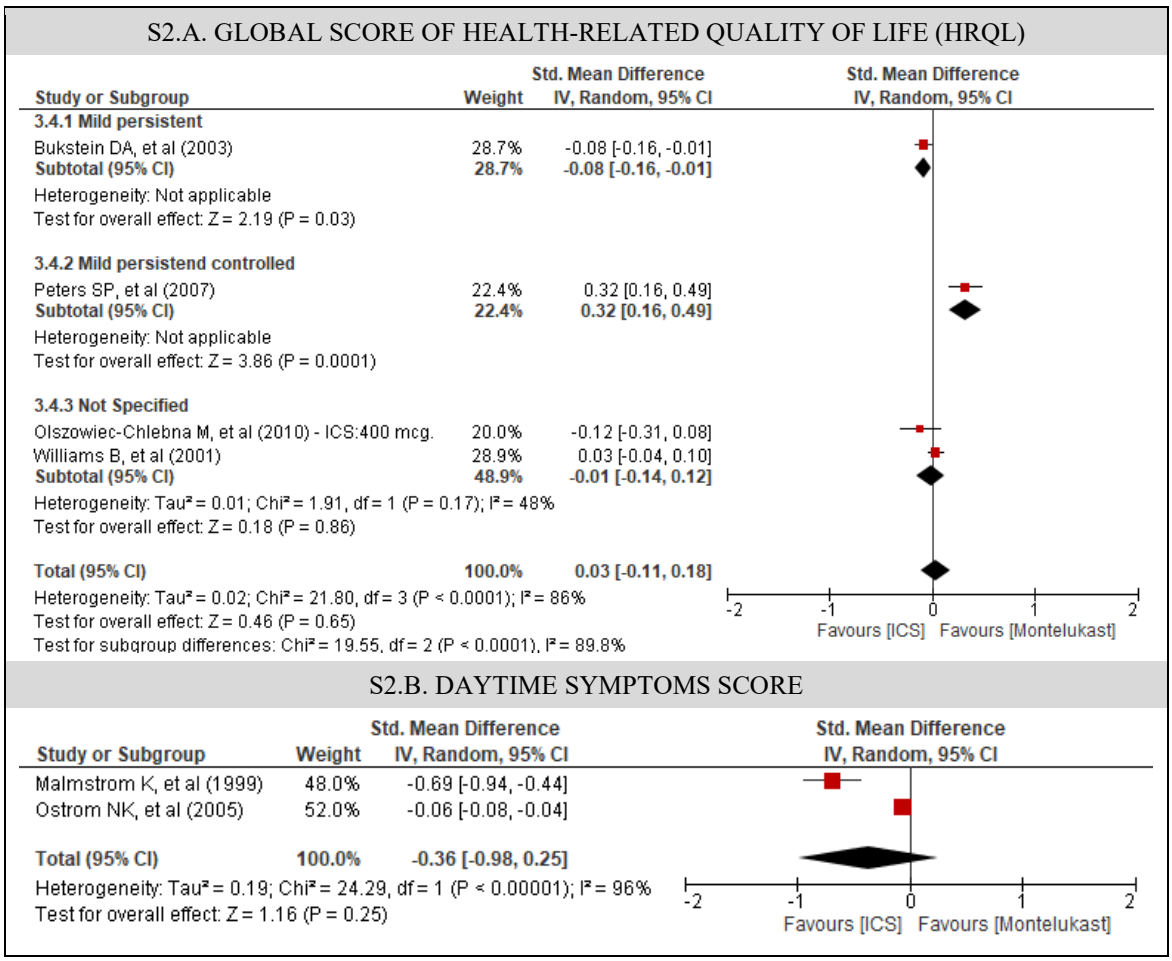


Figure S3. Sensitivity analysis - forest plot of studies comparing patients with asthma treated with Placebo vs Montelukast in terms of symptoms.

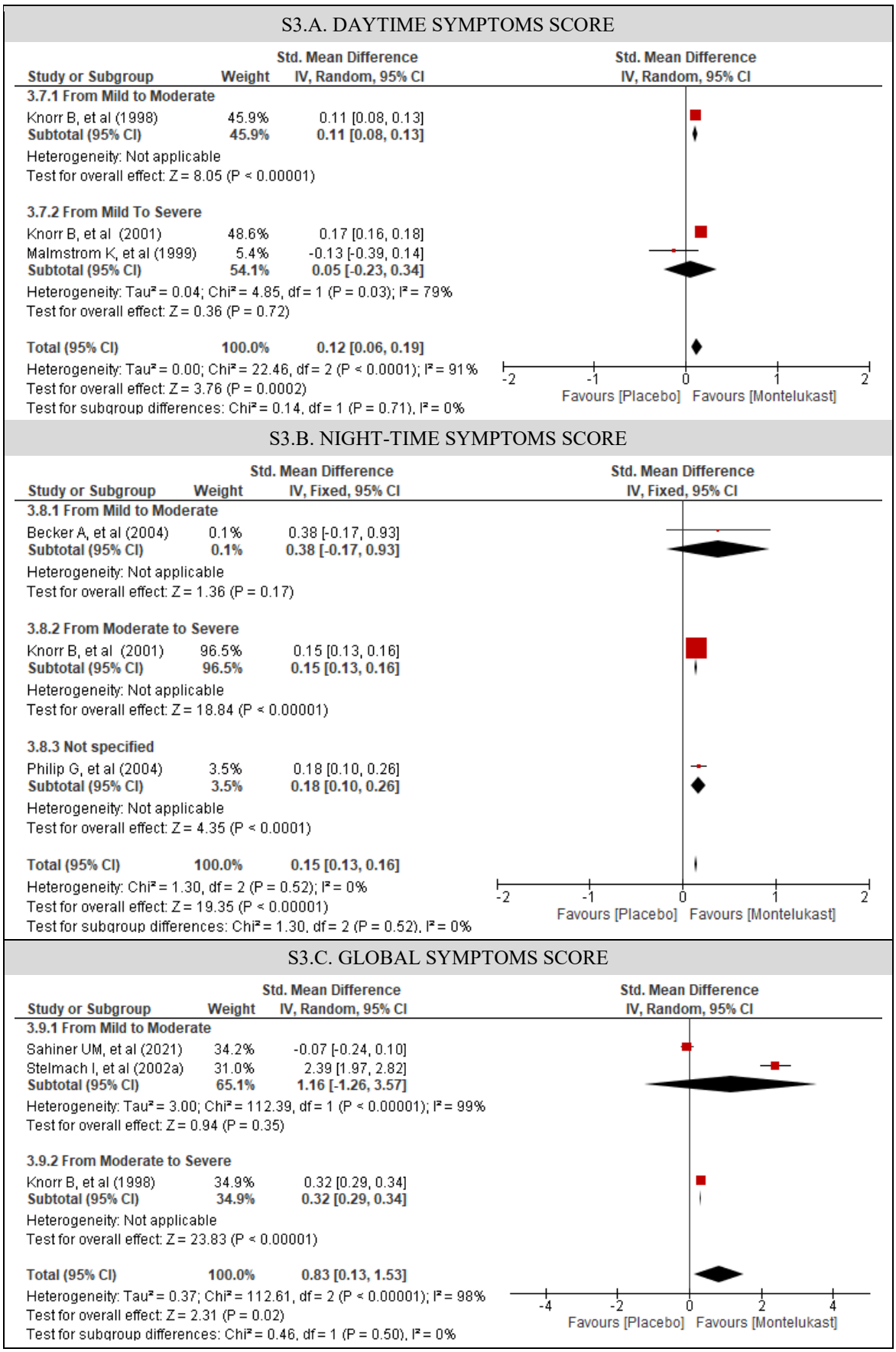
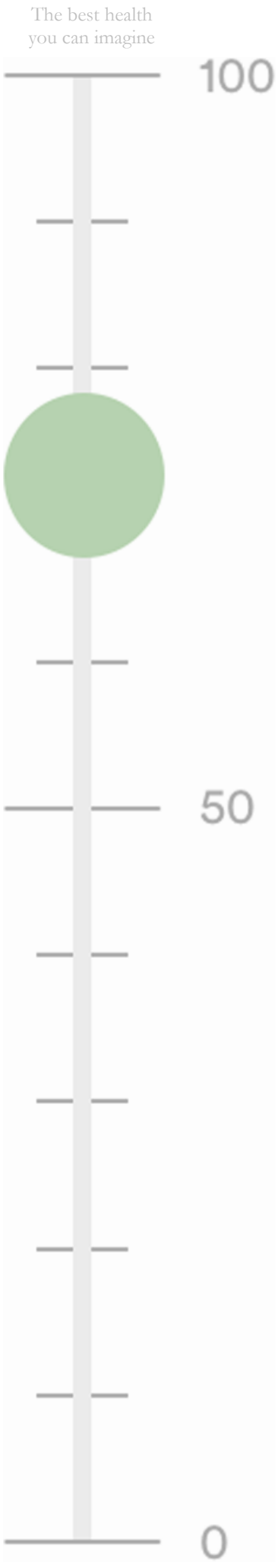


Table B. Adverse drug events

PMID	Description of Groups Study Withdrawals	Adverse drug events		
		Type of event	Intervention group	Control group
Knorr B [48], 1998	**Description** **(I):** Montelukast (4 mg) (n=201) **(C):** Placebo (n=135) **Withdrawals** **(I):** 4% (8 of 201) **(C):** 2.2% (3 of 135)	Upper respiratory tract infection	23.9% (48 of 201)	29.6% (40 of 135)
		Headache	18.9% (38 of 201)	21.5% (29 of 135)
		Asthma	16.4% (33 of 201)	22.2% (30 of 135)
		Pharyngitis	13.9% (28 of 201)	12.6% (17 of 135)
		Abdominal pain	5.0% (10 of 201)	10.4% (14 of 135)
		Influenza	8.5% (17 of 201)	4.4% (6 of 135)
		Cough	6.0% (12 of 201)	7.4% (10 of 135)
		Fever	7.5% (15 of 201)	3.7% (5 of 135)
°Knorr B [50], 2001	**Description** **(I):** Montelukast (5 mg) (n=461) **(C):** Placebo (n=228) **Withdrawals** **(I):** 9.8% (45 of 461) **(C):** 11.4% (26 of 228)	Asthma	29.7% (137 of 461)	37.7% (86 of 228)
		Fever	27.1% (125 of 461)	26.8% (61 of 228)
		Upper respiratory infection	26.7% (123 of 461)	27.6% (63 of 228)
		Vomiting	16.3% (75 of 461)	19.7% (45 of 228)
		Nervous System and Psychiatric Disorders	13.0% (60 of 461)	13.2% (30 of 288)
		Cough	12.6% (58 of 461	11.4% (26 of 228)
		Pharyngitis	11.7% (54 of 461)	15.4% (35 of 228)
		Abdominal pain	11.1% (51 of 461)	9.2% (21 of 228)
		Diarrhoea	9.76% (45 of 461)	7.5% (17 of 228)
		Headache	7.6% (35 of 461)	7.5% (17 of 288)
		Irritability	1.5% (7 of 461)	2.2% (5 of 288)
		Nervousness	0.9% (4 of 461)	0.9% (2 of 288)
		Behaviour disturbance	0.7% (3 of 461)	0.4% (1 of 288)
		Enuresis	0.7% (3 of 461)	0% (0 of 288)
		Insomnia	0.7% (3 of 461)	0.4% (1 of 288)
		Falling	0.4% (2 of 461)	0% (0 of 288)
		Gait abnormality	0.4% (2 of 461)	0% (0 of 288)
		Hyperkinesia	0.4% (2 of 461)	1.3% (3 of 288)
		Dream abnormality	0.2% (1 of 461)	0% (0 of 288)
		Excitement	0.2% (1 of 461)	0% (0 of 288)
		Aggressive behaviour	0.2% (1 of 461)	0.4% (1 of 288)
		Parasomnia	0.2% (1 of 461)	0% (0 of 288)
		Somnolence	0.2% (1 of 461)	0% (0 of 288)
		Anxiety	0% (0 of 461)	0.4% (1 of 288)
		Bipolar disorder	0% (0 of 461)	0.4% (1 of 288)
		Crying	0% (0 of 461)	0.4% (1 of 288)
		Dizziness	0% (0 of 461)	0.4% (1 of 288)
		Personality change	0% (0 of 461)	0.4% (1 of 288)
Garcia-Garcia ML [38], 2005	**Description** **(I):** Montelukast (5 mg) (n=263) **(C):** Fluticasone (200 µg) (n=278) **Withdrawals** **(I):** 7.3% (36 of 495) **(C):** 6.6% (33 of 499)	Headache	3.8% (10 of 263)	1.8% (5 of 278)
		Asthma	1.1% (3 of 263)	0.7% (2 of 278)
		Laboratory adverse Experian	0.8% (2 of 263)	0.0% (0 of 278)
Ostrom NK [39], 2005	**Description** **(I):** Montelukast (5 mg) (n=167) **(C):** Fluticasone (100 µg) (n=172) **Withdrawals** **(I):** 21.0% (35 of 167) **(C):** 13.0% (25 of 172	Asthma exacerbations	14.5% (25 of 167)	19.8% (33 of 172)
		Headache	11.9% (20 of 167)	12.2% (21 of 172)
		Sore throat	11.9% (20 of 167)	9.9% (17 of 172)
		Upper respiratory tract infection	10.8% (18 of 167)	11.6% (20 of 172)
		Fever	7.2% (12 of 167)	9.9% (17 of 172)
		Cough	6% (10 of 167)	10% (17 of 172)
*Stelmach I [37], 2005	**Description** **(I):** Montelukast (5 or 10 mg) (n=17) **(C):** Budesonide (400 or 800 µg) (n=16) **Withdrawals** **(I):** 5.8% (1 of 17) **(C):** 6.3% (1 of 16)	**(AE):** Information not reported in the article.		

PMID	Description of Groups Study Withdrawals	Adverse drug events		
		Type of event	Intervention group	Control group
Spahn JD [55], 2006	**Description** **(I):** Montelukast (5 mg) (n=11) **(C):** Placebo (n=10) **Withdrawals** **(I):** 9.0% (1 of 11) **(C):** 10.0% (1 of 10)	**(AE):** Both treatments were well tolerated, with no serious adverse events noted.		
Szefler S [40], 2007	**Description** **(I):** Montelukast (5 mg) (n=197) **(C):** Budesonide 500 µg (n=197) **Withdrawals** **(I):** 2.5% (5 of 197) **(C):** 1.0% (2 of 197)	Upper respiratory tract infection	28.9% (57 of 197)	26.9% (53 of 197)
		Pyrexia	23.4% (46 of 197)	17.8% (35 of 197)
		Otitis media	17.3% (34 of 197)	11.2% (22 of 197)
		Sinusitis	13.7% (27 of 197)	12.7% (25 of 197)
		Nasopharyngitis	11.7% (23 of 197)	11.7% (23 of 197)
		Headache	11.2% (22 of 197)	9.6% (19 of 197)
		Pharyngitis	10.2% (20 of 197)	6.1% (12 of 197)
Máspero J [46], 2008	**Description** **(I):** Montelukast (5 mg) (n=267) **(C):** Salmeterol / Fluticasone (100/200µg) (n=281) **Withdrawals** **(I):** 11.2% (30 of 267) **(C):** 6.4% (18 of 281)	**(AE):** Information not reported in the article.		
Bérubé D [47], 2014	**Description** **(I):** Montelukast (4 or 5 mg) (n=73) **(C):** Montelukast (4 or 5 mg) + ICs (different doses) (n=252) **Withdrawals** There were 40 (12.2%) patients who were discontinued from the study	A total of 3 serious adverse events were experienced by 3 patients: asthma episode (1), bronchitis (1) and pneumonia (1), none related to the study medication. There were 25 (13.7%) non-serious adverse events, probably related to montelukast. The most frequent non-serious adverse events related to montelukast were: Nightmares and sleep terror (n = 6), abdominal pain (n = 5), insomnia (n = 2), and headache (n = 2).		

(*) Citations identified from other reviews; **(°)** Data obtained after contacting sponsor; (I) Intervention group; (C) Control group.



ANNEX 2:
Supplementary material for article 2

Mayoral K, Garin O, Caballero-Rabasco MA, Praena-Crespo M, Bercedo A, Hernandez G, Castillo J, Lizano Barrantes C, Pardo Y, Ferrer M; ARCA group. ***Smartphone App for monitoring Asthma in children and adolescents.*** Qual Life Res. 2021 Nov;30(11):3127-3144.
doi: 10.1007/s11136-020-02706-z. PMID: 33387290.

Smartphone App for monitoring Asthma in Children and Adolescents

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Electronic Supplementary Material

Figure 1. Search strategy

((((asthma[MeSH Terms]) AND (children[MeSH Terms])) OR ((asthma[MeSH Terms]) AND (adolescent[MeSH Terms])))) AND (disease management[MeSH Terms]) AND ("2010"[Date - Publication]: "2017"[Date - Publication]) Sort by: PublicationDate.

Figure 2. Flow diagram of the study selection process

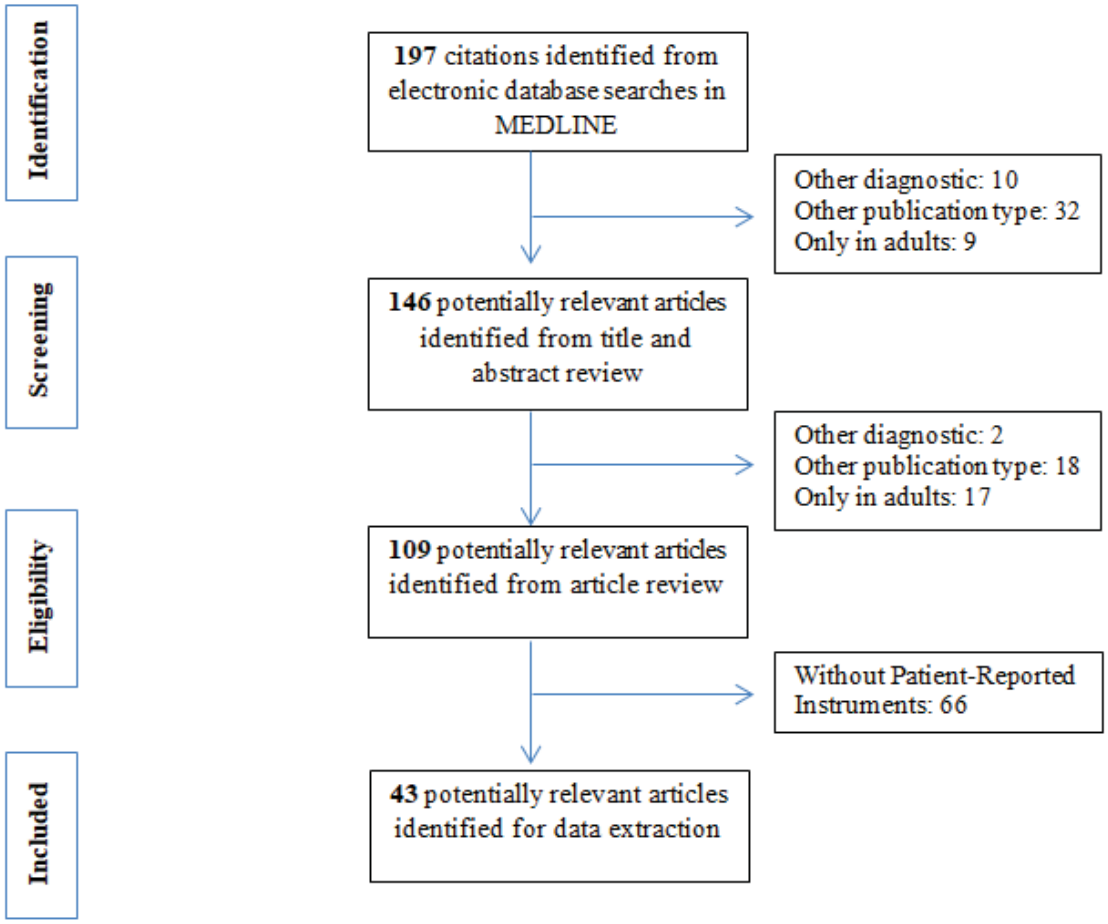


Table 1. Summary of primary studies, reviews, systematic reviews and guidelines identified

	PMID	Author	Instrument	Construct	Comments
PRIMARY STUDIES					
1	20143280	Schauerte G, et al. 2010	Q5 - hospital admissions, days at hospital, emergency visits and use of relievers	-	Questionnaire in German
2	20858029	Pulgaron ER, et al. 2010	Asthma Knowledge Questionnaire (AKQ14)	Illness knowledge and coping	
			Coping Scale for Children and Youth (CSCY)	Illness knowledge and coping	
			Pediatric Asthma Quality of Life Questionnaire (PAQLQ)	HRQoL	
3	21621947	Saini B, et al. 2011	Asthma knowledge questionnaire (AKQ14)	Illness knowledge and coping	
4	22348448	Margellos-Anast H, et al. 2012	-	Triggers	Without development publication
			-	Symptoms control	Without development publication
5	23745594	Turyk M, et al. 2013	-	Triggers	Without development publication
6	23902670	Khan R, et al. 2014	-	Symptoms control	Without development publication
7	24261522	Cicutto L, et al. 2013	Pediatric Asthma Quality of Life Questionnaire (PAQLQ)	HRQoL	
8	24654704	Thakur N, et al. 2014	American Thoracic Society–Division of Lung Diseases Epidemiology Questionnaire	Symptoms control	Asthma control measured with spirometry
9	24859124	Yim S, et al. 2014 (Article in Korean)	Perception of disease, behavior of adaptation to treatment	Illness perception	Without development publication
10	25200397	Abramson MJ, et al. 2014	Inhaler adherence scale	Adherence	(Abstract published in congress)
			Pediatric Asthma Impact Scale (PAIS)	HRQoL	
			Pediatric Asthma Quality of Life Questionnaire (PAQLQ)	HRQoL	
11	25512287	Xing Y, et al. 2014	Asthma control test (ACT)	Symptoms control	
12	25539026	Hamburger R, et al. 2015	-	HRQoL	Without development publication
13	25789861	Gibeon D, et al. 2015	Asthma Control Questionnaire (ACQ)	Symptoms control	
			Pediatric Asthma Quality of Life Questionnaire (PAQLQ)	HRQoL	
14	25840630	Boonsawat W, et al. 2015	Asthma control test (ACT)	Symptoms control	
15	26431213	Horner SD, et al. 2016	Severity of Chronic Asthma scale (SCA)	Symptoms control	
			Home Management survey	-	
16	26823211	Heffler E, et al. 2016	Asthma control test (ACT)	Symptoms control	
17	27631740	Janevic MR, et al. 2016	Childhood Asthma Control Test (C-ACT)	Symptoms control	
18	27720018	Liu AH, et al. 2016	Childhood Asthma Control Test (C-ACT)	Symptoms control	
			Asthma control test (ACT)	Symptoms control	
19	27736038	Verkleij M, et al. 2016	Childhood Asthma Control Test (C-ACT)	Symptoms control	
			Pediatric Asthma Quality of Life Questionnaire (PAQLQ)	HRQoL	
			The Utrecht Coping List for Adolescents (UCL-A) questionnaire	Illness knowledge and coping	
			Parents' report of behavioral problems (CBCL)	-	
			Parenting stress (PSI/NOSI)	-	

20	27908846	Ahmed S, et al. 2016	Asthma control test (ACT)	Symptoms control	
			Mini Asthma Quality of Life Questionnaire (Mini AQLQ)	HRQoL	
			EQ-VAS	HRQoL	
			Beliefs about Medicines Questionnaire (BMQ)	Inhaler beliefs	
21	28157474	Monene KA, et al. 2017	-	Symptoms control	Without development publication
22	28801654	Menzies-Gow A, et al. 2017	Asthma control test (ACT)	Symptoms control	
			Childhood Asthma Control Test (C-ACT)	Symptoms control	
23	29190172	Allen ED, et al. 2018	Asthma control test (ACT)	Symptoms control	
24	21486882	Hoeksema LJ, et al. 2011	Asthma control test (ACT)	Symptoms control	
25	22068359	Mansfield C, et al. 2011	-	Symptoms control	Without development publication
26	22290628	Mishra AK, et al. 2012	Childhood asthma severity (CHAS)	Symptoms control	
27	23211647	Lee SC, et al. 2013	Childhood Asthma Control Test (C-ACT)	Symptoms control	
			Pediatric Asthma Quality of Life Questionnaire (PAQLQ)	HRQoL	
28	24094124	Ekim A, et al. 2013	Asthma Responsibility Questionnaire (ARQ)	Illness knowledge and coping	
29	24109935	Rigopoulou AV, et al. 2013	Asthma Responsibility Questionnaire (ARQ)	Illness knowledge and coping	
30	24591799	Zemedkun K, et al. 2014	Asthma control test (ACT)	Symptoms control	
			-	Illness perceptions	Without development publication
31	25358278	Camp PG, et al. 2014	-	Symptoms control	Without development publication
			-	Triggers	Without development publication
			-	Illness perceptions	Without development publication
			-	Asthma exacerbations	Without development publication
			-	Inhaler technique	Without development publication
32	27049680	Bruzzese JM, et al. 2016	Asthma Prevention Index	Illness knowledge and coping	Without development publication
			Asthma Management Index	Illness knowledge and coping	Without development publication
			Asthma Responsibility Questionnaire (ARQ)	Illness knowledge and coping	
REVIEWS, SYSTEMATIC REVIEWS AND GUIDELINES					
33	26829581	Gomersal, T, et al. 2016	Pediatric Asthma Quality of Life Questionnaire (PAQLQ)	HRQoL	
34	22196525	Szefler, S. J., et al. 2012	Test for Respiratory and Asthma Control in Kids (TRACK)	Symptoms control	
35	22523000	Piacentini, G. L. et al. 2012	Childhood Asthma Control Test (C-ACT)	Symptoms control	
			Asthma Control Questionnaire (ACQ)	Symptoms control	
36	23916401	Carroll, W. et al. 2013	Childhood Asthma Control Test (C-ACT)	Symptoms control	
37	25187271	Voorend-van Bergen, S. et al. 2014	Asthma Control Questionnaire (ACQ)	Symptoms control	
			Childhood Asthma Control Test (C-ACT)	Symptoms control	
			Asthma Treatment Assessment Questionnaire (ATAQ)	Symptoms control	

			Test for Respiratory and Asthma Control in Kids (TRACK)	Symptoms control	
38	25649079	Szefler, S. J. et al. 2015	Asthma Control Questionnaire (ACQ)	Symptoms control	
			Asthma control test (ACT)	Symptoms control	
			Childhood Asthma Control Test (C-ACT)	Symptoms control	
39	26531216	Pedersen, S. et al. 2016	Childhood Asthma Control Test (C-ACT)	Symptoms control	
40	28903951	Pike, K. C., et al. 2017	Asthma control test (ACT)	Symptoms control	
41	28108245	Arakawa, H., et al. 2017	Childhood Asthma Control Test (C-ACT)	Symptoms control	
			Japanese Pediatric Asthma Control Program (JPAC)	Symptoms control	It is not a questionnaire
42	23248807	Lougheed, M. D, et al. 2012	Daytime symptoms Night-time symptoms	Symptoms control	It is not a questionnaire
43	28441001	Désirée Larenas-Linnemann, et al. 2017	Asthma Control Questionnaire (ACQ)	Symptoms control	
			Asthma control test (ACT)	Symptoms control	

Table 2. Summary of systematic reviews found through manual search

	PMID	Author	Instrument	Construct
1.	29461017	Gray WN et al. 2018	Asthma control test (ACT)	Symptoms control
			Asthma Responsibility Questionnaire (ARQ)	Illness knowledge and coping
			Beliefs about Medicines Questionnaire (BMQ)	Inhaler beliefs
2.	26181764	Broadbent, E et al. 2015	Illness Perception Questionnaire (IPQ)	Illness perception
3.	23058645	Jia CE et al. 2013	Asthma Control Questionnaire (ACQ)	Symptoms control
			Asthma control test (ACT)	Symptoms control
4.	20046623	Kamper SJ et al. 2009	Global rating of change	Self-perceived health change
5.	No PMID	Gibbons E et al. 2009	Pediatric Asthma Quality of Life Questionnaire (PAQLQ)	HRQoL
			Standardised Paediatric Asthma Quality of Life Questionnaire PAQLQ(S)	HRQoL
			Mini Paediatric Asthma Quality of Life Questionnaire (Mini PAQLQ)	HRQoL
			Health Utilities Index-Mark III	HRQoL
			EQ 5D	HRQoL
			Child Health Questionnaire (CHQ)	HRQoL
			Child Health and Illness Profile (CHIP)	HRQoL
			Health Related Quality of Life Questionnaire for Children and Young People and their Parents KIDSCREEN	HRQoL
			Pediatric Quality of Life Inventory (PedsQL)	HRQoL
			TNO AZL Children's Quality of Life (TACQOL)	HRQoL
			About My Asthma (AMA)	HRQoL
			Childhood Asthma Questionnaires (CAQ)	HRQoL
6.	22433763	Rajmil L et al. 2012	Child Health and Illness Profile (CHIP)	HRQoL
			EuroQol-5D Youth (EQ-5D-Y)	HRQoL
			Child Health Questionnaires (CHQ)	HRQoL
			Health Related Quality of Life Questionnaire for Children and Young People and their Parents (KIDSCREEN)	HRQoL
			Generic German Quality of Life Questionnaire for Children (KINDL)	HRQoL
			Pediatric Quality of Life Inventory (PedsQL)	HRQoL
			Quality of Life in young children; SPPC, Self-Perception Profile for Children (QUALIN)	HRQoL
			Netherlands Organisation for Applied Scientific Research-Academic Medical Centre child quality-of-life questionnaire (TAPQOL)	HRQoL
			Vecu et Santé Perçué de l'Adolescent (VSP-A)	HRQoL
			Pediatric Asthma Quality of Life Questionnaire (PAQLQ)	HRQoL
7.	23669217	Roncada C et al. 2013	Adolescent Asthma Quality of Life Questionnaire (AAQOL)	HRQoL
			About My Asthma (AMA)	HRQoL
			Asthma-Related Quality of Life (ARQOL)	HRQoL
			Asthma Symptoms and Disability Questionnaire (ASDQ)	HRQoL
			Childhood Asthma Questionnaires (CAQ)	HRQoL
			Disability Kids (DISABKIDS)	HRQoL
			How Are You (HAY)	HRQoL
			Integrated Therapeutics Group Child Asthma Short Form (ITG-CASF)	HRQoL

			Kinder Lebensqualität Fragebogen (KINDL-R)	HRQoL
			Life Activities Questionnaire for Childhood Asthma (LAQCA)	HRQoL
			Pediatric Asthma Health Outcome Measure (PAHOM)	HRQoL
			Pediatric Asthma Quality Of Life Questionnaire (PAQLQ)	HRQoL
			Pediatric Quality of Life Inventory 4.0 (PedsQL)	HRQoL
			Quality of Life Questionnaire for Japanese School-aged Children with Asthma (JSCA-QOL v3)	HRQoL
			TNO-AZL Questionnaires for Children's Health-Related Quality Quality of Life (TACQOL-Asthma)	HRQoL
8.	24964767	Worth A et al. 2014	Asthma Control Test (ACT)	Symptoms control
			Childhood Asthma Control Test (C-ACT)	Symptoms control
			Asthma Control Questionnaire (ACQ	Symptoms control
			Childhood Asthma Questionnaire (CAQ)	HRQoL
			Paediatric Asthma Quality of Life Questionnaire (PAQLQ)	HRQoL
			Pediatric Quality of Life Inventory (PedsQL)	HRQoL
9.	27130811	Gillette C et al. 2016	Inhaler Technique	Inhaler Technique
10.	28732842	Mahon J et al. 2017	Inhalers	Inhaler Technique

Figure 3. Original ARCA application screenshots corresponding to Figure 3

Figure 4. Original ARCA application screenshots corresponding to Figure 4

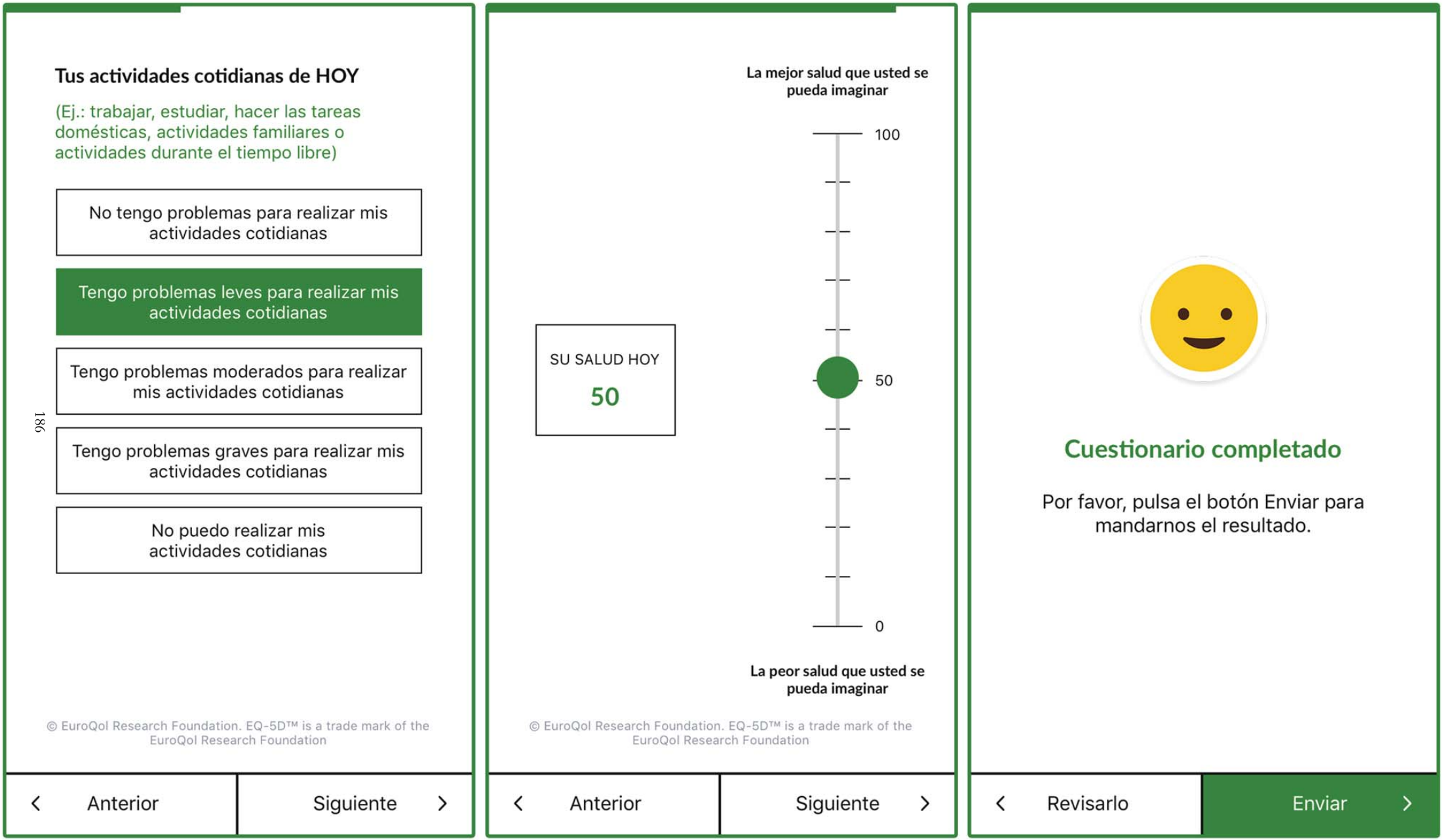
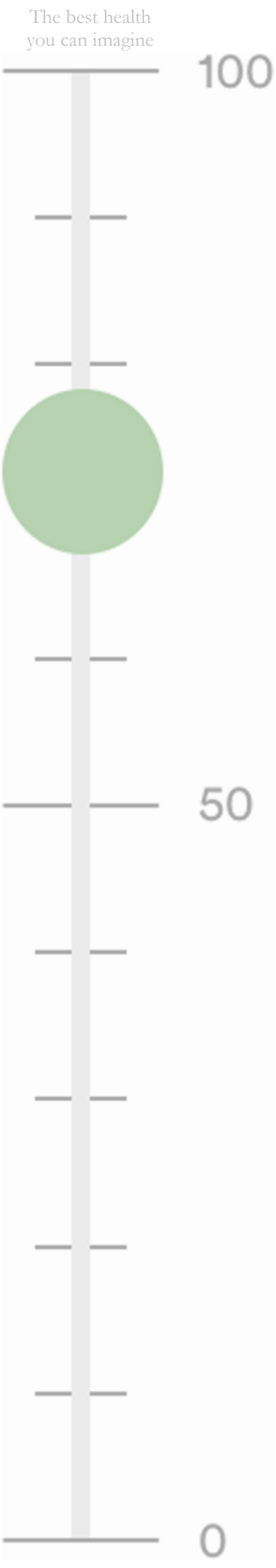


Figure 5. Original ARCA application screenshots corresponding to Figure 5



ANNEX 3:
Supplementary material for article 3

Mayoral K, Garin O, Lizano-Barrantes C, Pont A, Caballero-Rabasco AM, Praena-Crespo M, Valdesoiro-Navarrete L, Guerra MT, Castillo JA, Mir I, Tato E, Alonso J, Serra-Sutton V, Pardo Y, Ferrer M; ARCA Group. ***Measurement properties of the EQ-5D-Y administered through a smartphone app in children with asthma: a longitudinal questionnaire study.*** Health Qual Life Outcomes. 2022 Mar 28;20(1):51.
doi: 10.1186/s12955-022-01955-5. PMID: 35346225.

Table S1. Distribution of Health-Related Quality of Life (HRQL) scores, self-response version (n=81)

Distribution of scores	EQ-5D-Y I Utility Index	EQ-VAS[a]	PROMIS-PAIS[b] Raw score
Sample	81	81	56
Theoretical Range	+1, -0.5392	100, 0	8, 40
	Best-worst	Best-worst	Best-worst
Observed Range	+1.0, +0.51	100, 25	8, 29
Floor effect	0.0%	0.0%	0.0%
Ceiling effect	55.0%	24.7%	28.6%
Mean (SD)	0.92 (0.12)	81.8 (18.8)	11.7 (4.7)
Missing	1 (1.2%)	0 (0.0%)	0 (0.0%)

[a]EQ-VAS: EuroQol-Visual Analogue Scale
[b]PROMIS-PAIS: Patient-Reported Outcomes Measurement Information System - Pediatric Asthma Impact Scale

Table S2. Distribution of Health-Related Quality of Life (HRQL) scores, proxy-response version (n= 38)

Distribution of scores	EQ-5D-Y Utility Index	EQ-VAS[a]	PROMIS-PAIS[b] Raw score
Sample	38	38	19
Theoretical Range	+1, -0.5392	100, 0	8, 40
	Best-worst	Best-worst	Best-worst
Observed Range	+1.0, +0.57	100, 50	8, 24
Floor effect	0.0%	0.0%	0.0%
Ceiling effect	72.2%	21.1%	42.1%
Mean (SD)	0.95 (0.11)	89.7 (11.1)	12.4 (5.6)
Missing	2 (5.3%)	0 (0.0%)	0 (0.0%)

[a]EQ-VAS: EuroQol-Visual Analogue Scale
[b]PROMIS-PAIS: Patient-Reported Outcomes Measurement Information System - Pediatric Asthma Impact Scale

Table S3. Demographic characteristics of participants who completed the 6-month follow-up evaluation and those who did not.

		Baseline and 6-month follow-up (n = 62)	**Only baseline (n = 52)**	***P* value**
Age, mean (SD)		9.1 (1.5)	8.8 (1.9)	.37
	6 – 7	16 (25.8%)	22 (42.3%)	.06
	8 – 11	46 (74.2%)	30 (57.7%)	
Sex, n (%)				
	Girls	23 (37.1%)	22 (42.3%)	.57
	Boys	39 (62.9%)	30 (57.7%)	
Symptoms Control **ACQ**[a], mean (SD)		0.80 (1.00)	0.90 (0.91)	.43
	Well controlled (< 0.75)	37 (61.7%)	27 (52.9%)	.39
	Intermediate (0.75 – 1.5)	13 (21.7%)	10 (19.6%)	
	Not well controlled (> 1.5)	10 (16.7%)	14 (27.5%)	
Asthmatic exacerbations (last 6 months)				
	Yes	21 (33.9%)	32 (61.5%)	.003
	No	41 (66.1%)	20 (38.5%)	
Number of prescribed SABA[b]				
	0	5 (8.3%)	4 (7.8%)	.90
	1	53 (88.3%)	46 (90.2%)	
	2	2 (3.3%)	1 (2.0%)	
Frequency of SABA inhaler use (previous 4 weeks)				
	No use	5 (8.3%)	4 (7.8%)	.63
	Less than once per week	35 (58.3%)	24 (47.1%)	
	Once or twice per week	13 (21.7%)	14 (27.5%)	
	Almost every day / Every day	7 (11.1%)	9 (17.6%)	
Secondhand smoke exposure				
	Not exposed	46 (90.2%)	32 (78.0%)	.11
	Exposed (home, car or both)	5 (9.8%)	9 (22.0%)	
	Missing	11	11	

[a]ACQ: Asthma Control Questionnaire
[b]SABA: Short-Acting β-Agonists

"Last but not least, I wanna thank me.
I wanna thank me for believing in me.
I wanna thank me for doing all this hard work.
I wanna thank me for having no days off.
I wanna thank me for never quitting.
I wanna thank me for tryna do more right than wrong,
I wanna thank me for just being me at all times."

Snoop Dogg

Universitat Autònoma de Barcelona